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Pandemic lineages of extraintestinal pathogenic *Escherichia coli*

L. W. Riley

Division of Infectious Diseases and Vaccinology, School of Public Health, University of California, Berkeley, CA, USA

Abstract

Pathogenic *Escherichia coli* strains cause a wide variety of intestinal and extraintestinal infections. The widespread geographical clonal dissemination of intestinal pathogenic *E. coli* strains, such as *E. coli* O157:H7, is well recognized, and its spread is most often attributed to contaminated food products. On the other hand, the clonal dissemination of extraintestinal pathogenic *E. coli* (ExPEC) strains is also recognized, but the mechanism of their spread is not well explained. Here, I describe major pandemic clonal lineages of ExPEC based on multilocus sequence typing (MLST), and discuss possible reasons for their global dissemination. These lineages include sequence type (ST) 131, ST393, ST69, ST95, and ST73, which are all associated with both community-onset and healthcare-associated infections, in particular urinary tract infections and bloodstream infections. As with many other types of drug-resistant Gram-negative and Gram-positive bacterial infections, drug-resistant ExPEC infections are recognized to be caused by a limited set of clonal lineages. However, reported observations on these major pandemic lineages suggest that the resistance phenotype is not necessarily the determinant of their clonal dissemination. Both epidemiological factors and their intrinsic biological 'fitness' are likely to contribute. An important public health and clinical concern is that pandemicity itself may be a determinant of progressive drug resistance acquisition by clonal lineages. New research is urgently needed to better understand the epidemiological and biological causes of ExPEC pandemicity.

Keywords: *Escherichia coli* clonal lineages, ExPEC, intestinal pathongenic *E. coli*, MLST, ST69, ST78, ST95, ST131, ST393
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Corresponding author: L. W. Riley, Division of Infectious Diseases and Vaccinology, School of Public Health, University of California, Berkeley, CA 94720, USA
E-mail: lwriley@berkeley.edu

Introduction

Escherichia coli represents a diverse collection of Gram-negative bacterial organisms that occur as pathogens and as mammalian intestinal commensals. Intestinal pathogenic *E. coli* strains are generally divided into those that cause diarrhoea by: (i) expressing heat-labile or heat-stable toxin (enterotoxigenic *E. coli* (ETEC)) or Shiga toxin (Shiga toxin-producing *E. coli* (STEC), including enterohemorrhagic *E. coli* (EHEC)); (ii) invading the intestinal mucosa (enteroinvasive *E. coli* (EIEC)); (iii) causing attaching and effacing lesions in the intestinal mucosa (enteropathogenic *E. coli* (EPEC)); and (iv) other less well-defined mechanisms (e.g. enteroaggregative *E. coli* (EaggEC)) [1]. Whereas ETEC, EIEC, EPEC, and EaggEC remain important causes of diarrhoea among children in developing countries, the most prevalent intestinal pathogenic *E. coli* strains in developed countries are STEC/EHEC. The most common EHEC, *E. coli* O157:H7, is usually community-acquired via contaminated food or water. A newly recognized clonal lineage belonging to serotype O104:H4 that carries virulence traits of both EHEC and EaggEC was responsible for a massive outbreak of bloody diarrhoea, haemolytic–uraemic syndrome and death in Germany in 2011 that was traced to contaminated bean sprouts [2,3].

Widespread geographical clonal dissemination of intestinal pathogenic *E. coli* is frequently detected, primarily because these organisms cause outbreaks of diarrhoea, which can be readily investigated. These investigations often implicate food products that enter domestic and global food distribution networks.

As an extraintestinal pathogen, *E. coli* is the most common cause of community-acquired urinary tract infections (UTIs) and the most common Gram-negative bacterium associated

with bloodstream infections (BSIs) in both developed and developing countries. Community-onset UTIs or healthcare-associated BSIs caused by extraintestinal pathogenic *E. coli* (ExPEC) are not often recognized to occur as an outbreak or an epidemic. However, ExPEC strains belonging to related lineages are distributed locally, regionally, and globally. The mechanism of clonal dissemination of ExPEC is not obvious. This review will describe the major pandemic clonal groups of ExPEC responsible for community-onset and healthcare-associated infections, and discuss possible reasons for their dissemination.

Definitions

'Clone' is often used to describe an organism descending from a common precursor strain by non-sexual reproduction, with phenotypic or genotypic traits characterized by a strain typing method showing it to belong to the same group. In this review, the term '*E. coli* clone' will be used to refer to a set of *E. coli* strains that share an indistinguishable genotypic characteristic based on a method used to genotype them. According to such a definition, the most precise way to characterize clones would be to perform whole genome sequencing, which is increasingly being applied to study infectious disease transmission. Short of whole genome sequencing, however, multilocus sequence typing (MLST) is one highly reproducible method that is commonly applied to genotype *E. coli*. With this genotyping method, *E. coli* strains are assigned a sequence type (ST) with a numerical designation, according to two widely used and standardized schemes (http://mlst.warwick.ac.uk; http://www.pasteur.fr/recherche/genopole/PF8/mlst/EColi.html; Achtman and Pasteur, respectively) [4,5].

Although MLST is useful for demonstrating phylogenetic relationships of a large collection of bacterial lineages, it does not have the discriminatory power to show genetic changes in strains during transmissions that occur over a short time period (e.g. outbreaks). A more discriminating test is pulsed-field gel electrophoresis (PFGE), which is another widely used method for genotyping *E. coli*. PFGE forms the basis for national and international surveillance systems, such as the PulseNet in the USA and PulseNet International (http://www.cdc.gov/pulsenet/; http://www.cdc.gov/globalhealth/programs/pulsenet.htm). PFGE is often used to trace contaminated food products during outbreaks or epidemics.

Because PFGE is more discriminating than MLST, if it is used first to genotype a collection of *E. coli* isolates from sources not recognized to be outbreaks or epidemiologically related, their phylogenetic relationships could be missed. This review will apply the MLST definition to describe *E. coli* strains as clones or clonal groups in discussing their geographical dissemination or phylogenetic relationships. Their PFGE patterns (pulsotypes) will be described in discussing their modes of transmission.

Selected Pandemic ExPEC Lineages

E. coli that causes extraintestinal infections was first called ExPEC by Johnson and Russo in 2002 [6]. An assignment of *E. coli* isolates to ExPEC status based on a set of virulence genes was proposed by Johnson *et al.* [7]. Here, published studies that used MLST to genotype ExPEC isolates obtained from consecutively collected, non-duplicate clinical samples not selected by drug resistance were first reviewed (Table 1) [8–16]. The predominant clonal ExPEC groups (ST131, ST69, ST95, and ST73) described in eight or more of these reports were then selected for this review. For historical reasons, ST393 is also discussed. No other typing methods allow comparison of such a large number of reports, and hence they are not discussed in this review.

ST393 *E. coli* O15:K52:H1

During 1986 and 1987, a community-wide outbreak of infections caused by multidrug-resistant *E. coli* serotype O15:

TABLE 1. Multilocus sequence type analysis of non-duplicate *Escherichia coli* isolates obtained from population-based surveys or consecutively collected clinical samples, 1997–2012

Place (number of isolates)	Year	Type of study	Samples	Predominant ST clonal groups found[a]	References
San Francisco, USA (246)	2007–2010	Hospital	Blood	131, 95, 73, 69, 12, 10, 405, 38	Adams-Sapper *et al.* [8]
Manchester, Preston, UK (300)	2007, 2009	Hospital	Urine	73, 131, 69, 95, 10, 127	Gibreel *et al.* [9]
North-western England (88)	2004–2005	Clinical laboratories	Urine, blood	131, 73, 95, 69, 410, 416, 155, 391	Lau *et al.* [10]
Montreal, Canada (256)	2006	Outpatient clinic	Urine	69, 131, 95, 73	Manges *et al.* [11]
Nottingham, UK (121)	2008–2009	Hospital	Urine	131, 73, 69, 95	Croxall *et al.* [12]
Yorkshire, Humber, UK (770)	2010–2012	Clinical laboratories	Blood	73, 131, 69, 95, 12, 404, 10, 127, 141	Horner *et al.* [13]
Different regions, Spain (500)	2009	Five hospitals	All specimen types	131, 69, 393	Blanco *et al.* [14]
Paris, France (304)	2008–2009	Ten hospitals	All specimen types	131, 10, 73	Brisse *et al.* [15]
Clichy, France (110)	1997–2006	Hospital	Blood, ascites	95, 73, 14, 10, 23, 131, 69	Bert *et al.* [16]

ST, sequence type.
[a]Cluster of strains recovered from two or more independent patients per clonal group (from highest to lowest frequency, left to right).

K52:H1 was recognized in south London [17]. This was one of the first recognized community-setting outbreaks of ExPEC infections, which mostly included UTI, but also cases of BSI, meningitis, and endocarditis. During the same period, several hospitals in London reported an increased prevalence of bacteraemia caused by serogroup O15 [18–20]. Prior to this period, serotype O15:K52:H1 was uncommon in London. Subsequently, serotype O15:K52:H1 has been isolated from hospital and community-onset infections in Denmark, Spain, other western European countries, and several states in the USA [21–27].

Prior to genotyping by MLST, serotype O15:K52:H1 strains were described as belonging to a clonal group on the basis of their serotype and *E. coli* Reference (ECOR) phylogenetic group membership (group D), shared drug susceptibility pattern, O15:K52:H1-specific *fumC* single-nucleotide polymorphism [28], and a consensus virulence factor (VF) profile, shown in Table 2 [25]. By MLST, these strains belong to ST393, a member of the ST31 complex [25].

ST393 was reported from Korea in 2006–2007 [29]. In a national survey, ST393 strains expressing CTX-M-type extended-spectrum β-lactamase (ESBL), along with two other STs (ST131 and ST69), were found to constitute 30% of multidrug-resistant ExPEC isolates from five hospitals in different regions of Spain over a 1-month period in 2009 [14]. ST393 was one of five most common ESBL-producing STs among 654 ESBL-producing ExPEC isolates from four hospitals in north-western Spain from 2005 to 2008 [30]. In an 11-year study in Canada, ST393 was one of seven major ExPEC STs in the late 2000s [31]. Thus, ST393 continues to spread geographically, and remains a predominant ExPEC clonal group in parts of Europe.

An analysis of 100 archived international serotype O15:K52:H1 strains isolated from 100 distinct human sources from 1975 to 2006 for resistance and virulence genes has shown that this ExPEC clonal group progressively gained resistance over this 30-year period, while stably maintaining its virulence gene profiles [25]; the resistance score increased by an average of 2.8 antimicrobial drugs every 10 years.

The sudden appearance in London of serotype O15:K52:H1 in the late 1980s and its subsequent spread elsewhere are not explained. This clonal group's first recognition most likely occurred because the strains were multidrug-resistant. That is, drug-resistant strains are more likely to be cultured, tested, and stored in clinical laboratories, and hence be analysed further. Population-based, rather than convenience, samples have revealed non-resistant strains of serotype O15:K52:H1 [25]. In a collection of 100 serotype O15:K52:[H1] isolates obtained from the International *Escherichia* and *Klebsiella* Centre (WHO) (the bracket indicates motile and non-motile strains of serotype O15:K52), 45% were susceptible to 13 drugs tested [25]. As will be described below, a large proportion of drug-resistant community-acquired or healthcare-associated UTIs and BSIs are caused by ExPEC strains belonging to a small set of clonal groups, even when selective pressures from drugs potentially exist for all strains. Thus, one question that this review will address is whether the multidrug resistance phenotype of an ExPEC strain determines its clonal expansion and prevalence.

E. coli ST131

In the mid-2000s, PFGE analyses of *E. coli* isolates producing ESBL CTX-M-15 in the UK and Canada identified a pulsotype cluster with >80% similarity, designated clone A in the UK and clone 15A in Canada [32,33]. Because these PFGE patterns did not satisfy the criteria for relatedness outlined by Tenover *et al.* [34], these strains were initially not recognized to belong to a related lineage. Subsequent genotyping by MLST identified them as belonging to the same lineage, i.e. ST131 complex [5,35], which is a member of phylogenetic group B2 and serotype O25b:H4. More recently, variants of ST131 belonging to serotypes O16:H5 and NT:H4 have been reported from

TABLE 2. Phenotypic and genotypic characteristics of pandemic extraintestinal pathogenic *Escherichia coli* clonal lineages

MLST	Serogroups, serotypes	ECOR phylogenetic group	Prototypic virulence factor genes	References
ST393	O15b:K52:H1	D	*iha* (adhesin-siderophore), *fimH* (type 1 fimbriae), *fyuA* (yersiniabactin receptor), *iutA* (aerobactin receptor), and *kpsM II* (group 2 capsule)	[25]
ST131	O25b:H4, O16:H5, NT:H4, O157	B2	*iha* and *fimH* (adhesins), *sat* (toxin), *fyuA*/*irp2* and *iutA*/*iucD* (siderophore systems), *kpsM II*, *usp* (uropathogenic specific protein), *traT* (serum resistance-associated), *ompT* (outer membrane protease), and *malX* (pathogenicity island marker)	[36,37,39,42]
ST69	O11, O15, O17, O44, O73, O77, O86, O125ab, O25b	D	F10 and F16 papA alleles, papG allele II, sfa/focDE (S and F1C fimbriae), focG (F1C fimbriae adhesin), iha, hlyD, cnf1, fyuA, iutA, iroN, malX, and afa/dra (Dr antigen-binding adhesins), cdtB, and K1 kpsMT	[59,60]
ST95	O1:K1:H7, O2:K1:H7, O18:K1:H7, O45:K1:H7	B2	*fimH*, *fimAvMT78*, *papG II*, *iucD*, *iroN*, *kpsM II-K1*, *cvaC*, *iss*, *traT*, *malX*, *usp*, and *tsh*	[11,16,71]
ST73	O6:H	B2	*papC*, *papEF*, *papG*, *sfa/foc*, *fimH*, *hra*, *hlyA*, *cnf1*, *pic*, *vat*, *iroN*, *fyuA*, *kpsM II*, *usp*, and *ompT*	[16,76]

ECOR, *Escherichia coli* Reference; MLST, multilocus sequence typing; ST, sequence type.

Europe, Japan, and South Asia [36–38]. One study from Australia found an ST131 strain belonging to serogroup O157 [39]. The prototypic ST131 VF profile is shown in Table 2. Many excellent reviews have been published on the microbiological, epidemiological and clinical characteristics of infections caused by ST131, which is currently the most frequently studied of the pandemic ExPEC clonal lineages [5,35,40–45].

Worldwide, a substantial proportion of the increase in drug-resistant ExPEC infections, especially those caused by strains resistant to extended spectrum β-lactams and fluoroquinolones, can be attributed to the spread of this single lineage. Most reports describe ST131 strains that typically produce CTX-M-type ESBLs, especially CTX-M-15, encoded by $bla_{CTX\text{-}M\text{-}15}$ on a plasmid; they are usually resistant to fluoroquinolones, owing to chromosomal gene mutations (*gyrA* and *parC*) [5,26,46]. The types of CTX-M ESBL gene carried by ST131 can vary geographically, however [31,36–38,47–50]. The reported frequency of drug resistance and resistance profiles among ST131 strains depends on the study design—population vs. sample surveys, hospital vs. community-based studies, and sources of the isolates (blood, urine, wound, cerebrospinal fluid, and stools). ST131 isolates identified in faecal samples of 332 healthy volunteer subjects in Paris did not express any CTX-M ESBL [51].

The origin of ST131 is unknown. A retrospective analysis of ESBL-producing *E. coli* isolates from the Calgary Health Region in Canada from 2000 to 2007 identified ST131 as early as 2003 [52], and in France it was identified as early as 1994 [53] (Table 3). In a 2007 SENTRY and MYSTIC study, a reference strain used for virulence profile typing was a fluoroquinolone-susceptible ST131 strain (H15) isolated in 1985 [42]. ST131 strains are commonly isolated from both healthcare and community-associated infections, but whether they originate in the community or healthcare setting is not well established. In a study at a general public hospital in San Francisco, ST131 accounted for 23% of 239 *E. coli* BSI isolates consecutively collected from July 2007 to September 2010 [8]. Analysis by time of the first blood culture collection (<48 h vs. >48 h) revealed that >70% of the cultures grew *E. coli* within <48 h of admission, suggesting that most of these infections were acquired prior to hospitalization [8]. Although these community-onset infections could, nevertheless, have had a healthcare association, it is clear that ST131 is now a pandemic clonal lineage, and is responsible for a large proportion of drug-resistant ExPEC infections in a variety of clinical settings.

ST69 complex (clonal group A (CgA))

From October 1999 to January 2000, 255 *E. coli* isolates from consecutive urine samples from 228 women with uncomplicated community-acquired UTIs were analysed at a public university campus in northern California [54]. Of 55 isolates found to be resistant to trimethoprim–sulphamethoxazole, 28 (51%) shared an identical gel electrophoretic banding pattern based on ERIC2-PCR typing [55], which was described as CgA [54]. By MLST, CgA strains were subsequently found to belong to the ST69 complex [56]. ST69 strains belong to ECOR phylogenetic group D and serogroups that include O11, O15, O17, O44, O73, O77, O86, O125ab, and O25b [11,14,56–58]. The prototype ST69 strain (O11; ATCC BAA-457) has the VF profile shown in Table 2 [59,60].

Since the first recognition in 1999, CgA and ST69 strains have been reported from many other regions of the world from both community-acquired and healthcare-associated UTIs and BSIs [8,57,61–65]. Most strains are multidrug-resistant, and typically harbour a single arrangement of a gene cassette (*dfrA17–aadA5*) encoding dihydrofolate reductase and aminoglycoside adenyltransferase, respectively, on a class 1 integron [66,67]. ST69 strains expressing ESBL are currently not common. Thus, if a study selects ExPEC isolates on the basis of extended-spectrum cephalosporin resistance, ST69 may be missed or under-represented in such a study sample.

Population-based prospective follow-up studies at the above-mentioned California community found that CgA and other clonal groups of ExPEC causing UTI fluctuate over time. A 1-year follow-up study showed that the prevalence of CgA declined by 38%, but that the prevalence of trimethoprim–

TABLE 3. Non-human sources of pandemic extraintestinal pathogenic *Escherichia coli* clonal groups and the year of their first isolation recorded in the multilocus sequence typing (MLST) database

MLST	Food and food animal source	Companion and wild animal	Year and source of first isolate in MLST database[a]	References
ST393	Unreported	Dog	2001, BSI	[27]
ST131	Poultry, swine, cattle	Dogs, cats, horse, seagull, urban rat	1992, poultry 2001, human UTI	[39,93–96,98,99,101–105]
ST69 or CgA	Cow, pork, poultry	Seagull	1999, human UTI	[96,97,102,106]
ST95	Poultry, honeydew melon,	Wild birds, dog	1941, human UTI	[71,96,100]
ST73	Unreported	Dogs, cats	1917, unknown	[77]

BSI, bloodstream infection; UTI, urinary tract infection.
[a]Achtman scheme: http://mlst.warwick.ac.uk.

sulphamethoxazole resistance remained the same [68]. Six other clonal groups as defined by ERIC2-PCR typing were identified and found to be responsible for 32% of trimethoprim–sulphamethoxazole-resistant UTIs. Another study in the same community analysed 780 *E. coli* isolates from women with UTIs in October–January in 1999–2000, 2000–2001, 2003–2004, and 2004–2005 [69]. The prevalence of trimethoprim–sulphamethoxazole resistance showed no trend over this period, but only four clonal groups, including CgA, accounted for more than half of the trimethoprim–sulphamethoxazole-resistant UTIs [69]. In a hospital-based study in San Francisco of *E. coli* BSI isolates consecutively collected from 2007 to 2010, ST69 complex was the fourth most common ExPEC ST (after ST131, ST95, and ST73) [8]. ST69 was recovered from a blood culture obtained <48 h after admission in 83% of all cases, as compared with 73% for ST131. These studies suggest that ST69 is a clonal ExPEC group circulating predominantly in the community as opposed to healthcare settings.

ST95 complex

ST95 ExPEC strains belong to phylogenetic group B2, and serotypes O1:K1:H7, O2:K1:H7, and O18:K1:H7 [70]. A typical VF profile is shown in Table 2 [71]. K1 capsule-bearing serotypes, including those belonging to ST95, are also traditionally associated with neonatal meningitis [72,73]. ST95 strains include avian pathogenic *E. coli* strains that cause colibacillosis in domestic and wild birds [74,75]. In the San Francisco study described above, ST95 was the second most common clonal ExPEC group isolated from patients with BSI. In a hospital in Clichy, France, it was the most common clonal group among *E. coli* isolates obtained between 1997 and 2006 from blood and ascitic fluid [16].

One distinct feature of this clonal lineage is the relative low frequency of multidrug resistance—more than half of 40 ST95 isolates from the San Francisco hospital study were susceptible to all drugs tested, whereas all 51 ST131 isolates in the same study were resistant to at least one drug [8]. Interestingly, a more recent (2010) ST95 BSI isolate from this same study was found to carry $bla_{CTX\text{-}M}$ and bla_{KPC} genes [8]. In Montreal, only one of four ST95 isolates from patients with UTIs was resistant to any drug, and, between 2007 and 2009, uropathogenic ST95 isolates from laboratories across north-western England had the lowest resistance score among the nine commonest ST clonal groups [9,11]. These observations may lead to a suggestion that the ST95 clonal lineage is a recently introduced pandemic strain that is still undergoing drug resistance selection. However, the earliest isolation of this strain recorded in the MLST database occurred in 1941 (Table 3). This, and the observation made with ST393 above [25], nevertheless highlight the point that drug resistance phenotype itself is not a major determinant of clonal dissemination of an ExPEC organism.

ST73 *E. coli* O6:H1

ST73 strains belong to ECOR phylogroup B2 and serotype O6:H1 [76,77]. It was the most common ST among the major clonal ExPEC groups from urine and blood in two studies in the UK from the late 2000s [9,13] (Table 1). It was the third most common ST causing BSI among patients admitted to a hospital in San Francisco and in ten different hospitals in Paris, France [8,15]. It has also been reported to be one of the predominant ExPEC types expressing CTX-M-15 ESBL from Cairo, Egypt [78]. It is isolated from healthcare-associated and community-associated or community-onset infections. ST73 strains with closely related PFGE types have been isolated from humans, dogs, and cats, suggesting cross-species transmission of this genotype [77]. Incidentally, the prototypic pyelonephritogenic strain CFT073, first isolated from the blood of a woman with pyelonephritis [79], and that is often used as a reference strain in animal model studies, belongs to ST73 [77]. The characteristic VF profile genes are shown in Table 2 [76].

Other clonal ExPEC lineages

Table 1 shows other clonal ExPEC strains identified among the predominant ExPEC clonal groups in more than one region—ST10, ST12, and ST127. Genotyping studies of selected isolates based on resistance to extended-spectrum cephalosporins or fluoroquinolones have identified predominant clonal groups that appear to be more restricted geographically. For example, ST38 (O86:H18) was found to be the most common clonal group among ESBL-producing ExPEC isolates in Japan in a survey of 37 hospitals between 2002 and 2003 [80]. In the UK, among ESBL-negative but ciprofloxacin-resistant bloodstream isolates from a survey conducted in 2001–2002, the most common ST was ST405 [81]. These studies demonstrate that there are other clonal ST groups that are perhaps threatening to become pandemic strains. What drives them to cause a pandemic is unknown. Potential mechanisms are discussed below.

Role of Drug Resistance in ExPEC Clonal Dissemination

One would expect antimicrobial drug use in healthcare settings in different regions of the world to exert selective pressures on a wide variety of ExPEC lineages, and hence we should observe many drug-resistant genotypes. However, studies

everywhere based on population-based surveys or consecutively collected samples show that a limited set of *E. coli* genotypes account for a large proportion of multidrug-resistant strains. Such geographical dissemination and predominance of bacterial lineages is not limited to *E. coli* species. This phenomenon appears to be a general feature of other drug-resistant Gram-negative and Gram-positive bacteria. However, recent observations made with ST95 suggest that this dissemination is not likely to be related to drug resistance as such, as a large proportion of the ST95 and ST393 isolates appear to be susceptible to all drugs tested. That is, drug-susceptible strains can also cause pandemics. Mechanisms of clonal dissemination could therefore include biological characteristics unrelated to drug resistance (Fig. 1).

Biological Factors that May Facilitate Clonal Expansion

For intestinal *E. coli* pathogens, such as ETEC, EPEC, EIEC, and STEC/EHEC, the ability to cause diarrhoea can be specifically attributed to distinct virulence determinants that define them as belonging to these groups of intestinal pathogens [1]. With ExPEC, such characterizations are not as straightforward. In the past, pathogenic *E. coli* strains were placed in ECOR phylogenetic group B2 and, to a lesser extent, in group D, whereas commensal *E. coli* strains were placed in group A [82–84]. We know today that group D strains (e.g. ST69, ST393, and ST405) are common ExPEC lineages globally.

In the 2000s, Johnson *et al.* [6,85–87] proposed a VF profile typing method based on PCR-based analysis of key genes associated with recognized virulence phenotypes such as mucosal colonization, iron acquisition, cytotoxins, and polysaccharide capsules, as well as a marker of a pathogenicity island (Table 2). A VF profile analysis comparing ST131 and non-ST131 strains has shown that ST131 strains in different regions of the world possess higher virulence scores (number of distinct virulence markers/ST) and a set of genes that are significantly more frequent in ST131 than in non-ST strains [14,42,88]. A Canadian study compared ST131 with other pandemic clonal lineages (ST393 and ST69) from cases of UTI from 2002 to 2004, and did not find a significant difference in

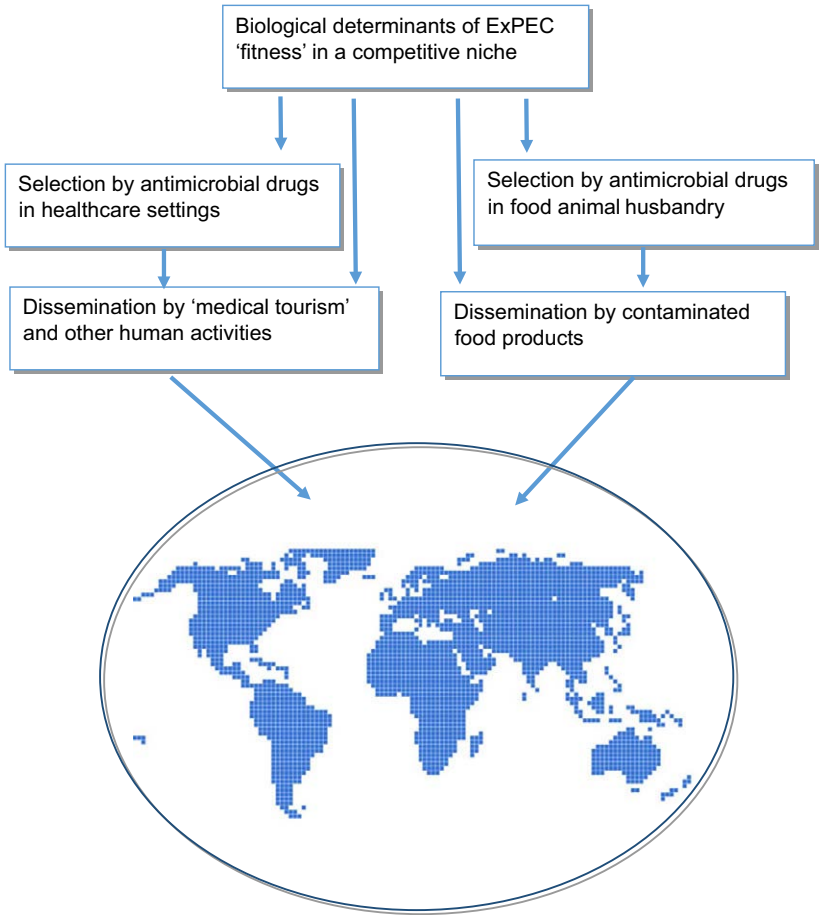

FIG. 1. Factors that may drive the pandemic spread of extraintestinal pathogenic *Escherichia coli* (ExPEC).

overall virulence scores; however, it found significant differences in some of the markers possessed by ST131 strains [61]. As ST393 and ST69 are also globally spread, these gene differences are not likely to be responsible for their dissemination. To date, no set of so-called VF genes has been clearly shown to be linked to clonal dissemination of any ExPEC lineage. Virulence is not necessarily connected with transmissibility.

It is possible that these pandemic lineages possess other biological factors that provide them with increased 'fitness', giving them a competitive advantage over other ExPEC or non-pathogenic *E. coli* lineages that reside in the same niche (Fig. 1). These factors may allow them to outcompete other strains and become the predominant bacterial population in that niche, from which they spread, the spread being facilitated by antimicrobial drug selective pressures in healthcare settings or food animal husbandry (where they acquire drug resistance), other human activities, or contaminated vehicles. Thus, their biological 'fitness' itself may be a 'risk factor' for such lineages to eventually acquire drug resistance (Fig. 1).

Animal model experiments

Mouse models of ascending UTI and sepsis are often used to compare the virulence potential of *E. coli* strains [89–91]. In a murine subcutaneous sepsis model, Johnson *et al.* [89] tested ST131 and non-ST131 isolates that were susceptible and resistant to fluoroquinolones, and found no difference in the severity of illness caused by these different strains. However, *pap* (P fimbriae), *vat* (vacuolating toxin), *kpsM II* (group 2 capsule), *ibeA* (invasion of brain endothelium) and *clbB/N* (colibactin synthesis) in any ExPEC ST strains were significantly associated with virulence [89]. At least according to the mouse model, there is no evidence that ST131 strains are any more virulent than other ExPEC strains, and this mouse virulence phenotype cannot explain its global dissemination. It should be noted that most *E. coli* isolates obtained from human subjects with UTI or BSI symptoms are, by definition, virulent. Hence, virulence assays are not likely to provide meaningful clues regarding the disseminative capacity of ExPEC lineages.

Epidemiological Factors that Facilitate Clonal Expansion

The recognized VFs of intestinal pathogenic *E. coli* organisms do not facilitate their clonal distribution. The geographical spread of common intestinal pathogenic *E. coli* strains, such as those belonging to EHEC serotype O157:H7, is largely mediated by contaminated food products. Genotyping of serotype O157:H7 by PFGE is frequently used to trace sources or settings of community outbreaks, and to link isolates from human cases of bloody diarrhoea to isolates from implicated food products [92]. Can ExPEC strains spread similarly and cause outbreaks? Like enteric *E. coli* pathogens, ExPEC strains also colonize the intestine before they cause diseases such as UTI and BSI. They enter the intestine via the oral route.

Genotyping by ERIC2-PCR and PFGE unmasked a cluster of a clonal ExPEC lineage causing uncomplicated, community-acquired UTI that came to be genotyped as ST69 in a California university campus in the late 1990s [54]. These women had no healthcare contact prior to their episode of UTI. Other clusters of clonal lineages, such as ST131, ST95, ST393, and ST73, isolated from community-acquired UTIs as well as from community-onset BSIs demonstrate that, indeed, outbreaks of ExPEC do occur, and that a large proportion of the increase or change in prevalence of these lineages in a setting may be explained by epidemiological spread, rather than local selection by antimicrobial drugs. These observations have led to the suggestion that these lineages may be spread in contaminated food products. Several reports have described the isolation of clonal ExPEC strains from non-human sources, including food products, food animals, and companion and wild animals (Table 3); isolation from household person-to-person transmissions has also been reported [39,77,93–106]. However, large community or geographically widespread outbreaks of orally transmitted enteric bacterial pathogens by companion or person-to-person transmission do not occur, and these two modes of transmission therefore cannot explain the global geographical distribution of the pandemic ExPEC lineages.

It should be pointed out, however, that pulsotypes of ExPEC isolates from food or food animal sources that match 100% to those of human isolates are rare. An analysis of 495 *E. coli* isolates from animal and environmental sources collected in the USA between 1965 and 2002 identified several ST69 (CgA) strains, but only one, isolated from a cow, showed 94% similarity by PFGE to a human UTI CgA isolate from California [97]. Another study of 579 ST131 isolates from 1967 to 2009 found that, among 170 pulsotypes, there was little pulsotype commonality between human and food or food animal isolates [107]. This is not surprising, as these studies compared *E. coli* isolates from human and non-human sources from different geographical sites and time periods. PFGE is used to detect clonal dissemination or transmission that occurs over a short period of time. Unless the human isolates are analysed prospectively and concurrently with isolates from locally consumed food products, an exact PFGE match is difficult to demonstrate. Such studies, although not yet common, do show a closer match of pulsotypes of human and food isolates [96]. Therefore, the role of food products as a potential vehicle for the spread of clonal lineages of ExPEC

cannot be ruled out at present. The practice of administering low-dose antibiotics as growth promoters in food animal husbandry may be a major driver of the selection and establishment of reservoirs of such drug-resistant ExPEC lineages (Fig. 1).

Summary

Undoubtedly, communities and healthcare institutions will continue to observe the emergence and fluctuation in time of epidemic-prone ExPEC lineages. The pandemic potential of ExPEC strains appears to involve both biological and epidemiological factors that facilitate increased transmission. One major concern is the evolution of drug resistance in these clonal strains. ST393 strains have been clearly shown to have gained increased resistance since their first identification in the late 1980s in Europe [25]. ST131 strains are progressively gaining new resistance phenotypes, including those that express KPC-2 carbapenemase and NDM-1 metallo-β-lactamase [108–112]. Furthermore, the genes encoding these drug resistance determinants are found in high-risk clonal lineages of Gram-negative bacterial pathogens other than *E. coli* [113]. It is unclear what can be done to prevent this evolution of drug resistance among pandemic strains. More research is clearly needed to understand the epidemiology and biology of the pandemicity of ExPEC organisms.

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Transparency Declaration

The author has no conflict with any contents of this article.

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