Population-based epidemiology of Escherichia coli ST1193 causing blood stream infections in a centralized Canadian region

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Abstract

Escherichia coli ST1193 is an emerging global clone associated with fluoroquinolone resistance. A population-based study described genomics, clinical factors, susceptibility patterns, and incidence rates of ST1193 (n = 69) causing incident blood stream infections in a centralized Canadian region 2016-18. ST1193 was responsible for community-acquired upper urinary tract infections among the elderly. The incidence rate (IR) per 100,000 person-years among Calgary residents increased from 1.0 (95%confidence interval [95%CI] 0.7-1.5) in 2016, to 1.7 (95%CI 1.3-2.3) in 2018 (p = 0.05). This was mainly due to the significant increase of ST1193 blood stream infections among female long-term care (LTC) residents. ST1193 IR with $bla_{CTX\text{-}Ms}$ was 3.18 times higher in 2018 than in 2016 (CI 95% 0.98-13.49). We identified a ST1193 isolate with only a parC S80I mutation that is different from previously published data. The population-based study identified a significant increase over a 2-year period of E. coli ST1193 blood stream infections among elderly females residing in LTC centers. There was also a notable increase of ST1193 with $bla_{CTX\text{-}Ms}$ in 2018. The rapid emergence of ST1193 is concerning and adding to the public health burden of multidrug resistant E. coli blood stream infections in Calgary.

Keywords: Blood stream infections; Escherichia coli ST1193; Population-based surveillance.

Introduction

Extra-intestinal pathogenic *E. coli* is a leading cause of community-acquired and healthcare-associated blood stream infections worldwide and responsible for substantial patient morbidity and mortality [1]. *E. coli* blood stream infections are associated with increased mortality and antimicrobial resistance (AMR) leads to prolonged length of hospital stay [2].

There is substantial published data regarding the global prevalence and trends of different extra-intestinal pathogenic *E. coli* clones in selected populations [1]. Host characteristics associated with these clones on a population-level are currently lacking [3]. A recent Canada-wide study investigated the prevalence of *E. coli* clones among young woman with urinary tract infections [4]. In that study ST131, ST69, ST73, ST127, and ST95 were responsible for 54% of all *E. coli.* A different Canadian study identified five dominant clones (i.e., ST131, ST73, ST69, ST95 and ST1193) among *E. coli* blood stream infections that comprised 55% of the population [5].

The fluoroquinolones contributed to the global emergence of *E. coli* [6]. These isolates emerged in the late 1980s and 1990s following the introduction of fluoroquinolones (especially ciprofloxacin) in clinical medicine. Fluoroquinone resistance was mainly due to mutations (*gyrA* S83L, *gyrA* D87N and *parC* S80I) in quinolone-resistance determining regions [6].

Population-based studies are optimal to determine the occurrence of clinical conditions, such as bloodstream infections, within a well-defined population at risk [7]. Combining molecular epidemiology with population-based data, is ideal to study the population dynamics of bacteria, in a well-defined human community.

E. coli ST1193 was first described in 2012 among fluoroquinolone resistant *E. coli* obtained from Australian humans and dogs [8]. Since 2018, publications describing the global emergence of ST1193 escalated [9, 10]. ST1193 belongs to phylogenetic group B2, is lactose negative, contains *fimH*64 and is associated with fluoroquinolone resistance [11]. This clone is mainly responsible for community-onset urinary tract infections [10] including infections in long term facilities [12] and neonatal sepsis [13]. The global prevalence of ST1193 varies from 3% to 23% among fluroquinolone resistance *E. coli* isolates [10, 11, 14, 15].

The population incidence rate of *E. coli* BSIs was 48.8/100000 in Calgary during 2016 [5]. ST1193 was the fifth most common and second most AMR clone in that cohort [5]. A follow-up active population-based surveillance study in 2018 determined the clinical factors, susceptibility patterns, incidence rates, and geographical distribution of ST1193 causing blood stream infections in Calgary. The clinical data was combined with genomics (whole-genome sequencing) to provide a unique perspective of the molecular epidemiology of this emerging clone in a well-defined human population.

Materials and methods

Study population and clinical data

The Alberta Precision Laboratories is a regional, centralized laboratory system that performs all clinical microbiology services (hospital and community patients) within the Calgary region, Alberta, Canada. All Calgary *E. coli* isolates (adult and pediatric) from blood cultures

processed by Alberta Precision Laboratories in 2016 ($n = 686$) and 2018 ($n = 747$) were eligible for inclusion.

Clinical information from source patients at the time of the *E. coli* blood stream infection, was obtained using Sunrise Clinical Manager (All-scripts Healthcare Solutions, Inc., Chicago, IL, USA). A case of *E. coli* blood stream infection was defined as a patient with systemic inflammatory response and documented growth of an *E. coli* isolate in a blood culture. Incident cases were defined as Calgary residents with the first isolation of *E. coli* from blood. Repeat *E. coli* from blood were excluded. Blood stream infections were classified as community-acquired, hospital-acquired, or healthcare-associated [16].

Bacterial isolates, identification, and susceptibility testing

All *E. coli* isolates recovered between January 1st and December 31st of 2016 and January 1st and December 31st, 2018, were obtained from the frozen depository.

Identification and susceptibility testing were done using the matrix-assisted laser desorption ionization–time of flight mass spectrometry (Vitek AMS; bioMérieux Vitek Systems Inc., Hazelwood, MO) and VITEK 2 instrument (Vitek AMS; bioMerieux Vitek Systems Inc., Hazelwood, MO) respectively. Susceptibilities to the following drugs were determined: ampicillin, amoxicillin-clavulanic acid, piperacillin-tazobactam, ceftriaxone, meropenem, ertapenem, amikacin, gentamicin, tobramycin, ciprofloxacin, and trimethoprim-sulfamethoxazole. Throughout this study, results were interpreted using Clinical Laboratory Standards Institute criteria for broth dilution [17].

Molecular characterization

All *E. coli* isolates ($n = 1786$) were initially screened with a ST1193 specific PCR [14]. Positive isolates ($n = 92$) underwent Illumina WGS, using procedures described previously [18, 19]. For details, including the creation of SNP-based phylogenetic tree and hierarchal clustering analysis, please refer to the supplementary data.

Statistical analysis

Incidence rates (IR) per 100,000 person-years and respective 95% confidence intervals (95%CI) were estimated by year, sex, age group and long-term care status using the Poisson distribution as described before [5, 20]. Statistical significance was set at 5% level. For details, please refer to supplementary data.

Results and discussion

This study described the molecular epidemiology, clinical factors, and incidence rates of ST1193 causing blood stream infections in a large centralized Canadian region during 2016 and 2018. *E. coli* was the most common bacterium obtained from blood in the Calgary region during 2016 (i.e., 31.1% of 2201 isolates [$n = 685$]) and 2018 (i.e., 33.4% of 2237 [$n = 747$]). A total of 1432 unique *E. coli* were PCR screened for ST1193 and 92 (6.4%) were positive. WGS showed that 69/92 isolates belonged to ST1193. The prevalence of ST1193 increased from 26/685 (3.8%) in 2016 to 42/747 (5.6%) in 2018.

ST1198 showed high (≥25%) non-susceptible rates to ceftriaxone (26%), ciprofloxacin (96%), trimethoprim-sulfamethoxazole (54%), gentamicin (30%) and tobramycin (30%) (Table 1). Resistance mechanisms included the presence of *bla*$_{\text{CTX-M-15}}$, *bla*$_{\text{CTX-M-14}}$, *bla*$_{\text{CTX-M-27}}$, *bla*$_{\text{CTX-M-55}}$, *bla*$_{\text{CMY-2}}$ *bla*$_{\text{CTX-M-42}}$, *aac(3)-IIa, aac(3)-IId, aac(6')-Ib-cr, aadA1, aadA2, aadA5, aph(3'')-Ib, aph(6)-Id*, *dfrA8, dfrA12, dfrA17, sul1, sul2* (for details on the prevalence of these resistance markers, please refer to Supplemental Table 2).

Table 1. Patient characteristics and susceptibilities of different ST1193 clades (2016 and 2018)

	ST1193 *n*=69 (%)
Year:	
2016	26 (38%)
2018	43 (62%)
Sex:	
Male	43 (62%)
Female	26 (38%)
Clinical:	
Primary sepsis	20 (29%)
Urinary Tract Infections	33 (48%)
Acute Biliary Infections	4 (6%)
Intra-abdominal Infections	3 (4%)
Pneumonia	7 (10%)
Neonatal sepsis	2 (3%)
Origin:	
Community-acquired	36 (52%)
Healthcare associated	26 (38%)
Hospital-acquired	7 (10%)
Not susceptible:	
Ampicillin	52 (75%)
Amoxycline-clavulanate	14 (20%)
Piperacillin-tazobactam	2 (3%)
Ceftriaxone	18 (26%)
Ertapenem	0
Meropenem	0
Ciprofloxacin	64 (93%)
Trimethoprim-sulfamethoxazole	37 (54%)
Gentamicin	21 (30%)
Tobramycin	21 (30%)
Amikacin	0

The overall annual population incidence rate of *E. coli* ST1193 blood stream infections among residents of the Calgary region was 2.7 /100000 in person-years in 2016 and 2018 with elderly (>74 yrs) showing the highest incidence rates (47.1/100000). The IR per 100,000 person-years increased from 1.0 (95%CI 0.7-1.5) in 2016, to 1.7 (95%CI 1.3-2.3) in 2018

($p = 0.05$) [Fig. 1, Supplemental Table 1]. This was especially evident in females older than 74 yrs. (i.e., an increase from 9.8 per 100,000 person-years (95%CI 2.0-28.5) in 2016 to 37.8 per 100,000 person years (95%CI 19.6-66.1) [$p = 0.03$] (Fig. 1, Supplemental Table 1). The change of IR/100000 person-years over the 2-year period, was mainly due to the significant increase of ST1193 blood stream infection rates among long term care residents (i.e., an increase from 10.1 per 100,000 person-years (95%CI 0.3-56.2) in 2016 to 93.5 per 100,000 (95%CI 44.8-171.9) in 2018 [$p = 0.01$]. Spatial analysis showed no evidence of local geographic clustering in 2016 or 2018.

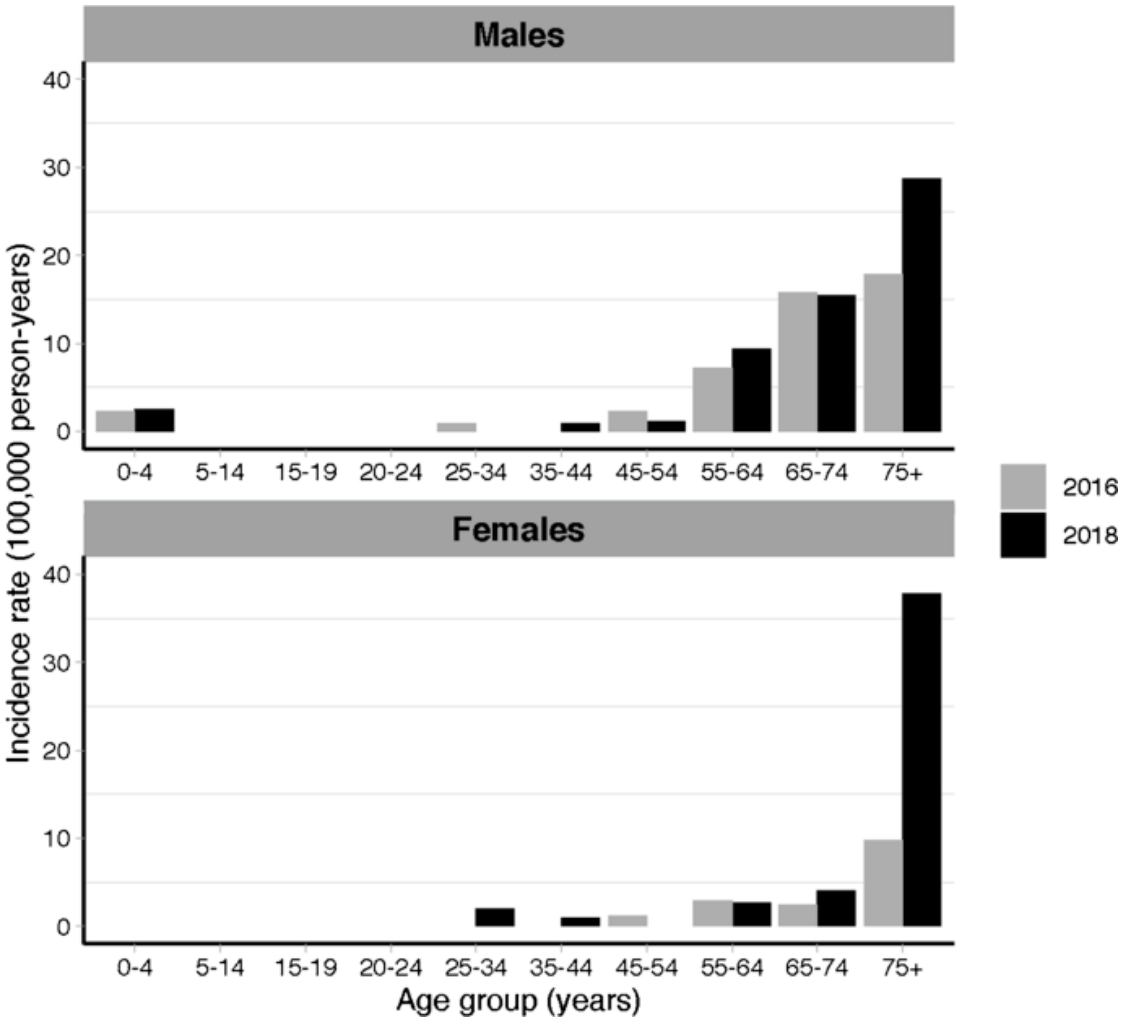

Fig. 1. Incidence rates per 100,000 person-years among Calgary residents with ST1193 blood stream infections (2016-18)

E. coli ST1193 blood stream infections were community-acquired in over half of the patient (54%) followed by healthcare associated (36%) and hospital-acquired infections (10%) [Table 1]. Just under half ($n = 33$ [48%]) of patients presented with upper urinary tract infections, followed by blood stream infections with unknown source [$n = 20$ (29%)], pneumonia [$n = 7$ (10%)], acute biliary tract infections [$n = 4$ (6%)], intra-abdominal infections [$n = 3$ (4%)] and neonatal infections ($n = 2$ [3%]) (Table 1). The ST1193 results are similar to blood stream infections due to ST131 in Calgary, with the difference that ST131

infections were more likely to be health-care associated [21]. ST131, especially clade C1, is also an important pathogen in Calgary long term care residents [20].

Johnson and colleagues performed genomic analysis on a large global collection of ST1193 ($n = 355$) [9]. ST1193 emerged from STc14 approximately 25 years ago that were accompanied with the transition of type 1 pilli from *fimH*27 (present in the ancestral ST14) to *fimH*64 (present in ST1193), the switching from K5 to K1 capsular types and mutations in the quinolone resistance-determining region (QRDR), specifically in *parC,* (i.e. S80I), *parE* (i.e. L416F) and *gyrA* (i.e. S83L, D87N) [9].

Genomic examination of the Calgary WGS data ($n = 69$) showed that 1 isolate had less than 20 times coverage and was excluded. One isolate was a double locus variant of ST1193 (i.e., ST11316), contained *fimH*27, was positive for *bla*$_{\text{TEM-1}}$ and *sul1,* tested negative for QRDR mutations and were excluded from Fig. 2.

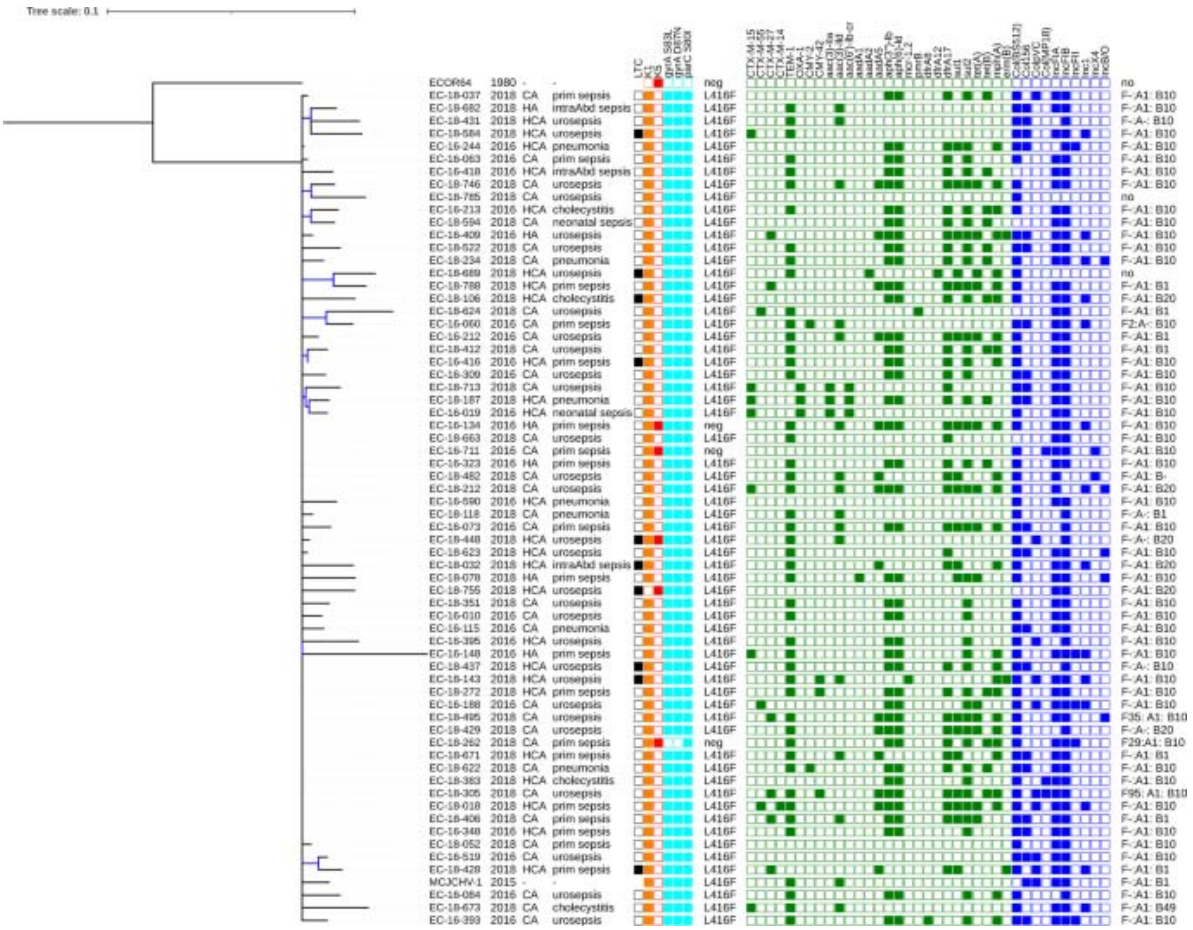

Fig. 2. A maximum-likelihood phylogenetic tree of *E. coli* ST1193 ($n = 67$) causing blood stream infections, Calgary 2016 and 2018. ST1193 belonged to a single clade (using our BAPS definition). The number of SNP differences between the ST1193 genomes were less than 28. HCA: healthcare associated, CA: community acquired, HA: hospital-acquired, LTC, long term care centers, capsular types; K1 and K5, Quinolone resistance-determining region mutations: *gyrA*S83L, *gyrA*D87N, *parC*S80I, *parE*L416F; Replicon types: Col, FIA, FIB, FII, IncI1, IncX4, IncB/O/K/Z, pMLST plasmid types: F-:A-: B1, F-:A-: B10, F-:A-: B20, F-:A1: B-, F-:A1: B1, F-:A1: B10, F-:A1: B20, F-:A1: B49, F2:A-: B10, F29:A1: B10, F35: A1: B10, F95: A1: B10. pMLST: no indicates untypable

Genomic analysis of the remaining isolates (*n* = 67) showed that Calgary ST1193 had similar genomic characteristics than global ST1193 [9]. Calgary ST1193 belonged to a single clade (using our BAPS definition) and contained serotype O75:H5, and *fimH64* (Fig. 2). The majority of ST1193 isolates were positive for the K1 capsular type (*n* = 64 [96%]) with mutations in gyrase A (i.e., *gyrA* S83L [*n* = 66 (98%)], *gyrA* D87N [*n* = 66 (98%)]) and DNA topoisomerase IV genes (*parC* S80I [*n* = 67 (100%)] and *parE* L416F *n* = 64 (96%]) [Fig. 2, Supplemental Table 2]. IncF (e.g. combinations of FIA, FIB replicons) [*n* = 63 (94%)], Col (B512) [*n* = 62 (93%)], and pMLST F-:A1: B10 type plasmid types (*n* = 41[61%]) were common (Fig. 2, Supplemental Table 2). Other Inc., Col-like and pMLST plasmid types were rare. Three isolates (4%) contained the K5 capsular type (Fig. 2, Supplemental Table 2).

Sokurenko and colleagues showed that the ST1193 *parC* and *gyrA* mutations were simultaneously acquired through homologous recombination [11]. This is different from other successful *E. coli* clones such as ST131, that acquired QRDR mutations in a stepwise manner [22]. Interesting genomic results were obtained with one Calgary ST1193 isolate (i.e., 18-262) that contained K5 and a single QRDR mutation (*parC* S80I) (Fig. 2). Illumina WGS was repeated with isolate no 18-262 and identical genomic results were obtained.

CTX-M β-lactamases were detected among 17 (25%) of ST1193 isolates (Fig. 2, Supplemental Table 2). The majority of *bla*$_{\text{CTX-Ms}}$ were *bla*$_{\text{CTX-M-15}}$, (*n* = 7) followed by *bla*$_{\text{CTX-M-27}}$ (*n* = 6), *bla*$_{\text{CTX-M-55}}$ (*n* = 3) and *bla*$_{\text{CTX-M-14}}$ (*n* = 1). ST1193 with *bla*$_{\text{CTX-Ms}}$ increased in 2018 (i.e., 4/17 (24%) in 2016 versus 13/17 (76%) in 2018). The 2018 increase occurred across the different CTX-Ms, with no apparent genomic clustering of isolates with *bla*$_{\text{CTX-Ms}}$ (Fig. 2). CTX-Ms increased from 15.4% (4 out of 26 isolates obtained in 2016) to 39.5% (17 out of 43 isolates obtained in 2018; (Fisher's Exact *P* value = 0.05). The IR of patients with CTX-M ST1193 blood stream infections increased from 0.32 cases in 2016 to 1.03 cases per 100,000 people in 2018 (*p* = 0.049). The IR/100,000 of ST1193 with *bla*$_{\text{CTX-Ms}}$ was 3.18 times higher in 2018 than in 2016 (CI 95% 0.98-13.49). ST131 emerged during the 1990s and 2000s initially as a fluoroquinolone resistant clone and gradually acquired CTX-Ms in the mid-2000s and early 2010s [21,22,23]. ST131 with *bla*$_{\text{CTX-Ms}}$ is an important cause of blood stream infections in Calgary [5, 20]. The rapid emergence of another cephalosporin-resistant *E. coli* clone is of concern that will add to the public health burden of multidrug resistant (MDR) *E. coli* blood stream infections in Calgary.

CMY β-lactamases were detected among 5 (7%) of ST1193 and consisted of *bla*$_{\text{CMY-2}}$ and *bla*$_{\text{CMY-42}}$. (Fig. 2, Supplemental Table 2). Overall, *bla*$_{\text{TEM-1}}$ was common (*n* = 48 [72%]), and *bla*$_{\text{OXA-1}}$ (*n* = 3 [4%]) was rare (Fig. 2, Supplemental Table 2). Certain antimicrobial resistance determinants were common e.g. *aph(3")-Ib* (*n* = 41 [61%]), *aph(6)-Id,* (*n* = 41 [61%]), *dfrA17 n* = 38 (57%) and *sul2* (*n* = 41 [61%]) [Fig. 2, Supplemental Table 2].

The presence of putative virulence factors was assessed among the ST1193 isolates and the following factors were common (more than 80% of isolates): *iha,* (IrgA homolog adhesion genes), (98%) *sat* (secreted autotransporter gene) (98%), *vat* (vacuolating autotransporter gene) (96%), *gad* (glutamate decarboxylate gene) (96%), *senB* (plasmid carreid enterotoxin gen) (94%), *fyuA* (yersiniabactin receptor) (84%), and *ompT* (outer membrane protein T) (84%). Similar ST1193 results were previously reported [9]. ST1193 putative virulence factors are also present among other *E. coli* clones [24].

This study has some limitations. Only Calgary patients with positive blood cultures for *E. coli* 1193 were included which excluded those with *E. coli* blood stream infections from whom no

samples were submitted for culture. Therefore, incidence rates should be considered as conservative estimates of ST1193 blood stream infections in Calgary.

Summary

This study present novel information regarding *E. coli* ST1193 blood stream infection in a well-defined urban population. We showed a significant increase of ST1193 blood stream infections among elderly females residing in long term care facilities over a 2-year period (2016-18). There was also a notable increase of ST1193 with $bla_{\text{CTX-Ms}}$ in 2018. We identified a ST1193 isolate with a single QRDR mutations (*parC* S80I) that is different from previously published data. The rapid emergence of ST1193 is of concern and adding to the public health burden of MDR *E. coli* blood stream infections in Calgary. Eliminating ST1193 could substantially decrease the AMR burden within *E. coli* causing blood stream infections in the Calgary region, especially among long term care residents. The rapid detection of ST1193 could also improve initial antibiotic selection.

Availability of data and material

Sequence data uploaded to GenBank.

Code availability

Not applicable.

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Contributions

All authors designed the study and approved the manuscript. GP and TM performed PCR, WGS and bioinformatics, DN performed the statistical analysis, RDV and JP combined the clinical and genomic data. JP wrote the 1st draft of the manuscript.

Ethics declarations

Conflict of interest

The authors have no conflicts of interest pertaining to this study and writing the manuscript.

Ethics approval

Ethics approval for this study was obtained through the University of Calgary Conjoint Health Research Ethics Board (REB16-2457).

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