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Escherichia coli sequence type 410 with carbapenemases: a paradigm shift within *E. coli* toward multidrug resistance

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ABSTRACT *Escherichia coli* sequence type ST410 is an emerging carbapenemase-producing multidrug-resistant (MDR) high-risk One-Health clone with the potential to significantly increase carbapenem resistance among *E. coli*. ST410 belongs to two clades (ST410-A and ST410-B) and three subclades (ST410-B1, ST410-B2, and ST410-B3). After a *fimH* switch between clades ST410-A and ST410-B1, ST410-B2 and ST410-B3 subclades showed a stepwise progression toward developing MDR. (i) ST410-B2 initially acquired fluoroquinolone resistance (via homologous recombination) in the 1980s. (ii) ST410-B2 then obtained CMY-2, CTX-M-15, and OXA-181 genes on different plasmid platforms during the 1990s. (iii) This was followed by the chromosomal integration of $bla_{\text{CMY-2}}$, *fstI* YRIN insertion, and ompC/ompF mutations during the 2000s to create the ST410-B3 subclade. (iv) An IncF plasmid "replacement" scenario happened when ST410-B2 transformed into ST410-B3: F36:31:A4:B1 plasmids were replaced by F1:A1:B49 plasmids (both containing $bla_{\text{CTX-M-15}}$) followed by $bla_{\text{NDM-5}}$ incorporation during the 2010s. User-friendly cost-effective methods for the rapid identification of ST410 isolates and clades are needed because limited data are available about the frequencies and global distribution of ST410 clades. Basic mechanistic, evolutionary, surveillance, and clinical studies are urgently required to investigate the success of ST410 (including the ability to acquire successive MDR determinants). Such information will aid with management and prevention strategies to curb the spread of carbapenem-resistant *E. coli*. The medical community can ill afford to ignore the spread of a global *E. coli* clone with the potential to end the carbapenem era.

KEYWORDS *Escherichia coli*, high-risk clones, carbapenemases, ST410

High-risk multidrug-resistant clones

The global spread of antimicrobial-resistant (AMR) genes within or between bacterial populations is due to the perseverance of certain successful multidrug-resistant (MDR) clones, and/or the movement of AMR genes within, and between diverse strains or lineages (1, 2). Successful MDR clones (also known as high-risk, super, epidemic, eminent, special, or problem clones) are not directly responsible for the movement of AMR genes, but they act as important "hoarders" of AMR genes (3).

"High-risk" is the term that will be used in this article to describe successful and dominant bacterial clones (2, 3). These clones are pivotal in the global emergence, spread, and subsequent increase of AMR genes within various bacterial populations (1). Such clones are likely to have enhanced infectivity and/or fitness properties that have allowed them to dominate within antimicrobial susceptible and AMR bacterial populations, where they effectively compete, cooperate, and construct within bacterial ecosystems (e.g., the human gastro-intestinal tract) (2, 3). This has ensured their long-term survival and subsequent effective transmission, especially in the presence of the selection pressures created by antimicrobial agents (4). MDR successful clones are important contributions to the spread of AMR determinants among various

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bacteria especially *Staphylococcus aureus* [especially methicillin-resistant (MRSA) strains], *Pseudomonas aeruginosa*, and the Enterobacterales (i.e., such as *Klebsiella pneumoniae*, *Escherichia coli*, and the *Enterobacter cloacae* complex) (1–3).

AMR extra-intestinal pathogenic *E. coli*

Human extra-intestinal pathogenic *E. coli* (ExPEC) are responsible for infections outside the gastro-intestinal tract and are the most common cause of global community-acquired and healthcare-associated urinary tract and bloodstream infections (5). This *E. coli* pathotype is the leading cause of community-onset hospitalization, sepsis, and death across the world, especially among the elderly (6). During 2019, AMR *E. coli* infections were directly responsible for 850,000 global deaths (7).

During the 1990s, ExPEC obtained from human clinical infections were mostly sensitive to a variety of antibiotic classes but especially the fluoroquinolones (e.g., ciprofloxacin or norfloxacin) and 3rd generation cephalosporins (e.g., cefotaxime, ceftriaxone, or ceftazidime) (8). The fluoroquinolones and 3rd generation cephalosporins are often used to treat serious ExPEC infections (9). During the 2000s, AMR increased rampantly among ExPEC but especially to the fluoroquinolones and 3rd generation cephalosporins (10). This global increase in fluoroquinolone- and 3rd generation cephalosporin-resistant ExPEC isolates has led to overuse of other antibiotic classes (especially the carbapenems with the subsequent increase in carbapenem resistance) (9, 11). Losing the use of the carbapenems will be devastating for medical practice (11). These agents are some of the most effective last-line treatment options for serious infections due to MDR Gram-negative bacteria (12). Hence, the World Health Organization added *E. coli* to its 2017 global "MDR watch list" (13).

MDR ExPEC clones

Certain ExPEC clones (i.e., ST69, ST73, ST95, ST131, and ST1193) are overpresented among non-selected *E. coli* populations (14). Non-selected ExPEC populations include all isolates, irrespective of their susceptibilities. Different *E. coli* clones (except for ST131 and ST1193) are overpresented among MDR ExPEC populations that consist of fluoroquinolone-resistant isolates, extended-spectrum β-lactamase (ESBL), and carbapenemase producers (15). High-risk MDR *E. coli* clones that are linked with fluoroquinolone resistance include ST131 and ST1193 (15). MDR high-risk clones that are associated with ESBLs include ST131, ST405, ST410, and ST648 (9). MDR clones that are linked with carbapenemases include ST410, ST131, ST167, and ST38 (15, 16).

E. coli ST410 is an emerging ESBL- and carbapenemase-producing global MDR *E. coli* clone (15–19). This manuscript aims to illustrate on how the acquisition of different AMR determinants over time has shaped the ST410 evolution. We will also compare this process with the most successful global MDR high-risk *E. coli* clone named ST131.

E. coli ST410

Introduction

The first published reports of *E. coli* ST410 appeared during 2009–2012 among global genomic surveys of ESBL- and carbapenemase-producing *E. coli* obtained from human and animal sources. These studies described ST410 with $bla_{\text{CTX-M-15}}$ from the USA (20), Spain (21, 22), Brazil (23), Canada (24), and Germany (25); ST410 with $bla_{\text{CTX-M-14}}$ from Spain (26) and Portugal (27); ST410 with $bla_{\text{NDM-1}}$ from the UK and Pakistan (28); and ST410 with $bla_{\text{KPC-2}}$ from Greece (29). The earliest known human ST410 isolate was obtained in 2002 from an elderly Canadian female with upper urinary tract infection (24) while the earliest known animal ST410 isolate was obtained in 2004 from a German dog with lower urinary tract infection (25). These early ESBL- and carbapenemase-producing ST410 isolates showed non-susceptibilities to the carbapenems (i.e., carbapenemase-producing isolates), the cephalosporins (i.e., ESBL-producing isolates), fluoroquinolones, aminoglycosides, trimethoprim-sulfamethoxazole, and the tetracyclines.

Publications of ESBL-producing ST410 (most often with $bla_{CTX\text{-}M\text{-}15}$) escalated during 2013–2017 that included isolates from additional countries in Europe [i.e., Switzerland (30), France (31), Romania (32), UK (33), and Denmark (34)], Africa [i.e., Mauritania (35)], and Asia [(i.e., Taiwan (36), China (37), and Japan (38)]. Gradually, reports of carbapenemase-producing ST410 increased globally with descriptions of KPC-2 from Israel (39), Taiwan (40), and China (41); NDM-1 from Canada (42) and Poland (43); NDM-4 from China (44); NDM-5 from South Korea (45) including the co-production of OXA-181 in Denmark (46), Myanmar (47), and Saudia Arabia (48); OXA-181 from China (49), Canada (50), and France (51); and OXA-48 from Poland (52) and New Zealand (53).

Microbiology and One Health global distribution

E. coli clonal complex (CC) 10 belongs to virulence-associated phylogenetic group A and is composed of several STs including ST10, ST167, and ST410 (14). *E. coli* ST410 contains the O8:H9 antigens and *fimH*24 type 1 pili (54). ST410 can also be positive for *fimH*53 and O/H non-typable (55). ExPEC has certain genetic traits named virulence-associated factors that differentiate this pathotype from commensal and diarrheagenic *E. coli* (56). Overall, ST410 shows significantly lower virulence-associated factor scores when compared to other ExPEC STs such as ST131 and ST405 (16, 57). Multilocus sequence typing (MLST) is currently the only reliable method to identify ST410 isolates (https://github.com/tseemann/mlst).

E. coli ST410 is a true One-Health pathogen and has been reported from humans, animals, and the environment obtained from all continents (excluding Australia and Antarctica) (Table 1; Fig. 1). This clone is responsible for different types of human infections including neonatal infections (58), urinary tract infections (59), blood stream infections (60), as well as rectal carriage (61). ST410 has also been reported from various animals (62–64) including livestock, wildlife, and companion animals as well as environmental sources including hospital wastewater (65), rivers/lakes (66), food produce (67), and food markets (68).

Prevalence

The prevalence of ST410 has mainly been reported among AMR-selected *E. coli* populations including fluoroquinolone-resistant and ESBL- and carbapenemase-producing isolates (Table 1). ST410 is often the 2nd or 3rd most common ST (behind ST131 and ST167) among such populations with prevalence rates of 3–17% among fluoroquinolone resistant isolates, 3–42% among ESBL-producing isolates, and 3–62% among carbapenemase-producing isolates (Table 1). Global surveillance data have suggested that ST410 is especially frequent among carbapenemase-producing *E. coli* (57), especially isolates positive for $bla_{OXA\text{-}181}$ (104) and, to a lesser extent, $bla_{NDM\text{-}5}$ (101). An interesting surveillance study from a Swiss veterinary hospital showed that 100% of cats and dogs (n = 24) were rectally colonized with OXA-181-producing ST410 after being hospitalized at this institution (95).

Overall, ST410 is rare among unselected *E. coli* populations (i.e., populations that include all isolates, irrespective of the presence or absence of AMR determinants) (105). However, 15/176 (6.7%) of *E. coli* infections among Chinese neonates were due to ST410 (106).

E. coli ST410 clades

Roer and colleagues from Denmark were the first group in 2018 to perform phylogenetic analysis on a large collection of ST410 genomes [i.e., 46 isolates from a national Danish surveillance program (DANMAP) and 78 international genomes] (19). The international collection spanned from 1975 to 2017 and was obtained from 14 different countries (i.e., Denmark, UK, USA, Germany, Canada, Brazil, Ireland, Japan, Nepal, Norway, Saudi Arabia, Singapore, Sweden, and Tanzania). Phylogenetic reconstruction divided ST410 into two clades namely antimicrobial susceptible A/*H*53 and AMR B/*H24* (19). Clade A contained

TABLE 1 Prevalence of ST410 among global *Escherichia coli* collections[a]

E. coli population country	Year	One Health distribution	Specimen type	Number *E. coli* isolates	ST410 prevalence	References
Fluoroquinolone resistant						
Greece	2012	Human	Various	35	17%	(69)
Brazil	2017	Human	Urine	61	3%	(70)
USA	2020	Animal	Various	110	4%	(71)
ESBL-producing						
Germany	2014	Animal, food	Various	21	24%	(55)
Israel	2014	Human	Stool	30	10%	(72)
China	2016	Animal	Cow milk	31	6%	(36)
Germany	2016	Human, animal	Various	90	30%	(73)
UK	2016	Animal	Various	38	24%	(74)
Denmark	2017	Human	Blood	491	3%	(34)
Thailand	2018	Human	Various	47	11%	(75)
Switzerland	2018	Animal	Urine	35	25%	(76)
Iran	2020	Human	Urine	37	3%	(77)
Malawi	2021	Human	Various	38	42%	(78)
Ethiopia	2021	Human	Urine	40	13%	(79)
Italy	2021	Human, animal	Various	579	6%	(80)
Bangladesh	2021	Human	Various	46	4%	(81)
Zimbabwe	2021	Human	Urine	48	25%	(59)
Mozambique	2022	Human	Blood	16	38%	(82)
Italy	2022	Human	Rectal swab	43	2%	(83)
Ghana	2022	Human	Various	102	21%	(84)
Nigeria	2022	Human	Various	107	14%	(85)
Malawi	2023	Human	Various	473	10%	(86)
Chile	2023	Animal	Various	19	26%	(63)
Carbapenemase-producing						
UK/Pakistan	2011	Human	Various	18	5%	(28)
Israel	2014	Human	Various	88	16%	(39)
Myanmar	2018	Human	Various	35	15%	(47)
China	2018	Human	Various	24	33%	(87)
Poland	2018	Human	Various	14	21%	(88)
Lebanon	2018	Human	Various	27	11%	(89)
Canada	2018	Human	Various	67	29%	(50)
France	2018	Human	Various	140	7%	(51)
China	2018	Human	Various	54	6%	(90)
Oman	2020	Human	Various	35	9%	(91)
Yemen	2020	Human	Various	6	50%	(92)
India	2020	Human	Blood	60	12%	(93)
South Korea	2020	Human	Various	13	8%	(94)
Switzerland	2020	Environment	Water	17	6%	(95)
Taiwan	2021	Human	Various	23	55%	(96)
Qatar	2021	Human	Various	38	21%	(97)
China	2021	Human	Various	144	10%	(98)
South Korea	2021	Human	Various	707	6%	(99)
Global	2022	Human	Various	229	20%	(57)
China	2022	Human	Various	28	22%	(100)
Thailand	2022	Human	Various	120	62%	(101)
China	2023	Human	Blood	114	3%	(60)
Germany	2023	Human	Various	222	8%	(102)
Europe	2023	Human	Various	874	11%	(103)

[a]Extended-spectrum β-lactamases (ESBLs).

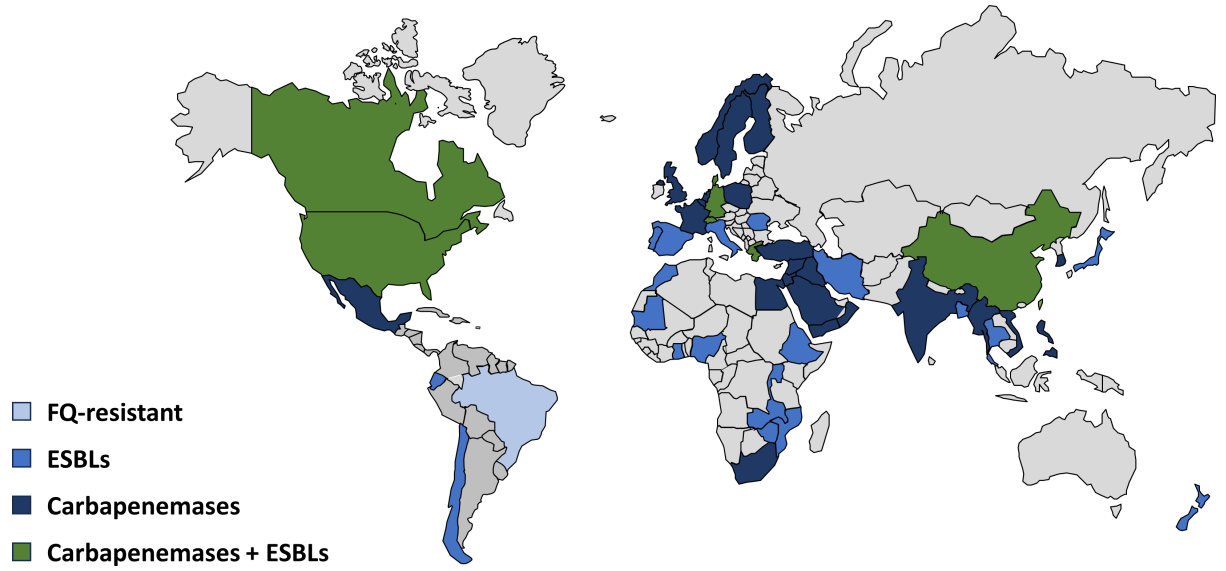

FIG 1 The global distribution of fluoroquinolone-resistant, extended-spectrum β-lactamase, and carbapenemase-producing *E. coli* ST410.

the *fimH*53 type 1 pili and clade B contained the *fimH*24 type 1 pili. The B/*H24* clade was further divided into the following subclades: B1/*H*24, B2/*H*24R, B3/*H*24Rx, and B4/*H*24RxC (19). The B1/*H24* subclade was antimicrobial susceptible; the B2/*H*24R subclade was fluoroquinolone resistant; and B3/*H*24Rx was fluoroquinolone resistant, linked with $bla_{\text{CMY-42}}$ and $bla_{\text{CTX-M-15}}$, while the B4/*H*24RxC subclade was fluoroquinolone resistant and linked with $bla_{\text{CMY-2}}$, $bla_{\text{CTX-M-15}}$, and $bla_{\text{OXA-181}}$ (and $bla_{\text{NDM-5}}$ to a lesser extent) (19). Approximately 20% of B3/*H*24Rx isolates also contained $bla_{\text{CMY-2}}$ and $bla_{\text{OXA-181}}$.

In 2022, Chen et al. updated the ST410 Roer clades (107). They performed core SNP phylogenetic analysis of 614 publicly available global genomes and also divided ST410 into two clades namely ST410-A and ST410-B. The ST410-B clade consisted of 3 subclades (i.e., ST410-B1, ST410-B2, and ST410-B3). In the updated analysis, the previous Roer subclades (i.e., B2/*H24*R and B3/*H24*Rx) belonged to a single subclade namely ST410-B2. The revised Chen ST410 clades corresponded to the following Roer clades (19): ST410-A was identical to A/*H53*, ST410-B1 was identical to B1/*H24*, ST410-B2 included B2/*H24*R, and B3/*H24*Rx and ST410-B3 corresponded to B4/*H24*RxC (107). A summary of the Roer and Chen ST410 clade classifications and associations with different AMR determinants is shown in Table 2. For the remainder of this manuscript, we will use the 2022 updated Chen ST410 clade definitions.

Surveys of the frequencies and global distribution of different ST410 clades are rare and showed that certain clades seem to be scarce (i.e., antimicrobial susceptible ST410-A and ST410-B1) while the MDR ST410-B2 and ST410-B3 subclades are common in France (17), China (18), and Denmark (19). Results from an *E. coli* carbapenemase global genomic survey (n = 229) with a large presentation of lower- and middle-income countries (LMICs) collected during 2015–2017 from 45 countries showed an overall dominance of the ST410-B3 subclade, consisting of nearly 80% of the total ST410 population (57). ST410-B2 isolates, consisting of 20% of the ST410 population, contained the following carbapenemase types (i.e., KPC-2, VIM-23, OXA-48, and OXA-181) and were obtained from various countries including Georgia, Kuwait, Mexico, Morocco, South Africa, the USA, and Vietnam. Interestingly, ST410-B3 isolates were specifically linked with OXA-181 and NDM-5 carbapenemases and were acquired from different countries (than ST410-B2), especially from LMICs such as Jordan, Egypt, and Thailand. Results from that global survey showed that ST410 MDR clades B2 and B3 have a different global distribution and are linked with different types of carbapenemases.

TABLE 2 *E. coli* ST410 clades: associations with different antimicrobial resistance determinants[a] [b]

	ST410-A (A/*H*53)	ST410-B1 (B1/B2/*H24*R)	ST410-B2 (B3/*H24*Rx)	ST410-B3 (B4/*H24*RxC)
Geographic location	?	?	Global	Global
QRDR mutations				
gyrA S83L	–	–	100%	100%
gyrA D87N	–	–	100%	100%
parC S80I	–	–	100%	100%
parE S458L	–	–	100%	100%
Carbapenemases				
KPC-2	–	–	20%	Rare
KPC-3	–	–	Rare	Rare
NDM-1	–	–	Rare	–
NDM-4	–	–	–	Rare
NDM-5	–	–	–	>30%
NDM-7	–	–	–	Rare
OXA-48	–	–	Rare	–
OXA-181	–	–	20–30%	60-70%
VIM-23	–	–	Rare	–
Other β-lactamases				
OXA-1	–	–	>60%	>60%
CMY-2	–	–	20–30%	>95%
CMY-42	–	–	30–40%	–
CTX-M-14	–	–	Rare	Rare
CTX-M-15	–	–	>70%	>90%
Other CTX-Ms	–	–	Rare	Rare
TEM-1	–	–	20–30%	>70%
TEM-ESBLs	–	–	Rare	–
SHV-ESBLs	–	–	Rare	–
Aminoglycoside modifying enzymes				
aadA2	–	–	5–10%	40%
aadA5	–	–	5–10%	>60%
aac(3')-IIa	–	–	Rare	–
acc(3')-IId	–	–	10–20%	>80%
aac(6')-Ib-cr	–	–	60–70%	>90%
aph(3')-Ib	–	–	–	30–40%
aph(6')–1d	–	–	5–10%	>90%
PBP-3 mutations (*ftsI*)				
YRIN	–	–	–	>95%
YRIK	–	–	15%	–
Other AMR determinants				
fosA	–	–	–	–
qnrS1	–	–	15–20%	60–70%
dfrA12	–	–	5–10%	30–40%
dfrA17	–	–	30–40%	80–90%
sul1	–	–	50–60%	>95%
sul2	–	–	5–10%	>90%
tetA	–	–	90%	–
tetB	–	–	–	>95%

[a]Roer classification (19): A/H52, B1/H24, B2/H24R, B3/H24Rx, and B4/H24RxC.
[b]Chen classification (107): ST410-A1, ST410-B1, ST410-B2, and ST410-B3.

Acquisition of antimicrobial resistance determinants among ST410 clades

Fluoroquinolone resistance

Among *E. coli*, mutations within the quinolone resistance determining regions (QRDR) are the most common causes of fluoroquinolone resistance (108). Three specific QRDR mutations are essential for high-level clinical resistance in *E. coli* to the fluoroquinolones, namely *gyrA*S83L (TCG to TTG), *gyrA*D87N (GAC to AAC), and *parC*S80I (AGC to AGT). The QRDR mutations in *E. coli* are normally acquired in a sequential manner: *gyrA*S83L appeared first, followed by *parC*S80I, while *gyrA*D87N arrived later (109). The sequential acquisition of such QRDR mutations increased fluoroquinolone resistance in a stepwise manner (i.e., the gradual increase in fluoroquinolone minimum inhibitory concentrations as each mutation was added). Plasmid-mediated fluoroquinolone resistance determinants [e.g., *qnr*, *aac(6')-Ib-cr*] are less common among *E. coli* (than QRDR mutations) but also contributed to fluoroquinolone resistance among this species (108).

The ST410-A and ST410-B1 clades are susceptible to fluoroquinolones and do not contain QRDR mutations or plasmid-mediated fluoroquinolone resistance determinants. The ST410-B2 and ST410-B3 subclades are resistant to the fluoroquinolones due to the three typical *E. coli* QRDR mutations, namely *gyrA*S83L, *gyrA*D87N, and *parC* S80I (17, 18, 107). ST410-B2 and ST410-B3 also contained the *parE* mutation S458L (Table 2). The acquisition of these QRDR mutations in ST410-B2 and ST410-B3 subclades was due to a single multi-allelic homologous recombination event and not the typical *E. coli* stepwise acquisition (107). The possible donors of these large recombination regions were likely *E. coli* ST940 and ST694 (107). The same QRDR mutation recombination process was previously described in a different *E. coli* high-risk clone, namely ST1193 (110, 111).

The prevalence of the plasmid-mediated fluoroquinolone resistance determinants *aac(6')-Ib-cr* (>90%) and *qnrS1* (>50%) is high among ST410-B2 and ST410-B3 isolates but especially among the ST410-B3 subclade (Table 2). Other types of plasmid-mediated fluoroquinolone resistance determinants are rare among ST410 (Table 2). *AAC(6')-Ib-cr* is an aminoglycoside-modifying enzyme that also inactivates the fluoroquinolones.

CTX-M β-lactamases

The most common causes of resistance to the 3rd generation cephalosporins among *E. coli* are the ESBLs and more specifically the CTX-M enzymes (9, 112). The prevalence of CTX-M β-lactamases increased rapidly during the mid- to late 2000s and is currently the most common global ESBL among *E. coli* (9). This is especially true for *E. coli* causing bloodstream infections where more than 90% of ESBLs were identified as either CTX-M-14 or CTX-M-15 (24, 105). From 2010 and onward, the prevalence of *E. coli* with CTX-M-27 has been increasing over time among ESBL-producing isolates (113, 114).

ESBLs are absent among ST410-A and ST410-B1 clades. CTX-M types have been described among ST410-B2 and ST410-B3 subclades. The CTX-M-15 allele is by far the most frequent type of ESBL among ST410-B2 and ST410-B3 isolates (e.g., >80% prevalence) (Table 2) (19, 57). Non-CTX-M-15 types of ESBLs (i.e., TEMs, SHVs, CTX-M-1, CTX-M-2, CTX-M-3, CTX-M-14, CTX-M-32, and CTX-M-65) are rare among ST410 isolates (Table 2) (18, 19, 107).

Long read whole genome sequencing revealed interesting information regarding the plasmids harboring $bla_{\text{CTX-M-15}}$ within the ST410-B2 and ST410-B3 subclades. The $bla_{\text{CTX-M-15}}$ is situated on IncF plasmids that are typed as F36:31:A4:B1 (using the plasmid MLST scheme) within ST410-B2 isolates (107). However, within the ST410-B3 subclade, the $bla_{\text{CTX-M-15}}$ was situated on IncF plasmids that were identified as the F1:A1:B49 (107). The F36:31:A4:B1 and F1:A1:B49 ST410 plasmids showed less than 45% sequence homologies, indicating that they were different types of IncF plasmids. Shared regions between the two ST410 IncF plasmids included the Tn*3*-$bla_{\text{TEM-1}}$-IS*26*-IS*Ecp1*-$bla_{\text{CTX-M-15}}$-Tn*3*-*cat*-$bla_{\text{OXA-1}}$-*aac(6')-Ib-cr*-IS*26* resistance module (107). Both IncF types of plasmids contained several toxin-antitoxin systems and truncated gene transfer modules.

CMY β-lactamases

E. coli possess a chromosomal gene that encodes for an AmpC β-lactamase. Usually, low amounts of these enzymes are produced because the AmpC gene is regulated by a weak promoter and a strong attenuator (115). *E. coli* can also contain plasmid-mediated (or imported) AmpC β-lactamases that include CMY, ACT, FOX, ACT, and DHA types (115). Among *E. coli*, CMY-2 are the most common imported AmpC β-lactamases (116).

CMY β-lactamases (i.e., CMY-2 and CMY-42) have been described among ST410 isolates but the distribution and frequencies differ among the different clades (19, 107). CMYs were absent among ST410-A and ST410-B1 isolates, $bla_{\text{CMY-42}}$ was limited to ST410-B2, while $bla_{\text{CMY-2}}$ was very common within ST410-B3 isolates (and rare among ST410-B2) (Table 2). Long read whole genome sequencing revealed that the $bla_{\text{CMY-42}}$ within ST410-B2 isolates was located on ~38 kb IncI(Gamma) plasmids while the $bla_{\text{CMY-2}}$ was located on 110 kb IncC plasmids (107). However, within the ST410-B3 subclade, the CMY-2 gene was integrated within an ~73 kb tRNA-Ser site chromosomal genomic island (107, 117).

Carbapenemases

The carbapenemases are the most important causes of carbapenem resistance among Enterobacterales because carbapenemase genes can be transferred between different Enterobacterales species (118). *E. coli* is the second most common carbapenemase-producing Enterobacterales species (behind *Klebsiella* species) (119, 120). Large global genomic surveys of carbapenemase-producing *E. coli* are currently rare. The most common carbapenemases among *E. coli* are the NDMs (i.e., NDM-1 and NDM-5), OXA-48-like β-lactamases (i.e., OXA-48 and OXA-181), and KPC enzymes (i.e., KPC-2 and KPC-3) (57). The VIM and IMP carbapenemases tend to be rare in *E. coli*.

Several types of carbapenemases were described within ST410 and included KPCs (i.e., KPC-2 and KPC-3), NDMs (i.e., NDM-1, NDM-4, NDM-5, and NDM-7), OXA-48-like (i.e., OXA-48 and OXA-181), and VIMs (i.e., VIM-4 and VIM-23) (Table 2). The distribution and frequencies were different among ST410 clades (17, 18, 107). Carbapenemases were absent among ST410-A and ST410-B1. The KPCs, NDM-1, OXA-48, and VIMs were limited to ST410-B2 while NDM-4, NDM-5, and NDM-7 were limited to ST410-B3 (Table 2). OXA-181 are found among ST410-B2 and ST410-B3 but in different frequencies [i.e., approximately 20–30% of ST410-B2 contained OXA-181 as compared to 60–70% of ST410-B3 (19, 107) (Table 2).

Overall, OXA-181 and NDM-5 (sometimes co-produced in the same isolate) were the most frequent ST410 carbapenemases and were specifically linked to the ST410-B3 subclade (19, 57, 107). Long read whole genome sequencing showed that $bla_{\text{OXA-181}}$ from ST410-B2 and ST410-B3 was situated in Tn*2013* and harbored on nearly identical 51 kb IncX3 plasmids with 99.9–100% similarities to the previously published plasmid p72_X3_OXA181 obtained from *K. pneumoniae* ST307 obtained from South Africa (121, 122). The IncX3 plasmids also contained *qnrS1* and truncated ColKp3 replicons (122). Highly similar IncX3 plasmids with OXA-181 were previously described from different Enterobacterales species worldwide (104).

The NDM-5 genes within ST410-B3 were located on mosaic narrow-host range IncF plasmids that were identified as F1:A1:B49. These were the same IncF plasmids responsible for the high frequency of $bla_{\text{CTX-M-15}}$ among ST410-B3 isolates (107). The $bla_{\text{NDM-5}}$ flanking region consisted of IS*26*-$bla_{\text{NDM-5}}$-ble_{MBL}-*trpF*-*desD*-*IS*CR1. The F1:A1:B49 plasmids contained several toxin-antitoxin systems and truncated gene transfer modules.

Penicillin-binding protein (PBP3), outer membrane protein (ompC), and ompF point mutations

The *E. coli ftsI* gene encodes for PBP3 (123). Certain PBP3 amino acid insertions (i.e., YRIN, YRIK, or TIPY) confer reduced susceptibilities to several β-lactams, including aztreonam,

ceftazidime, cefepime, ceftazidime/avibactam, and ceftolozane/tazobactam (124). PBP3 mutations were absent among ST410-A and ST410-B1. Most (>95%) of the ST410-B3 isolates contained the *ftsI* YRIN insertion, while some (approximately 15%) of ST410-B2 isolates contained the *ftsI* YRIK insertion (Table 2) (17, 107). ST410-B3 likely acquired an ~130 Kb recombination region that included *fstI* mutations and lipopolysaccharide synthesis genes (e.g., lpxC) from another *E. coli* high-risk MDR clone namely ST167 (17, 107). The ompC (i.e., R195L) and ompF (i.e., C->T,–46) mutations were limited to ST410-B3 isolates (17).

Other antimicrobial resistance determinants

Certain "other" AMR determinants (e.g., *dfrA17*, *sul1*, or *tetA*) were common among ST410-B2 and ST410-B3 while *aadA5, acc(3')-IId , aph(6')–1d, sul2*, and *tetB* were more frequent among ST410-B3 (when compared to ST410-B2) (Table 2).

Evolution: acquisition of different AMR determinants shaped ST410 clades

ST410 BactDating estimated that the most recent common ancestor, namely ST410-A, appeared around the mid-1800s [i.e., 1855 (95% confidence interval, CI, 1808–1893)], approximately 170 years ago (18, 107). ST410-B1 likely emerged around the mid-1930s [i.e., 1935 (95% CI, 1920–1950)] that was associated with a type I pili switch from *fimH*53 to *fimH*24. The fluoroquinolone-resistant ST410-B2 subclade emerged around the late 1980s to early 1990s [i.e., 1990 (95% CI, 1983–1996)], which correlated with the introduction of the fluoroquinolones (i.e., norfloxacin and ciprofloxacin) in clinical medicine during the early to mid-1980s (125). The ST410-B3 subclade evolved from ST410-B2 around the mid-2000s (i.e., 2006 [95% CI, 2004–2009]) (18, 107).

The evolution of ST410 is highlighted by the gradual acquisition of different AMR determinants over time as antimicrobial susceptible clades (i.e., ST410-A and ST410-B1) evolved into MDR subclades (i.e., ST410-B2 and ST410-B30) (Fig. 2). The fluoroquinolone-resistant ST410-B2 subclade evolved from ST410-B1 by the acquisition of three QRDR mutations (i.e., *gyrA* S83L, *gyrA* D87N, and *parC* S80I) via a large homologous recombination event with *E. coli* ST940 and ST694 being the donors (107). The divergence of ST410-B2 from ST410-B1 also correlated with the acquisition of $bla_{\text{CTX-M-15}}$ situated within F36:31:A4:B1 plasmids in the late 1990s that became common and distributed widely among this subclade (Fig. 2; Table 2). IncC plasmids containing $bla_{\text{CMY-2}}$ and IncX3 plasmids with $bla_{\text{OXA-181}}$ likely entered the ST410-B2 population in the early to mid-2000s but did not become populous among this subclade (Fig. 2). Recent genomic surveys have shown that approximately 15–20% of ST410-B2 contained $bla_{\text{CMY-2}}$ and $bla_{\text{OXA-181}}$ (Table 2) (17, 107).

The emergence of the ST410-B3 subclade from ST410-B2 was accompanied by the chromosomal integration of $bla_{\text{CMY-2}}$, the acquisition of *ftsI* YRIN insertion, and ompC/ompF mutations, as well as the replacement of F36:31:A4:B1 plasmids with F1:A1:B49 plasmids also harboring $bla_{\text{CTX-M-15}}$ (Fig. 2) (17, 107). F1:A1:B49 plasmids with CTX-M-15 and IncX3 plasmids with OXA-181 became dominant over time within the ST410-B3 population (Fig. 2; Table 2). Recent genomic surveys showed that >90% and approximately 70–80% of ST410-B3 contain $bla_{\text{CTX-M-15}}$ and $bla_{\text{OXA-181}}$, respectively (17, 107). The NDM-5 gene was gradually incorporated into the same F1:A1:B49 plasmids starting around ~2010 (95% CI, 2009–2013), likely via IS*26*-mediated insertion (Fig. 2) (107). The contributions of QRDR, *ftsI*, and ompC/ompF mutations, as well as the acquisition of plasmids with CMY-2, CTX-M-15, OXA-181, and NDM-5 in the evolution of ST410 subclades over time, are shown in Fig. 2.

E. coli ST131

Introduction and ST131 clades

E. coli ST131 was first described among ExPEC with $bla_{\text{CTX-M-15}}$ obtained during 2000–2006 from several countries including Spain, France, Canada, Portugal, Switzerland,

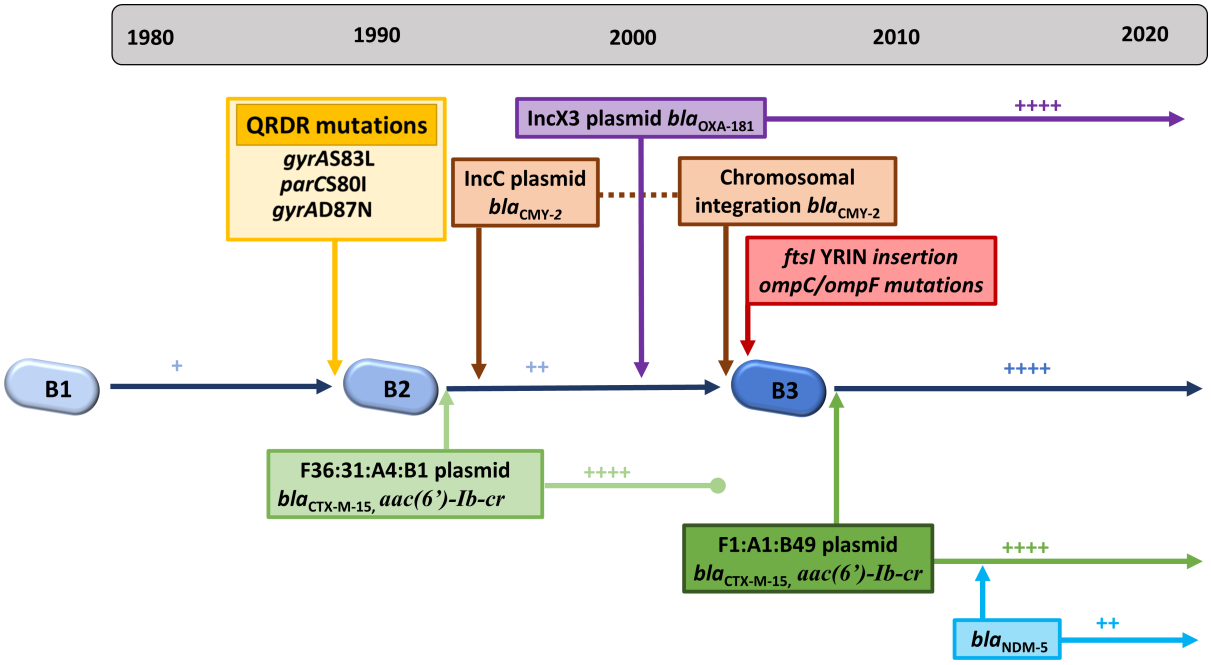

FIG 2 The stepwise acquisition over time of antimicrobial resistance determinants in the evolution of ST410 subclades.

Lebanon, India, Kuwait, and Korea (126, 127). These two initial studies showed that ST131 emerged independently in different parts of the world spanning three continents, seemingly at the same time. It became quickly apparent that ST131 was largely responsible for the global increase of fluoroquinolone- and ESBL-producing ExPEC during the 2000s (128).

ST131 belongs to three clades (fluoroquinolone susceptible clades namely A, B, and fluoroquinolone-resistant clade C) (129). Clade A is associated with serotype O16:H5 and *fimH*41, clade B is linked with serotype O25b:H4 and *fimH*22/*fimH27*, while all clade C isolates contain *fimH*30 and type with O25b:H4 (129). ST131-B gained fluoroquinolone resistance, certain bacteriophages, and pathogenicity islands to become ST131-C (130). ST131-C then divided into subclades (i.e., C1, C1-M27, and C2), which became 3rd generation cephalosporin-resistant over time, by acquiring different CTX-M genes (114, 131). MDR ST131-C1 and ST131-C2 account for 80% of global ST131 population (132, 133).

Acquisition of antimicrobial resistance determinants among ST131 clades

Fluoroquinolone resistance

Fluoroquinolone resistance has been a strong driver for ST131-C's success and global dissemination (131). ST131 acquired different QRDR mutations in a sequential manner (57, 133, 134). During the mid-1980s, ST131-B transformed into ST131-C0: *gyrA*S83L appeared first and was followed by *parC*S80I (Fig. 3). During the early 1990s, ST131-C0 acquired two additional QRDR mutations (i.e., *gyrA*D87N and *parC*E84V) and then split into ST131-C1 and ST131-C2 (Fig. 3) (57, 134).

The prevalence of the plasmid-mediated fluoroquinolone resistance determinant *aac(6')-Ib-cr* is high among ST131-C2 isolates (60–80%) (134, 135). *AAC(6')-Ib-cr* has provided a selective advantage for ST131-C2 in the presence of fluoroquinolones and has contributed significantly to the overall success of ST131 (135).

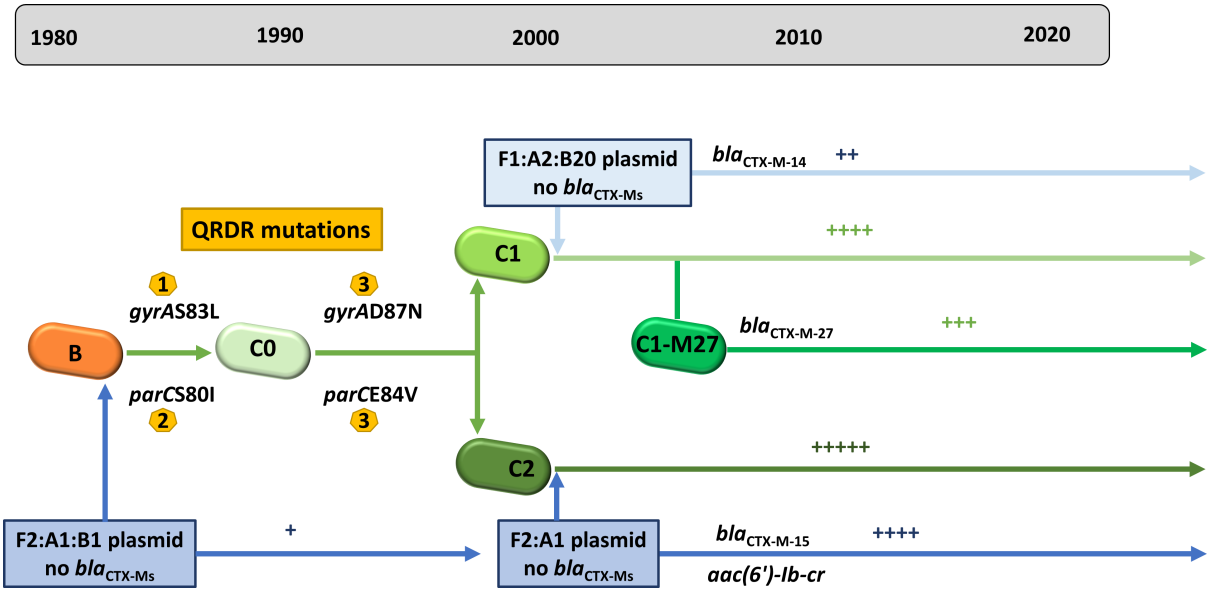

FIG 3 The stepwise acquisition over time of antimicrobial resistance determinants in the evolution of ST131 subclades.

CTX-M β-lactamases

There are different ST131 clade/CTX-M combinations (136). CTX-M β-lactamases are extremely rare in clades ST131-A, ST131-B, and ST131-C0. CTX-M-14 are linked with ST131-C1, CTX-M-27 with ST131-C1-M27, and CTX-M-15 with ST131-C2 (132, 134).

Within the ST131-C clades, different IncF subtypes are associated with specific CTX-M enzymes (137): e.g., F1:A2:B20 plasmids containing *bla*$_{\text{CTX-M-14}}$ and F1:A2:B20 plasmids with *bla*$_{\text{CTX-M-27}}$ are found in ST131-C1 and C1-M27, respectively. F2:A1:B1 plasmids with *bla*$_{\text{CTX-M-15}}$ are mainly detected in ST131-C2 (138). The specific ST131-C and CTX-M IncF type plasmid combinations spread globally and are examples of some of the greatest clone/plasmid evolutionary successes of the millennium (2, 131, 137).

Evolution: emergence of different MDR ST131 clades over time

The contributions of *fimH* shift, QRDR mutations, *aac(6')-Ib-cr*, and CTX-Ms in the evolution of ST131 over time are shown in Fig. 3. The ancestral clade, ST131-A, emerged in the mid- to late 1800s. In the early to mid-1900s, ST131-A underwent a type 1 pili shift from *fimH*41 to *fimH*22/*fimH*27 to establish ST131-B (130, 131). During the early 1980s, ST131-B transformed into ST131-C0 by acquiring the following (Fig. 3): (i) stepwise QRDR mutations and (ii) IncF plasmids with *bla*$_{\text{CTX-Ms}}$.

During the early to mid-1990s, ST131-C0 underwent the following transformation (Fig. 3): (i) ST131-C0 acquired additional QRDR mutations (via a stepwise process). (ii) ST131-C0 split into ST131-C1 and C2 (134). (iii) F1:A2:B20 plasmids (initially without CTX-Ms) entered the ST131-C1 lineage likely during the mid-1990s and gained *bla*$_{\text{CTX-M-14}}$ over time (137). (iv) The F2:A1:B1 plasmids (initially without CTX-Ms) entered the ST131-B clade likely around the 1950s and then moved to the ST131-C2 population during the early 1990s. These plasmids lost the B1 replicon and gained CTX-M-15 and *aac(6')-Ib-cr* over time (137). (v) In the mid-2000s, ST131-C1 acquired a genomic element (i.e., prophage M27PP1) to become ST131-C1_M27 (114). This was accompanied by a point mutation in *bla*$_{\text{CTX-M-14}}$ to become *bla*$_{\text{CTX-M-27}}$. ST131-C1-M27 then increased in frequency among *E. coli* producing ESBLs, especially during the mid-late 2010s (9).

Overall, the ST131 evolution scenario over time shared very similar characteristics (type 1 pili switch, QRDR mutations, and clade-specific IncF plasmids with CTX-Ms)

to ST410 clade evolution (Fig. 2 and 3). However, ST410 acquired QRDR mutations via a large homologous recombination event and took the "MDR process" further by incorporating additional AMR determinants (e.g., *ftsI*, ompC/ompF mutations, $bla_{OXA-181}$, bla_{NDM-5}, or bla_{CMY-2} chromosomal integration) to become a lineage that contained large number of AMR determinants.

CONCLUSION

Before the 2000s, ExPEC was not considered to be important global AMR players. At that time, localized ESBL-producing isolates (mostly TEM types) were reported, but widespread fluoroquinolone and 3rd generation cephalosporin-resistant *E. coli* were very rare (139, 140). The MDR landscape during the 1990s was mainly occupied by carbapenem-resistant *P. aeruginosa*, MRSA, penicillin-resistant *Streptococcus pneumoniae*, and ESBL-producing *K. pneumoniae*. However, the scenario changed dramatically in the early to mid-2000s when fluoroquinolone-resistant and ESBL-producing ExPEC isolates increased exponentially by the 2010s (15). In 2000 (i.e., Y2K), it was expected that widespread computer programming shortcuts would cause extensive havoc as the year changed from 1999 to 2000. As it turned out, ExPEC isolates were responsible for wide-spread AMR mayhem starting around 2000, as MDR isolates emerged and spread globally over a relatively short 10-year period (139, 140). Since ExPEC is mainly responsible for community-onset infections, the increase of MDR isolates was not initially recognized and flew for most part, under the radar of AMR surveillance studies (56, 139, 140).

MDR high-risk clones are important reservoirs of AMR genes and have played essential roles in the global emergence, spread, and subsequent increase of MDR (15). This is illustrated with the emergence of ST131 in Calgary, Canada. Studies spanning over an 11-year period (2000–2010) showed that fluoroquinolone-resistant and ESBL-producing ExPEC causing bloodstream infections were rare during the early 2000s (i.e., 6% and 0.3%, respectively) (24, 141). By 2010, the frequency of fluoroquinolone-resistant and ESBL-producing isolates increased to 26% and 14%, respectively (24, 141). This increase was mainly due to the "invasion" of *E. coli* ST131: in 2000, none of fluoroquinolone-resistant (n = 19) and none of ESBL-producing *E. coli* (n = 1) belonged to ST131 (24, 141). The frequencies of ST131 in 2010 increased to 65/119 (55%) and 49/63 (78%) among fluoroquinolone-resistant and ESBL-producing *E. coli*, respectively (24, 141). This scenario could easily happen with ST410 in the 2020s.

Overall, carbapenem resistance is currently still rare among *E. coli* populations (e.g., less than 5% of isolates) (142). *E. coli* ST410 is an emerging carbapenemase-producing global MDR clone with the potential to significantly increase carbapenem resistance among *E. coli* in the foreseeable future. Recent global surveillance studies have shown that carbapenem resistance among *E. coli* is steadily increasing over time (119, 120), and genomics have revealed that ST410 is a major contributor to these carbapenem-resistant isolates (57).

The ST410-B3 subclade dominates the population structure of this lineage and has played an important role in the global distribution of OXA-181 during the early to mid-2010s (19). The OXA-181 gene is housed within IncX3 plasmids and has provided low-level carbapenem resistance in *E. coli* (104). ST410-B3 had gradually incorporated a different carbapenemase, NDM-5 into existing IncF plasmids (Fig. 2) (107). NDM-5 (as opposed to OXA-181) is responsible for high levels of carbapenem resistance in *E. coli* (143). IncF are examples of low copy number and narrow host range plasmids (144). Due to the plasticity of IncF plasmids, they continually undergo extensive rearrangements, especially among the accessory genes such as AMR genes. The presence of addition/restriction systems combined with truncated transfer regions has led to IncF plasmid persistence and stability with subsequent fixation within certain *E. coli* lineages such as ST131 (144). IncF plasmids with bla_{NDM-5} will continue to co-evolve with ST410-B3, ensuring that high-level carbapenem resistance will become entrenched in

this subclade. The use of the carbapenems will continue to create selection pressures that enhance the risks for the selection of MDR high-risk clones, especially ST410-B3.

The ST410-B3 subclade has shown a stepwise progression toward developing MDR. After an initial *fimH* switch between clades ST410-A and B1, ST410-B2 acquired fluoroquinolone resistance (in the 1980s), as well as CMY-2, CTX-M-15, and OXA-181 genes (in the 1990s) (Fig. 2). This was followed by the chromosomal integration of bla_{CMY-2} (to offset fitness cost), *fstI* YRIN insertion (for reduced susceptibilities to ceftazidime/avibactam), and ompC/ompF mutations (for decreased permeability to β-lactams) to create MDR ST410-B3 in the mid-2000s (Fig. 2). Interestingly, an IncF plasmid "replacement" scenario happened when ST410-B2 transformed into ST410-B3 (i.e., F36:31:A4:B1 plasmid being replaced by F1:A1:B49 plasmids). Additionally, the NDM-5 gene was incorporated into these F1:A1:B49 plasmids (Fig. 2). ST131 show a similar stepwise progression toward developing MDR but not to the same extent as ST410 (Fig. 3). The pattern of gaining successive AMR determinants is also shared with certain *K. pneumoniae* MDR high-risk clones (e.g., ST147 or ST307) (145). This is an example of "MDR convergent evolution" where distantly related organisms independently evolve similar traits to adapt to similar necessities (4).

ST410 is a true One-Health MDR clone and has been obtained from humans, various animals, and the environmental sources (Table 1). This is different from ST131 that is mainly a human MDR clone and is relatively rare in animals and environment sources (138). It is possible that acquiring extensive AMR determinants including various carbapenemase genes was essential for the successful adaption and continuous survival of ST410 within various One Health environments.

There is an enormous public health burden due to *E. coli* MDR high-risk clones such as ST131 and ST410. These clones have played pivotal roles in the global spread of MDR *per se*. Yet, sparse information is available on the following ST410 aspects. (i) Very limited data are available about the frequencies and global distribution of ST410 clades (especially ST410-A and ST410-B1). This could be due in part to the selection of ST410 surveys (mainly ESBL- and carbapenemase-producing isolates) and lack of cost-effective methods for identifying ST410 isolates and clades (i.e., MLST for ST410 identification and WGS phylogenetic analysis to confirm different clades). We urgently need user-friendly cost-effective methods for the rapid identification of ST410 isolates and clades. Such methodologies have been pivotal in describing the global distribution of ST131 clades (146). (ii) It is unknown which specific biologic features have enabled ST410 to acquire various AMR determinants to become such a successful global One Health pathogen in a relatively short time.

Research projects aimed at investigating the important features responsible for the success of ST410 and ST131 need to be funded. This should include the ability of ST410-B3 to successfully acquire successive MDR determinants. Such information will aid in designing management and prevention strategies for both clones. These projects will also serve as models to predict the future emergence of successful clones among clinically relevant Gram-negative bacteria. The medical community can ill afford to ignore the spread of a global *E. coli* clone with the potential to end the carbapenem era.

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REFERENCES

1. Baker S, Thomson N, Weill FX, Holt KE. 2018. Genomic insights into the emergence and spread of antimicrobial-resistant bacterial pathogens. Science 360:733–738. https://doi.org/10.1126/science.aar3777
2. Mathers AJ, Peirano G, Pitout JDD. 2015. The role of epidemic resistance plasmids and international high-risk clones in the spread of multidrug-resistant *Enterobacteriaceae*. Clin Microbiol Rev 28:565–591. https://doi.org/10.1128/CMR.00116-14
3. Woodford N, Turton JF, Livermore DM. 2011. Multiresistant gram-negative bacteria: the role of high-risk clones in the dissemination of antibiotic resistance. FEMS Microbiol Rev 35:736–755. https://doi.org/10.1111/j.1574-6976.2011.00268.x
4. Baquero F, Martínez JL, F Lanza V, Rodríguez-Beltrán J, Galán JC, San Millán A, Cantón R, Coque TM. 2021. Evolutionary pathways and trajectories in antibiotic resistance. Clin Microbiol Rev 34:e0005019. https://doi.org/10.1128/CMR.00050-19
5. Laupland KB, Church DL. 2014. Population-based epidemiology and microbiology of community-onset bloodstream infections. Clin Microbiol Rev 27:647–664. https://doi.org/10.1128/CMR.00002-14
6. Bonten M, Johnson JR, van den Biggelaar AHJ, Georgalis L, Geurtsen J, de Palacios PI, Gravenstein S, Verstraeten T, Hermans P, Poolman JT. 2021. Epidemiology of *Escherichia coli* bacteremia: a systematic literature review . Clin Infect Dis 72:1211–1219. https://doi.org/10.1093/cid/ciaa210
7. Antimicrobial Resistance C. 2022. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. Lancet 399:629–655. https://doi.org/10.1016/S0140-6736(21)02724-0
8. Pitout JDD. 2012. Extraintestinal pathogenic *Escherichia coli*: an update on antimicrobial resistance, laboratory diagnosis and treatment. Expert Rev Anti Infect Ther 10:1165–1176. https://doi.org/10.1586/eri.12.110
9. Peirano G, Pitout JDD. 2019. Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: update on molecular epidemiology and treatment options. Drugs 79:1529–1541. https://doi.org/10.1007/s40265-019-01180-3
10. Pitout JD, Chan WW, Church DL. 2016. Tackling antimicrobial resistance in lower urinary tract infections: treatment options. Expert Rev Anti Infect Ther 14:621–632. https://doi.org/10.1080/14787210.2016.1188004
11. Tompkins K, van Duin D. 2021. Treatment for carbapenem-resistant *Enterobacterales* infections: recent advances and future directions. Eur J Clin Microbiol Infect Dis 40:2053–2068. https://doi.org/10.1007/s10096-021-04296-1
12. Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. 2011. Carbapenems: past, present, and future. Antimicrob Agents Chemother 55:4943–4960. https://doi.org/10.1128/AAC.00296-11
13. World Health Organization. 2017. Global priority list of antibiotic-resistant bacteria to guide research, discovery and development of new antibiotics. Available from: https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en
14. Manges AR, Geum HM, Guo A, Edens TJ, Fibke CD, Pitout JDD. 2019. Global extraintestinal pathogenic *Escherichia coli* (ExPEC) lineages. Clin Microbiol Rev 32:e00135-18. https://doi.org/10.1128/CMR.00135-18
15. Pitout JD, Peirano G, DeVinney R. 2023. The contributions of multidrug resistant clones to the success of pandemic extra-intestinal pathogenic *Escherichia coli*. Expert Rev Anti Infect Ther 21:343–353. https://doi.org/10.1080/14787210.2023.2184348
16. Cummins EA, Snaith AE, McNally A, Hall RJ. 2021. The role of potentiating mutations in the evolution of pandemic *Escherichia coli* clones. Eur J Clin Microbiol Infect Dis. https://doi.org/10.1007/s10096-021-04359-3
17. Patiño-Navarrete R, Rosinski-Chupin I, Cabanel N, Gauthier L, Takissian J, Madec J-Y, Hamze M, Bonnin RA, Naas T, Glaser P. 2020. Stepwise evolution and convergent recombination underlie the global dissemination of carbapenemase-producing *Escherichia coli*. Genome Med 12:10. https://doi.org/10.1186/s13073-019-0699-6
18. Feng Y, Liu L, Lin J, Ma K, Long H, Wei L, Xie Y, McNally A, Zong Z. 2019. Key evolutionary events in the emergence of a globally disseminated, carbapenem resistant clone in the *Escherichia coli* ST410 lineage. Commun Biol 2:322. https://doi.org/10.1038/s42003-019-0569-1
19. Roer L, Overballe-Petersen S, Hansen F, Schønning K, Wang M, Røder BL, Hansen DS, Justesen US, Andersen LP, Fulgsang-Damgaard D, Hopkins KL, Woodford N, Falgenhauer L, Chakraborty T, Samuelsen Ø, Sjöström K, Johannesen TB, Ng K, Nielsen J, Ethelberg S, Stegger M, Hammerum AM, Hasman H. 2018. *Escherichia coli* sequence type 410 is causing new International high-risk clones. mSphere 3:e00337-18. https://doi.org/10.1128/mSphere.00337-18
20. Sidjabat HE, Paterson DL, Adams-Haduch JM, Ewan L, Pasculle AW, Muto CA, Tian GB, Doi Y. 2009. Molecular epidemiology of CTX-M-producing *Escherichia coli* isolates at a tertiary medical center in Western Pennsylvania. Antimicrob Agents Chemother 53:4733–4739. https://doi.org/10.1128/AAC.00533-09
21. López-Cerero L, Egea P, Serrano L, Navarro D, Mora A, Blanco J, Doi Y, Paterson DL, Rodríguez-Baño J, Pascual A. 2011. Characterisation of clinical and food animal *Escherichia coli* isolates producing CTX-M-15 extended-spectrum beta-lactamase belonging to ST410 phylogroup A. Int J Antimicrob Agents 37:365–367. https://doi.org/10.1016/j.ijantimicag.2011.01.001
22. Novais Â, Viana D, Baquero F, Martínez-Botas J, Cantón R, Coque TM. 2012. Contribution of IncFII and broad-host IncA/C and IncN plasmids to the local expansion and diversification of phylogroup B2 *Escherichia coli* ST131 clones carrying blaCTX-M-15 and qnrS1 genes. Antimicrob Agents Chemother 56:2763–2766. https://doi.org/10.1128/AAC.06001-11
23. Peirano G, Asensi MD, Pitondo-Silva A, Pitout JDD. 2011. Molecular characteristics of extended-spectrum beta-lactamase-producing *Escherichia coli* from Rio de Janeiro, Brazil. Clin Microbiol Infect 17:1039–1043. https://doi.org/10.1111/j.1469-0691.2010.03440.x

24. Peirano Gisele, van der Bij AK, Gregson DB, Pitout JDD. 2012. Molecular epidemiology over an 11-year period (2000 to 2010) of extended-spectrum beta-lactamase-producing *Escherichia coli* causing bacteremia in a centralized Canadian region. J Clin Microbiol 50:294–299. https://doi.org/10.1128/JCM.06025-11
25. Schink AK, Kadlec K, Schwarz S. 2011. Analysis of bla(CTX-M)-carrying plasmids from *Escherichia coli* isolates collected in the BfT-GermVet study. Appl Environ Microbiol 77:7142–7146. https://doi.org/10.1128/AEM.00559-11
26. Coelho A, Mora A, Mamani R, López C, González-López JJ, Larrosa MN, Quintero-Zarate JN, Dahbi G, Herrera A, Blanco JE, Blanco M, Alonso MP, Prats G, Blanco J. 2011. Spread of *Escherichia coli* O25B:H4-B2-ST131 producing CTX-M-15 and SHV-12 with high virulence gene content in Barcelona (Spain). J Antimicrob Chemother 66:517–526. https://doi.org/10.1093/jac/dkq491
27. Correia S, Pacheco R, Radhouani H, Diniz JC, Ponce P, Jones-Dias D, Caniça M, Igrejas G, Poeta P. 2012. High prevalence of ESBL-producing *Escherichia coli* isolates among hemodialysis patients in Portugal: appearance of ST410 with the bla(CTX-M-14) gene. Diagn Microbiol Infect Dis 74:423–425. https://doi.org/10.1016/j.diagmicrobio.2012.08.017
28. Mushtaq S, Irfan S, Sarma JB, Doumith M, Pike R, Pitout J, Livermore DM, Woodford N. 2011. Phylogenetic diversity of *Escherichia coli* strains producing NDM-type carbapenemases. J Antimicrob Chemother 66:2002–2005. https://doi.org/10.1093/jac/dkr226
29. Mavroidi A, Miriagou V, Malli E, Stefos A, Dalekos GN, Tzouvelekis LS, Petinaki E. 2012. Emergence of *Escherichia coli* sequence type 410 (ST410) with KPC-2 beta-lactamase. Int J Antimicrob Agents 39:247–250. https://doi.org/10.1016/j.ijantimicag.2011.11.003
30. Huber H, Zweifel C, Wittenbrink MM, Stephan R. 2013. ESBL-producing uropathogenic *Escherichia coli* isolated from dogs and cats in Switzerland. Vet Microbiol 162:992–996. https://doi.org/10.1016/j.vetmic.2012.10.029
31. Dahmen S, Haenni M, Châtre P, Madec J-Y. 2013. Characterization of blaCTX-M IncFII plasmids and clones of *Escherichia coli* from pets in France. J Antimicrob Chemother 68:2797–2801. https://doi.org/10.1093/jac/dkt291
32. Usein C-R, Papagheorghe R, Oprea M, Condei M, Străuț M. 2016. Molecular characterization of bacteremic *Escherichia coli* isolates in Romania. Folia Microbiol (Praha) 61:221–226. https://doi.org/10.1007/s12223-015-0427-6
33. Guo Q, Ding B, Jové T, Stoesser N, Cooper VS, Wang M, Doi Y. 2016. Characterization of a novel IncHI2 plasmid carrying tandem copies of blaCTX-M-2 in a fosA6-harboring *Escherichia coli* sequence type 410 strain. Antimicrob Agents Chemother 60:6742–6747. https://doi.org/10.1128/AAC.01173-16
34. Roer L, Hansen F, Thomsen MCF, Knudsen JD, Hansen DS, Wang M, Samulioniené J, Justesen US, Røder BL, Schumacher H, Østergaard C, Andersen LP, Dzajic E, Søndergaard TS, Stegger M, Hammerum AM, Hasman H. 2017. WGS-based surveillance of third-generation cephalosporin-resistant *Escherichia coli* from bloodstream infections in Denmark. J Antimicrob Chemother 72:1922–1929. https://doi.org/10.1093/jac/dkx092
35. Ben Sallem R, Ben Slama K, Estepa V, Cheikhna EO, Mohamed AM, Chairat S, Ruiz-Larrea F, Boudabous A, Torres C. 2015. Detection of CTX-M-15-producing *Escherichia coli* isolates of lineages ST410-A, ST617-A and ST354-D in faecal samples of hospitalized patients in a mauritanian hospital. J Chemother 27:114–116. https://doi.org/10.1179/-1973947814Y.0000000172
36. Su Y, Yu CY, Tsai Y, Wang SH, Lee C, Chu C. 2016. Fluoroquinolone-resistant and extended-spectrum beta-lactamase-producing *Escherichia coli* from the milk of cows with clinical mastitis in Southern Taiwan. J Microbiol Immunol Infect 49:892–901. https://doi.org/10.1016/j.jmii.2014.10.003
37. Li S, Liu J, Zhou Y, Miao Z. 2017. Characterization of ESBL-producing *Escherichia coli* recovered from companion dogs in Tai'An, China. J Infect Dev Ctries 11:282–286. https://doi.org/10.3855/jidc.8138
38. Kawamura K, Sugawara T, Matsuo N, Hayashi K, Norizuki C, Tamai K, Kondo T, Arakawa Y. 2017. Spread of CTX-type extended-spectrum beta-lactamase-producing *Escherichia coli* isolates of epidemic clone B2-O25-ST131 among dogs and cats in Japan. Microb Drug Resist 23:1059–1066. https://doi.org/10.1089/mdr.2016.0246
39. Adler A, Miller-Roll T, Assous MV, Geffen Y, Paikin S, Schwartz D, Weiner-Well Y, Hussein K, Cohen R, Carmeli Y. 2015. A multicenter study of the clonal structure and resistance mechanism of KPC-producing *Escherichia coli* isolates in Israel. Clin Microbiol Infect 21:230–235. https://doi.org/10.1016/j.cmi.2014.10.008
40. Chen YT, Lin JC, Fung CP, Lu PL, Chuang YC, Wu TL, Siu LK. 2014. KPC-2-encoding plasmids from *Escherichia coli* and *Klebsiella pneumoniae* in Taiwan. J Antimicrob Chemother 69:628–631. https://doi.org/10.1093/jac/dkt409
41. Xu G, Jiang Y, An W, Wang H, Zhang X. 2015. Emergence of KPC-2-producing *Escherichia coli* isolates in an urban river in Harbin, China. World J Microbiol Biotechnol 31:1443–1450. https://doi.org/10.1007/s11274-015-1897-z
42. Peirano G, Ahmed-Bentley J, Fuller J, Rubin JE, Pitout JDD. 2014. Travel-related carbapenemase-producing gram-negative bacteria in Alberta, Canada: the first 3 years. J Clin Microbiol 52:1575–1581. https://doi.org/10.1128/JCM.00162-14
43. Fiett J, Baraniak A, Izdebski R, Sitkiewicz I, Żabicka D, Meler A, Filczak K, Hryniewicz W, Gniadkowski M. 2014. The first NDM metallo-beta-lactamase-producing *Enterobacteriaceae* isolate in Poland: evolution of IncFII-type plasmids carrying the bla(NDM-1) gene. Antimicrob Agents Chemother 58:1203–1207. https://doi.org/10.1128/AAC.01197-13
44. Qin S, Zhou M, Zhang Q, Tao H, Ye Y, Chen H, Xu L, Xu H, Wang P, Feng X. 2016. First identification of NDM-4-producing *Escherichia coli* ST410 in China. Emerg Microbes Infect 5:e118. https://doi.org/10.1038/emi.2016.117
45. Hong JS, Song W, Park HM, Oh JY, Chae JC, Han JI, Jeong SH. 2019. First detection of new Delhi metallo-beta-lactamase-5-producing *Escherichia coli* from companion animals in Korea. Microb Drug Resist 25:344–349. https://doi.org/10.1089/mdr.2018.0237
46. Overballe-Petersen S, Roer L, Ng K, Hansen F, Justesen US, Andersen LP, Stegger M, Hammerum AM, Hasman H. 2018. Complete nucleotide sequence of an *Escherichia coli* sequence type 410 strain carrying bla_{NDM-5} on an IncF multidrug resistance plasmid and $bla_{OXA-181}$ on an IncX3 plasmid. Genome Announc 6:e01542-17. https://doi.org/10.1128/genomeA.01542-17
47. Aung MS, San N, Maw WW, San T, Urushibara N, Kawaguchiya M, Sumi A, Kobayashi N. 2018. Prevalence of extended-spectrum beta-lactamase and carbapenemase genes in clinical isolates of *Escherichia coli* in Myanmar: Dominance of $bla_{(NDM-5)}$ and emergence of $bla_{(OXA-181)}$. Microb Drug Resist 24:1333–1344. https://doi.org/10.1089/mdr.2017.0387
48. Abd El Ghany M, Sharaf H, Al-Agamy MH, Shibl A, Hill-Cawthorne GA, Hong PY. 2018. Genomic characterization of NDM-1 and 5, and OXA-181 carbapenemases in uropathogenic *Escherichia coli* isolates from Riyadh. PLoS One 13:e0201613. https://doi.org/10.1371/journal.pone.0201613
49. Liu Y, Feng Y, Wu W, Xie Y, Wang X, Zhang X, Chen X, Zong Z. 2015. First report of OXA-181-producing *Escherichia coli* in China and characterization of the isolate using whole-genome sequencing. Antimicrob Agents Chemother 59:5022–5025. https://doi.org/10.1128/AAC.00442-15
50. Mataseje LF, Boyd DA, Fuller J, Haldane D, Hoang L, Lefebvre B, Melano RG, Poutanen S, Van Caeseele P, Mulvey MR. 2018. Characterization of OXA-48-like carbapenemase producers in Canada, 2011-14. J Antimicrob Chemother 73:626–633. https://doi.org/10.1093/jac/dkx462
51. Gauthier L, Dortet L, Cotellon G, Creton E, Cuzon G, Ponties V, Bonnin RA, Naas T. 2018. Diversity of carbapenemase-producing *Escherichia coli* isolates in France in 2012-2013. Antimicrob Agents Chemother 62:e00266-18. https://doi.org/10.1128/AAC.00266-18
52. Izdebski R, Bojarska K, Baraniak A, Literacka E, Herda M, Żabicka D, Guzek A, Półgrabia M, Hryniewicz W, Gniadkowski M. 2015. NDM-1- or OXA-48-producing *Enterobacteriaceae* colonising polish tourists following a terrorist attack in Tunis. Euro Surveill 20:21150. https://doi.org/10.2807/1560-7917.es2015.20.23.21150
53. Howard JC, Anderson T, Creighton J, Freeman JT. 2018. Geographical and temporal clustering of OXA-48-producing *Escherichia coli* ST410 causing community-onset urinary tract infection in Christchurch. J Antimicrob Chemother 73:2900–2901. https://doi.org/10.1093/jac/dky269

54. Kocsis B, Gulyás D, Szabó D. 2022. Emergence and dissemination of extraintestinal pathogenic high-risk International clones of *Escherichia coli*. Life (Basel) 12:2077. https://doi.org/10.3390/life12122077
55. Fischer J, Rodríguez I, Baumann B, Guiral E, Beutin L, Schroeter A, Kaesbohrer A, Pfeifer Y, Helmuth R, Guerra B. 2014. blaCTX-M-(1)(5)-carrying *Escherichia coli* and *Salmonella* isolates from livestock and food in Germany. J Antimicrob Chemother 69:2951–2958. https://doi.org/10.1093/jac/dku270
56. Pitout JDD. 2012. Extraintestinal pathogenic *Escherichia coli*: a combination of virulence with antibiotic resistance. Front Microbiol 3:9. https://doi.org/10.3389/fmicb.2012.00009
57. Peirano G, Chen L, Nobrega D, Finn TJ, Kreiswirth BN, DeVinney R, Pitout JDD. 2022. Genomic epidemiology of global carbapenemase-producing *Escherichia coli*. Emerg Infect Dis 28:924–931. https://doi.org/10.3201/eid2805.212535
58. Xiao R, Li Y, Liu X, Ding Y, Lai J, Li Y, Kang W, Zou P, Wang J, Du Y, Zhang J, Wang Y. 2023. Antibiotic susceptibility of *Escherichia coli* isolated from neonates admitted to neonatal intensive care units across China from 2015 to 2020. Front Cell Infect Microbiol 13:1183736. https://doi.org/10.3389/fcimb.2023.1183736
59. Takawira FT, Pitout JD, Thilliez G, Mashe T, Gutierrez AV, Kingsley RA, Peirano G, Matheu J, Midzi SM, Mwamakamba LW, Gally DL, Tarupiwa A, Mukavhi L, Ehlers MM, Mtapuri-Zinyowera S, Kock MM. 2021. Molecular epidemiology of extended-spectrum beta-lactamase-producing extra-intestinal pathogenic *Escherichia coli* strains over a 2-year period (2017-2019) from Zimbabwe. Eur J Clin Microbiol Infect Dis. https://doi.org/10.1007/s10096-021-04379-z
60. Huang L, Hu H, Xu C, Zhou M, Li Y, Li Y, Wu S, Dong N. 2023. Characterization of NDM-5-producing *Escherichia coli* strains isolated from pediatric patients with bloodstream infections in a Chinese hospital. Genes 14:520. https://doi.org/10.3390/genes14020520
61. Giufrè M, Errico G, Monaco M, Del Grosso M, Sabbatucci M, Pantosti A, Cerquetti M, Pagnotta M, Marra M, Carollo M, Rossini A, Fogato E, Cesana E, Gentiloni Silverj F, Zabzuni D, Tinelli M. 2022. Whole genome sequencing and molecular analysis of carbapenemase-producing *Escherichia coli* from intestinal carriage in elderly Inpatients. Microorganisms 10:1561. https://doi.org/10.3390/microorganisms10081561
62. Benlabidi S, Raddaoui A, Lengliz S, Cheriet S, Hynds P, Achour W, Ghrairi T, Abbassi MS. 2023. Occurrence of high-risk clonal lineages ST58, ST69, ST224, AND ST410 among extended-spectrum beta-lactamase-producing *Escherichia coli* isolated from healthy free-range chickens (*Gallus gallus domesticus*) in a rural region in Tunisia. Genes (Basel) 14:875. https://doi.org/10.3390/genes14040875
63. Hayer J, Salgado-Caxito M, Opazo-Capurro A, Muñoz PG, Millán J, Piñeiro A, Munita JM, Rivas L, Benavides JA. 2023. Multiple Clonal transmissions of clinically relevant extended-spectrum beta-lactamase-producing *Escherichia coli* among livestock, dogs, and wildlife in Chile. J Glob Antimicrob Resist 34:247–252. https://doi.org/10.1016/j.jgar.2023.07.009
64. Johansson V, Nykäsenoja S, Myllyniemi A-L, Rossow H, Heikinheimo A. 2022. Genomic characterization of ESBL/AmpC-producing and high-risk clonal lineages of *Escherichia coli* and *Klebsiella pneumoniae* in imported dogs with shelter and stray background. J Glob Antimicrob Resist 30:183–190. https://doi.org/10.1016/j.jgar.2022.05.021
65. Ju X, Wu Y, Chen G, Zhang R. 2023. *Escherichia coli* high-risk clone ST410 harboring $bla_{(NDM-13)}$ isolated from hospital wastewater in China. Environ Sci Pollut Res Int 30:91487–91491. https://doi.org/10.1007/s11356-023-28193-6
66. Zou H, Han J, Zhao L, Wang D, Guan Y, Wu T, Hou X, Han H, Li X. 2023. The shared NDM-positive strains in the hospital and connecting aquatic environments. Sci Total Environ 860:160404. https://doi.org/10.1016/j.scitotenv.2022.160404
67. Nobili G, La Bella G, Basanisi MG, Damato AM, Coppola R, Migliorelli R, Rondinone V, Leekitcharoenphon P, Bortolaia V, La Salandra G. 2022. Occurrence and characterisation of colistin-resistant *Escherichia coli* in raw meat in southern Italy in 2018-2020. Microorganisms 10:1805. https://doi.org/10.3390/microorganisms10091805
68. He WY, Lv LC, Pu WX, Gao GL, Zhuang ZL, Lu YY, Zhuo C, Liu JH. 2023. Characterization of an international high-risk *Escherichia coli* ST410 clone coproducing NDM-5 and OXA-181 in a food market in China. Microbiol Spectr 11:e0472722. https://doi.org/10.1128/spectrum.04727-22
69. Mavroidi A, Miriagou V, Liakopoulos A, Tzelepi E, Stefos A, Dalekos GN, Petinaki E. 2012. Ciprofloxacin-resistant *Escherichia coli* in central greece: mechanisms of resistance and molecular identification. BMC Infect Dis 12:371. https://doi.org/10.1186/1471-2334-12-371
70. Moreira da Silva RCR, de Oliveira Martins Júnior P, Gonçalves LF, de Paulo Martins V, de Melo ABF, Pitondo-Silva A, de Campos TA. 2017. Ciprofloxacin resistance in uropathogenic *Escherichia coli* isolates causing community-acquired urinary infections in Brasilia. J Glob Antimicrob Resist 9:61–67. https://doi.org/10.1016/j.jgar.2017.01.009
71. Hayer SS, Lim S, Hong S, Elnekave E, Johnson T, Rovira A, Vannucci F, Clayton JB, Perez A, Alvarez J. 2020. Genetic determinants of resistance to extended-spectrum cephalosporin and fluoroquinolone in *Escherichia coli*. mSphere 5:e00990-20. https://doi.org/10.1128/mSphere.00990-20
72. Vervoort J, Gazin M, Kazma M, Kotlovsky T, Lammens C, Carmeli Y, Goossens H, Malhotra-Kumar S, SATURN WP1 and MOSAR WP2 study groups. 2014. High rates of intestinal colonisation with fluoroquinolone-resistant ESBL-harbouring *Enterobacteriaceae* in hospitalised patients with antibiotic-associated diarrhoea. Eur J Clin Microbiol Infect Dis 33:2215–2221. https://doi.org/10.1007/s10096-014-2193-9
73. Falgenhauer L, Imirzalioglu C, Ghosh H, Gwozdzinski K, Schmiedel J, Gentil K, Bauerfeind R, Kämpfer P, Seifert H, Michael GB, Schwarz S, Pfeifer Y, Werner G, Pietsch M, Roesler U, Guerra B, Fischer J, Sharp H, Käsbohrer A, Goesmann A, Hille K, Kreienbrock L, Chakraborty T. 2016. Circulation of clonal populations of fluoroquinolone-resistant CTX-M-15-producing *Escherichia coli* ST410 in humans and animals in Germany. Int J Antimicrob Agents 47:457–465. https://doi.org/10.1016/j.ijantimicag.2016.03.019
74. Timofte D, Maciuca IE, Williams NJ, Wattret A, Schmidt V. 2016. Veterinary hospital dissemination of CTX-M-15 extended-spectrum beta-lactamase-producing *Escherichia coli* ST410 in the United Kingdom. Microb Drug Resist 22:609–615. https://doi.org/10.1089/mdr.2016.0036
75. Bubpamala J, Khuntayaporn P, Thirapanmethee K, Montakantikul P, Santanirand P, Chomnawang MT. 2018. Phenotypic and genotypic characterizations of extended-spectrum beta-lactamase-producing *Escherichia coli* in Thailand. Infect Drug Resist 11:2151–2157. https://doi.org/10.2147/IDR.S174506
76. Zogg AL, Zurfluh K, Schmitt S, Nüesch-Inderbinen M, Stephan R. 2018. Antimicrobial resistance, multilocus sequence types and virulence profiles of ESBL producing and non-ESBL producing uropathogenic *Escherichia coli* isolated from cats and dogs in Switzerland. Vet Microbiol 216:79–84. https://doi.org/10.1016/j.vetmic.2018.02.011
77. Neamati F, Khorshidi A, Moniri R, Hosseini Tafreshi SA. 2020. Molecular epidemiology of antimicrobial resistance of uropathogenic *Escherichia coli* isolates from patients with urinary tract infections in a tertiary teaching hospital in Iran. Microb Drug Resist 26:60–70. https://doi.org/10.1089/mdr.2019.0184
78. Choonara FE, Haldorsen BC, Janice J, Mbanga J, Ndhlovu I, Saulosi O, Maida T, Lampiao F, Simonsen GS, Essack SY, Sundsfjord A. 2022. Molecular epidemiological characterisation of ESBL- and plasmid-mediated AmpC-producing *Escherichia coli* and *Klebsiella pneumoniae* at Kamuzu central hospital. Trop Med Infect Dis 7:245. https://doi.org/10.3390/tropicalmed7090245
79. Negeri AA, Mamo H, Gurung JM, Firoj Mahmud AKM, Fällman M, Seyoum ET, Feleke Desta A, Francis MS. 2021. Antimicrobial resistance profiling and molecular epidemiological analysis of extended spectrum beta-lactamases produced by extraintestinal invasive *Escherichia coli* isolates from ethiopia: the presence of international high-risk clones ST131 and ST410 revealed. Front Microbiol 12:706846. https://doi.org/10.3389/fmicb.2021.706846
80. Giufrè M, Mazzolini E, Cerquetti M, Brusaferro S, CCM2015 One-Health ESBL-producing Escherichia coli Study Group. 2021. "Extended-spectrum beta-lactamase-producing *Escherichia coli* from extraintestinal infections in humans and from food-producing animals in Italy: a 'one health' study". Int J Antimicrob Agents 58:106433. https://doi.org/10.1016/j.ijantimicag.2021.106433
81. Mazumder R, Hussain A, Abdullah A, Islam MN, Sadique MT, Muniruzzaman SM, Tabassum A, Halim F, Akter N, Ahmed D, Mondal D. 2021.

International high-risk clones among extended-spectrum beta-lactamase-producing *Escherichia coli* in Dhaka, Bangladesh. Front Microbiol 12:736464. https://doi.org/10.3389/fmicb.2021.736464
82. Santona A, Sumbana JJ, Fiamma M, Deligios M, Taviani E, Simbine SE, Zimba T, Sacarlal J, Rubino S, Paglietti B. 2022. High-risk lineages among extended-spectrum beta-lactamase-producing *Escherichia coli* from extraintestinal infections in Maputo central hospital, Mozambique. Int J Antimicrob Agents 60:106649. https://doi.org/10.1016/j.ijantimicag.2022.106649
83. Piccirilli A, Cherubini S, Brisdelli F, Fazii P, Stanziale A, Di Valerio S, Chiavaroli V, Principe L, Perilli M. 2022. Molecular characterization by whole-genome sequencing of clinical and environmental *Serratia marcescens* strains isolated during an outbreak in a neonatal intensive care unit (NICU). Diagnostics (Basel) 12:2180. https://doi.org/10.3390/diagnostics12092180
84. Mahazu S, Sato W, Ayibieke A, Prah I, Hayashi T, Suzuki T, Iwanaga S, Ablordey A, Saito R. 2022. Insights and genetic features of extended-spectrum beta-lactamase producing *Escherichia coli* isolates from two hospitals in Ghana. Sci Rep 12:1843. https://doi.org/10.1038/s41598-022-05869-6
85. Medugu N, Aworh MK, Iregbu K, Nwajiobi-Princewill P, Abdulraheem K, Hull DM, Harden L, Singh P, Obaro S, Egwuenu A, Thakur S. 2022. Molecular characterization of multi drug resistant *Escherichia coli* isolates at a tertiary hospital in Abuja, Nigeria. Sci Rep 12:14822. https://doi.org/10.1038/s41598-022-19289-z
86. Lewis JM, Mphasa M, Banda R, Beale MA, Mallewa J, Anscome C, Zuza A, Roberts AP, Heinz E, Thomson NR, Feasey NA. 2023. Genomic analysis of extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* colonising adults in Blantyre, Malawi reveals previously undescribed diversity. Microb Genom 9:mgen001035. https://doi.org/10.1099/mgen.0.001035
87. Luo Y, Luo R, Ding H, Ren X, Luo H, Zhang Y, Ye L, Cui S. 2018. Characterization of carbapenem-resistant *Escherichia coli* isolates through the whole-genome sequencing analysis. Microb Drug Resist 24:175–180. https://doi.org/10.1089/mdr.2017.0079
88. Izdebski R, Baraniak A, Zabicka D, Machulska M, Urbanowicz P, Fiett J, Literacka E, Bojarska K, Kozinska A, Zieniuk B, Hryniewicz W, Gniadkowski M, Group O-PS. 2018. *Enterobacteriaceae* producing OXA-48-like carbapenemases in Poland. J Antimicrob Chemother 73:620–625. https://doi.org/10.1093/jac/dkx457
89. Dagher C, Salloum T, Alousi S, Arabaghian H, Araj GF, Tokajian S. 2018. Molecular characterization of carbapenem resistant *Escherichia coli* recovered from a tertiary hospital in Lebanon. PLoS One 13:e0203323. https://doi.org/10.1371/journal.pone.0203323
90. Bi R, Kong Z, Qian H, Jiang F, Kang H, Gu B, Ma P. 2018. High prevalence of *bla* (NDM) variants among carbapenem-resistant *Escherichia coli* in northern Jiangsu province, China. Front. Microbiol 9:2704. https://doi.org/10.3389/fmicb.2018.02704
91. Al-Farsi HM, Camporeale A, Ininbergs K, Al-Azri S, Al-Muharrmi Z, Al-Jardani A, Giske CG. 2020. Clinical and molecular characteristics of carbapenem non-susceptible *Escherichia coli*: a nationwide survey from Oman. PLoS One 15:e0239924. https://doi.org/10.1371/journal.pone.0239924
92. Alsharapy SA, Gharout-Sait A, Muggeo A, Guillard T, Cholley P, Brasme L, Bertrand X, Moghram GS, Touati A, De Champs C. 2020. Characterization of carbapenem-resistant *Enterobacteriaceae* clinical isolates in al thawra university hospital. Microb Drug Resist 26:211–217. https://doi.org/10.1089/mdr.2018.0443
93. Devanga Ragupathi NK, Veeraraghavan B, Muthuirulandi Sethuvel DP, Anandan S, Vasudevan K, Neeravi AR, Daniel JLK, Sathyendra S, Iyadurai R, Mutreja A. 2020. First Indian report on genome-wide comparison of multidrug-resistant *Escherichia coli* from blood stream infections. PLoS One 15:e0220428. https://doi.org/10.1371/journal.pone.0220428
94. Park Y, Choi Q, Kwon GC, Koo SH. 2020. Emergence and transmission of new Delhi metallo-beta-lactamase-5-producing *Escherichia coli* sequence type 361 in a tertiary hospital in South Korea. J Clin Lab Anal 34:e23041. https://doi.org/10.1002/jcla.23041
95. Nigg A, Brilhante M, Dazio V, Clément M, Collaud A, Gobeli Brawand S, Willi B, Endimiani A, Schuller S, Perreten V. 2019. Shedding of OXA-181 carbapenemase-producing *Escherichia coli* from companion animals after hospitalisation in Switzerland: an outbreak in 2018. Euro Surveill 24:1900071. https://doi.org/10.2807/1560-7917.ES.2019.24.39.1900071
96. Huang YS, Tsai WC, Li JJ, Chen PY, Wang JT, Chen YT, Chen FJ, Lauderdale TL, Chang SC. 2021. Increasing New Delhi metallo-beta-lactamase-positive *Escherichia coli* among carbapenem non-susceptible *Enterobacteriaceae* in Taiwan during 2016 to 2018. Sci Rep 11:2609. https://doi.org/10.1038/s41598-021-82166-8
97. Abid FB, Tsui CKM, Doi Y, Deshmukh A, McElheny CL, Bachman WC, Fowler EL, Albishawi A, Mushtaq K, Ibrahim EB, Doiphode SH, Hamed MM, Almaslmani MA, Alkhal A, Butt AA, Omrani AS. 2021. Molecular characterization of clinical carbapenem-resistant *Enterobacterales* from Qatar. Eur J Clin Microbiol Infect Dis 40:1779–1785. https://doi.org/10.1007/s10096-021-04185-7
98. Li F, Ye K, Li X, Ye L, Guo L, Wang L, Yang J. 2021. Genetic characterization of carbapenem-resistant *Escherichia coli* from China, 2015-2017. BMC Microbiol 21:248. https://doi.org/10.1186/s12866-021-02307-x
99. Kim JS, Yu JK, Jeon SJ, Park SH, Han S, Park SH, Kang M, Jang JI, Park J, Shin EK, Kim J, Hong CK, Lee JH, Hwang YO, Oh YH. 2021. Dissemination of an international high-risk clone of *Escherichia coli* ST410 co-producing NDM-5 and OXA-181 carbapenemases in seoul, Republic of Korea. Int J Antimicrob Agents 58:106448. https://doi.org/10.1016/j.ijantimicag.2021.106448
100. Peng C, Feng DH, Zhan Y, Wang Q, Chen DQ, Xu Z, Yang L. 2022. Molecular epidemiology, microbial virulence, and resistance of carbapenem-resistant *Enterobacterales* isolates in a teaching hospital in Guangzhou, China. Microb Drug Resist 28:698–709. https://doi.org/10.1089/mdr.2021.0156
101. Abe R, Akeda Y, Sakamoto N, Takeuchi D, Sugawara Y, Yamamoto N, Kerdsin A, Matsumoto Y, Motooka D, Laolerd W, Santanirand P, Suzuki M, Shibayama K, Tomono K, Iida T, Hamada S. 2022. A nationwide plasmidome surveillance in Thailand reveals a limited variety of new Delhi metallo-beta-lactamase-producing carbapenem-resistant *Enterobacteriaceae* clones and spreading plasmids. J Clin Microbiol 60:e0108022. https://doi.org/10.1128/jcm.01080-22
102. Hans JB, Pfennigwerth N, Neumann B, Pfeifer Y, Fischer MA, Eisfeld J, Schauer J, Haller S, Eckmanns T, Gatermann S, Werner G. 2023. Molecular surveillance reveals the emergence and dissemination of NDM-5-producing *Escherichia coli* high-risk clones in Germany. Euro Surveill 28:2200509. https://doi.org/10.2807/1560-7917.ES.2023.28.10.2200509
103. Linkevicius M, Bonnin RA, Alm E, Svartström O, Apfalter P, Hartl R, Hasman H, Roer L, Räisänen K, Dortet L, et al. 2023. Rapid cross-border emergence of NDM-5-producing *Escherichia coli* in the European union/European economic area, 2012 to June 2022. Euro Surveill 28:2300209. https://doi.org/10.2807/1560-7917.ES.2023.28.19.2300209
104. Pitout JDD, Peirano G, Kock MM, Strydom KA, Matsumura Y. 2019. The global ascendency of OXA-48-type carbapenemases. Clin Microbiol Rev 33:e00102-19. https://doi.org/10.1128/CMR.00102-19
105. Holland MS, Nobrega D, Peirano G, Naugler C, Church DL, Pitout JDD. 2020. Molecular epidemiology of *Escherichia coli* causing bloodstream infections in a centralized Canadian region: a population-based surveillance study. Clin Microbiol Infect 26:1554. https://doi.org/10.1016/j.cmi.2020.02.019
106. Gu S, Lai J, Kang W, Li Y, Zhu X, Ji T, Feng J, Zhao L, Li Z, Dong L, Hou G, Zhu Y, Li Z, He C, Geng H, Pang D, Wang Y. 2022. Drug resistance characteristics and molecular typing of *Escherichia coli* isolates from neonates in class A tertiary hospitals: a multicentre study across China. J Infect 85:499–506. https://doi.org/10.1016/j.jinf.2022.09.014
107. Chen L, Peirano G, Kreiswirth BN, Devinney R, Pitout JDD. 2022. Acquisition of genomic elements were pivotal for the success of *Escherichia coli* ST410 . J Antimicrob Chemother 77:3399–3407. https://doi.org/10.1093/jac/dkac329
108. Fuzi M, Rodriguez Baño J, Toth A. 2020. Global evolution of pathogenic bacteria with extensive use of fluoroquinolone agents. Front Microbiol 11:271. https://doi.org/10.3389/fmicb.2020.00271
109. Huseby DL, Pietsch F, Brandis G, Garoff L, Tegehall A, Hughes D. 2017. Mutation supply and relative fitness shape the genotypes of ciprofloxacin-resistant *Escherichia coli*. Mol Biol Evol 34:1029–1039. https://doi.org/10.1093/molbev/msx052
110. Tchesnokova V, Radey M, Chattopadhyay S, Larson L, Weaver JL, Kisiela D, Sokurenko EV. 2019. Pandemic fluoroquinolone resistant *Escherichia coli* clone ST1193 emerged via simultaneous homologous recombinations in 11 gene loci. Proc Natl Acad Sci U S A 116:14740–14748. https://doi.org/10.1073/pnas.1903002116

111. Pitout J.D.D, Peirano G, Chen L, DeVinney R, Matsumura Y. 2022. *Escherichia coli* ST1193: following in the footsteps of *E. coli* ST131. Antimicrob Agents Chemother 66:e0051122. https://doi.org/10.1128/aac.00511-22
112. Pitout JDD. 2010. Infections with extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: changing epidemiology and drug treatment choices. Drugs 70:313–333. https://doi.org/10.2165/11533040-000000000-00000
113. Bevan ER, Jones AM, Hawkey PM. 2017. Global epidemiology of CTX-M beta-lactamases: temporal and geographical shifts in genotype. J Antimicrob Chemother 72:2145–2155. https://doi.org/10.1093/jac/dkx146
114. Matsumura Y, Pitout JDD, Gomi R, Matsuda T, Noguchi T, Yamamoto M, Peirano G, DeVinney R, Bradford PA, Motyl MR, Tanaka M, Nagao M, Takakura S, Ichiyama S. 2016. Global *Escherichia coli* sequence type 131 clade with *bla*CTX-M-27 gene. Emerg Infect Dis 22:1900–1907. https://doi.org/10.3201/eid2211.160519
115. Pitout JDD. 2013. *Enterobacteriaceae* that produce extended-spectrum beta-lactamases and AmpC beta-lactamases in the community: the tip of the iceberg? Curr Pharm Des 19:257–263. https://doi.org/https://10.2174/1381612811306020257
116. Pitout JDD. 2008. Multiresistant *Enterobacteriaceae*: new threat of an old problem. Expert Rev Anti Infect Ther 6:657–669. https://doi.org/10.1586/14787210.6.5.657
117. Pietsch M, Irrgang A, Roschanski N, Brenner Michael G, Hamprecht A, Rieber H, Käsbohrer A, Schwarz S, Rösler U, Kreienbrock L, Pfeifer Y, Fuchs S, Werner G, RESET Study Group. 2018. Whole genome analyses of CMY-2-producing *Escherichia coli* isolates from humans, animals and food in Germany. BMC Genomics 19:601. https://doi.org/10.1186/s12864-018-4976-3
118. Pitout JDD, Nordmann P, Poirel L. 2015. Carbapenemase-producing *Klebsiella pneumoniae*, a key pathogen set for global nosocomial dominance. Antimicrob Agents Chemother 59:5873–5884. https://doi.org/10.1128/AAC.01019-15
119. Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. 2020. *In vitro* activity of imipenem/relebactam against *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolated from intraabdominal and urinary tract infection samples: SMART surveillance United States 2015-2017. J Glob Antimicrob Resist 21:223–228. https://doi.org/10.1016/j.jgar.2019.10.028
120. Kazmierczak KM, Karlowsky JA, de Jonge BLM, Stone GG, Sahm DF. 2021. Epidemiology of carbapenem resistance determinants identified in meropenem-nonsusceptible *Enterobacterales* collected as part of a global surveillance program, 2012 to 2017. Antimicrob Agents Chemother 65:e0200020. https://doi.org/10.1128/AAC.02000-20
121. Lowe M, Kock MM, Coetzee J, Hoosien E, Peirano G, Strydom KA, Ehlers MM, Mbelle NM, Shashkina E, Haslam DB, Dhawan P, Donnelly RJ, Chen L, Kreiswirth BN, Pitout JDD. 2019. *Klebsiella pneumoniae* ST307 with $bla_{OXA-181}$, South Africa, 2014-2016. Emerg Infect Dis 25:739–747. https://doi.org/10.3201/eid2504.181482
122. Strydom KA, Chen L, Kock MM, Stoltz AC, Peirano G, Nobrega DB, Lowe M, Ehlers MM, Mbelle NM, Kreiswirth BN, Pitout JDD. 2020. *Klebsiella pneumoniae* ST307 with OXA-181: threat of a high-risk clone and promiscuous plasmid in a resource-constrained healthcare setting. J Antimicrob Chemother 75:896–902. https://doi.org/10.1093/jac/dkz550
123. Alm RA, Johnstone MR, Lahiri SD. 2015. Characterization of *Escherichia coli* NDM isolates with decreased susceptibility to aztreonam/avibactam: role of a novel insertion in PBP3 . J Antimicrob Chemother 70:1420–1428. https://doi.org/10.1093/jac/dku568
124. Sato T, Ito A, Ishioka Y, Matsumoto S, Rokushima M, Kazmierczak KM, Hackel M, Sahm DF, Yamano Y. 2020. *Escherichia coli* strains possessing a four amino acid YRIN insertion in PBP3 identified as part of the SIDERO-WT-2014 surveillance study. JAC Antimicrob Resist 2:dlaa081. https://doi.org/10.1093/jacamr/dlaa081
125. Hooper DC, Wolfson JS. 1985. The fluoroquinolones: pharmacology, clinical uses, and toxicities in humans. Antimicrob Agents Chemother 28:716–721. https://doi.org/10.1128/AAC.28.5.716
126. Coque TM, Novais A, Carattoli A, Poirel L, Pitout J, Peixe L, Baquero F, Cantón R, Nordmann P. 2008. Dissemination of clonally related *Escherichia coli* strains expressing extended-spectrum beta-lactamase CTX-M-15. Emerg Infect Dis 14:195–200. https://doi.org/10.3201/eid1402.070350
127. Nicolas-Chanoine M-H, Blanco J, Leflon-Guibout V, Demarty R, Alonso MP, Caniça MM, Park Y-J, Lavigne J-P, 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
128. Peirano G, Pitout JDD. 2010. Molecular epidemiology of *Escherichia coli* producing CTX-M beta-lactamases: the worldwide emergence of clone ST131 O25:H4. Int J Antimicrob Agents 35:316–321. https://doi.org/10.1016/j.ijantimicag.2009.11.003
129. Petty NK, Ben Zakour NL, Stanton-Cook M, Skippington E, Totsika M, Forde BM, Phan M-D, Gomes Moriel D, Peters KM, Davies M, Rogers BA, Dougan G, Rodriguez-Baño J, Pascual A, Pitout JDD, 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
130. Ben Zakour NL, Alsheikh-Hussain AS, Ashcroft MM, Khanh Nhu NT, Roberts LW, Stanton-Cook M, Schembri MA, Beatson SA. 2016. Sequential acquisition of virulence and fluoroquinolone resistance has shaped the evolution of *Escherichia coli* ST131. mBio 7:e00958-16. https://doi.org/10.1128/mBio.00958-16
131. Pitout JDD, Finn TJ. 2020. The evolutionary puzzle of *Escherichia coli* ST131. Infect Genet Evol 81:104265. https://doi.org/10.1016/j.meegid.2020.104265
132. Decano AG, Downing T. 2019. An *Escherichia coli* ST131 pangenome atlas reveals population structure and evolution across 4,071 isolates. Sci Rep 9:17394. https://doi.org/10.1038/s41598-019-54004-5
133. Peirano G, van der Bij AK, Freeman JL, Poirel L, Nordmann P, Costello M, Tchesnokova VL, Pitout JDD. 2014. Characteristics of *Escherichia coli* sequence type 131 isolates that produce extended-spectrum beta-lactamases: global distribution of the H30-Rx sublineage. Antimicrob Agents Chemother 58:3762–3767. https://doi.org/10.1128/AAC.02428-14
134. Peirano G, Lynch T, Matsumara Y, Nobrega D, Finn TJ, DeVinney R, Pitout JDD. 2020. Trends in population dynamics of *Escherichia coli* sequence type 131, Calgary, Alberta, Canada, 2006-2016[1]. Emerg Infect Dis 26:2907–2915. https://doi.org/10.3201/eid2612.201221
135. Phan MD, Peters KM, Alvarez Fraga L, Wallis SC, Hancock SJ, Nhu NTK, Forde BM, Bauer MJ, Paterson DL, Beatson SA, Lipman J, Schembri MA. 2022. Plasmid-mediated ciprofloxacin resistance imparts a selective advantage on *Escherichia coli* ST131. Antimicrob Agents Chemother 66:e0214621. https://doi.org/10.1128/AAC.02146-21
136. Mathers AJ, Peirano G, Pitout JDD. 2015. *Escherichia coli* ST131: the quintessential example of an international multiresistant high-risk clone. Adv Appl Microbiol 90:109–154. https://doi.org/10.1016/bs.aambs.2014.09.002
137. Johnson TJ, Danzeisen JL, Youmans B, Case K, Llop K, Munoz-Aguayo J, Flores-Figueroa C, Aziz M, Stoesser N, Sokurenko E, Price LB, Johnson JR, Castanheira M. 2016. Separate F-type plasmids have shaped the evolution of the H30 subclone of *Escherichia coli* sequence type 131. mSphere 1:e00121-16. https://doi.org/10.1128/mSphere.00121-16
138. Pitout JDD, DeVinney R. 2017. *Escherichia coli* ST131: a multidrug-resistant clone primed for global domination. F1000Res 6:F1000 Faculty Rev-195. https://doi.org/10.12688/f1000research.10609.1
139. Pitout JDD, Laupland KB. 2008. Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: an emerging public-health concern. Lancet Infect Dis 8:159–166. https://doi.org/10.1016/S1473-3099(08)70041-0
140. Pitout JDD, Nordmann P, Laupland KB, Poirel L. 2005. Emergence of *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBLs) in the community. J Antimicrob Chemother 56:52–59. https://doi.org/10.1093/jac/dki166
141. Peirano G, Pitout JDD. 2014. Fluoroquinolone-resistant *Escherichia coli* sequence type 131 isolates causing bloodstream infections in a Canadian region with a centralized laboratory system: rapid emergence of the H30-Rx sublineage. Antimicrob Agents Chemother 58:2699–2703. https://doi.org/10.1128/AAC.00119-14
142. Poirel L, Madec JY, Lupo A, Schink AK, Kieffer N, Nordmann P, Schwarz S. 2018. Antimicrobial resistance in *Escherichia coli*. Microbiol Spectr 6. https://doi.org/10.1128/microbiolspec.ARBA-0026-2017
143. Hornsey M, Phee L, Wareham DW. 2011. A novel variant, NDM-5, of the new Delhi metallo-beta-lactamase in a multidrug-resistant *Escherichia coli* ST648 isolate recovered from a patient in the United Kingdom. Antimicrob Agents Chemother 55:5952–5954. https://doi.org/10.1128/AAC.05108-11
144. Pitout JDD, Chen L. 2023. The significance of epidemic plasmids in the success of multidrug-resistant drug pandemic extraintestinal

pathogenic *Escherichia coli*. Infect Dis Ther 12:1029–1041. https://doi.org/10.1007/s40121-023-00791-4
145. Peirano G, Chen L, Kreiswirth BN, Pitout JDD. 2020. Emerging antimicrobial-resistant high-risk *Klebsiella pneumoniae* clones ST307 and ST147. Antimicrob Agents Chemother 64:e01148-20. https://doi.org/10.1128/AAC.01148-20
146. Matsumura Y, Pitout JDD, Peirano G, DeVinney R, Noguchi T, Yamamoto M, Gomi R, Matsuda T, Nakano S, Nagao M, Tanaka M, Ichiyama S. 2017. Rapid identification of different *Escherichia coli* sequence type 131 clades. Antimicrob Agents Chemother 61:e00179-17. https://doi.org/10.1128/AAC.00179-17