



# Population Dynamics of *Escherichia coli* Causing Bloodstream Infections over Extended Time Periods

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**ABSTRACT** *Escherichia coli* is a leading cause of community-acquired and health care-associated bloodstream infections (BSIs) worldwide. Limited information is available regarding the changes in population dynamics of human *E. coli* over extended time periods, especially among nonbiased *E. coli* isolates in large well-defined geographical regions. Coque and colleagues (I. Rodríguez, A. S. Figueiredo, M. Sousa, S. Aracil-Gisbert, et al., *mSphere* 6: e00868-21, 2021, <https://doi.org/10.1128/msphere.00868-21>) conducted a longitudinal study of *E. coli* BSIs in a Madrid hospital over a 21-year period (1996 to 2016). Certain *E. coli* B2 phylogroups (i.e., ST131 and ST73) dominated the community *E. coli* population in Madrid. These community clones were often introduced into the hospital setting. This study and other longitudinal surveys from England and Canada showed that ST131 subclades C1 and C2 were mainly responsible for the increase in fluoroquinolone and cephalosporin resistance among *E. coli* during the mid- to late 2000s.

**KEYWORDS** *Escherichia coli*, ST131, bloodstream infections

*Escherichia coli* is the most common cause of community-acquired and health care-associated bloodstream infections (BSIs) worldwide and is responsible for substantial health care costs and patient morbidity and mortality (1). *E. coli* BSIs are associated with increased in-hospital deaths, and resistance to front-line antibiotics prolonged the length of hospital stay (2).

In the 1990s, *E. coli* was susceptible to most antibiotic classes (3). During the 2000s, multidrug resistance (MDR) increased exponentially, especially to fluoroquinolones and third-generation cephalosporins (4). These drugs are often used to treat serious *E. coli* infections (5). This led to overuse of certain antibiotics such as carbapenems and increased carbapenem resistance. Losing the use of the carbapenems will be devastating for medical practice. They are the most effective last-line treatment options for MDR *E. coli* serious infections (6).

The population structure of human *E. coli* is dominated by the following sequence types (STs) (7): ST131, ST69, ST10, ST405, ST38, ST95, ST648, ST73, ST410, ST393, ST354, ST12, ST127, ST167, ST58, ST617, ST88, ST23, ST117, and ST1193. The prevalence of these STs depends on geographic location, inclusion criteria, sources, and time periods of studies (7).

ST131 is the most widespread clone among human *E. coli* isolates. It causes millions of human infections and deaths annually (8). ST131 belongs to three clades: susceptible A, B, and fluoroquinolone-/cephalosporin-resistant C. ST131-B acquired fluoroquinolone resistance to become ST131-C (9). ST131-C then split into subclades (C0, C1, C1\_M27, and C2) which became cephalosporin resistant by acquiring different CTX-M plasmids (*bla*<sub>CTX-M-14</sub> with C1, *bla*<sub>CTX-M-27</sub> with C1\_M27, and *bla*<sub>CTX-M-15</sub> with C2).

Limited information is available regarding the changes in population structure of human *E. coli* isolates over extended time periods, especially among nonbiased *E. coli*

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isolates in large well-defined geographical regions. Such information will aid with designing superior treatment and prevention strategies for *E. coli* BSIs.

To address this issue, Coque and colleagues conducted a longitudinal study of *E. coli* BSIs in a Madrid hospital over a 21-year period (1996 to 2016) (10). They used multiplex PCR and pulsed-field gel electrophoresis (PFGE) to classify 649 (representing 10% of the total population) *E. coli* isolates into major phylogroups (A, B1, B2 subgroups, C, D, E, and F). Isolates ( $n = 45$ ) representing highly related pulsotypes also underwent short-read whole-genome sequencing (WGS).

The *E. coli* BSI incidence increased from 5.5 (1996) to 10.8 (2016) BSI episodes/1,000 hospital admissions. *E. coli* phylogroup B2 was common and mainly obtained from community patients. Other *E. coli* phylogroups (D, B1, A, C, F, and E) were rare.

STc131 (phylogroup B2-I) was the most common and MDR clone in the Madrid study (i.e., 12.3% of the *E. coli* population). This ST often caused infections in the elderly (>80 years). The fluoroquinolone-resistant ST131 C subclades (C1 and C2) were dominant (71%), while ST131-A (9%) and ST131-B (20%) were rare. ST131-B was present among *E. coli* isolates causing BSIs during 1996. ST131-C0 was first detected in 2000, while ST131-C1 and ST131-A appeared during 2004. This was followed by ST131-C2 (with *bla*<sub>CTX-M-15</sub>) in 2006 and ST131-C1\_M27 (with *bla*<sub>CTX-M-27</sub>) in 2016. These interesting longitudinal data support the current understanding of ST131 evolution and expansion (11). Subclades ST131-C1 and -C2 were mainly responsible for the increase in fluoroquinolone and cephalosporin resistance during the mid- to late 2000s. The authors also identified the following dominant phylogroup B2 clones: STc73 (B2-II), STc127 (B2-III), STc-95 (B2-IX), and STc12 (B2-VI). The incidences of these other epidemic phylogenetic B2 groups varied throughout the study period. As with STc131, they persisted in the Madrid *E. coli* population for long time periods (up to 17 years).

Coque and colleagues showed that the increased incidence of hospital *E. coli* BSIs was tied to community epidemics (10). Their data indicated that certain *E. coli* B2 phylogroups (i.e., STc131 and STc73) dominated the Madrid community *E. coli* population and that these clones are often introduced into the hospital setting. Community “outbreaks” often predated the hospital dissemination. Such clones were seldom the cause of large hospital-acquired outbreaks.

Comparable *E. coli* BSI longitudinal studies were undertaken in England and Calgary, Canada. The England study undertook an 11-year (2001 to 2011) longitudinal hospital-based survey (12). They included 1,509 blood *E. coli* isolates obtained from 11 hospitals across England. Overall, the most common STs were ST73 (17%), ST131 (14%), ST95 (11%), and ST69 (6%). ST131 was first detected in 2003. The ST131 population was also dominated by MDR C subclades. The prevalence of ST131 clades remained stable from 2006 to 2011. Therefore, the expansion of ST131 was not driven by sequential introduction of increasingly resistant subclades (12). The proportion of other common STs (i.e., ST73, ST95, and ST69) remained unchanged over the study period.

The Calgary population-based surveillance is different from those in Madrid and England in that surveys (1999 to 2016) included all community and hospital *E. coli* isolates causing BSIs in a region of 1.4 million people (13). The most common STs were ST131 (21% of 686 isolates), ST73 (14%), ST69 (8%), ST95 (7%), and ST1193 (5%). ST131 infected mostly the elderly in long-term-care centers (14) (especially ST131-C1 with *bla*<sub>CTX-M-14</sub> and ST131-C1\_M27 with *bla*<sub>CTX-M-27</sub>). ST131 was relatively rare among *E. coli* BSIs during the early 2000s but increased significantly toward the latter part of the 2000s (15, 16). The overall prevalence of ST131 among total *E. coli* isolates from blood increased from 53/481 (11%) in 2006 to 150/621 (24.2%) in 2012 and 141/684 (20.6%) in 2016 (17). ST131-C2 was first detected in 1999, and ST131-C1 in 2001 and ST131-C1\_M27 in 2006 (16). As with the Madrid study, MDR C clades dominated the ST131 population. However, the proportion of the ST131 clades changed over time, which is different from the England and Madrid studies. ST131-C1 and ST131-B were common in 2006, while ST131-C2 with *bla*<sub>CTX-M-15</sub>, C1-M27 with *bla*<sub>CTX-M-27</sub>, and ST131-A

significantly increased from 2012 onward. ST131-C2 was the most MDR subclade in Calgary and increased exponentially over time (17).

ST1193 is an emerging global fluoroquinolone-resistant clone, especially in the United States (18, 19). In Calgary, ST1193 is increasingly significant among *E. coli* BSIs (2016 to 2018), especially among long-term-care residents (20). The rapid emergence of ST1193 is concerning and is adding to the public health burden of global MDR *E. coli* BSIs.

The Madrid study provided fascinating information regarding longitudinal population dynamics of *E. coli* STs (especially ST131) causing BSIs. Eliminating ST131 (especially the MDR C subclades) would substantially decrease the overall global incidence rate and MDR burden within *E. coli* isolates causing hospital BSIs. This will lead to considerable worldwide public health benefits.

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