Reservoirs of Extraintestinal Pathogenic Escherichia coli

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ABSTRACT Several potential reservoirs for the Escherichia coli strains that cause most human extraintestinal infections (extraintestinal pathogenic E. coli; ExPEC) have been identified, including the human intestinal tract and various non-human reservoirs, such as companion animals, food animals, retail meat products, sewage, and other environmental sources. Understanding ExPEC reservoirs, chains of transmission, transmission dynamics, and epidemiologic associations will assist greatly in finding ways to reduce the ExPEC-associated disease burden. The need to clarify the ecological behavior of ExPEC is all the more urgent because environmental reservoirs may contribute to acquisition of antimicrobial resistance determinants and selection for and amplification of resistant ExPEC. In this chapter, we review the evidence for different ExPEC reservoirs, with particular attention to food and food animals, and discuss the public health implications of these reservoirs for ExPEC dissemination and transmission.

INTRODUCTION

The existence of important infection-causing ExPEC lineages (i.e., genetically closely related E. coli clones or clonal groups) has been recognized for the past 40 years. However, identification and detailed characterization of specific lineages has only recently been advanced, owing to the development of new methods for bacterial genotyping. Since ExPEC can colonize and persist in the human intestinal tract without detriment to the host, the operational definition of ExPEC is critical for defining the chain of ExPEC transmission from non-human reservoir to human intestinal colonization to active infection.

ExPEC clonal groups have been defined differently over time largely in relation to the available phenotyping and genotyping technologies. Early studies identified 10 to 15 O-antigen–based serogroups (of the approximately 180 that occur in E. coli) as being associated with human extraintestinal infections (1, 2). The addition of K and H antigen typing provided finer resolution. DNA-based genotyping methods, such as multilocus sequence typing (MLST) have further advanced our understanding of these lineages. For the purposes of this review, ExPEC is defined as isolates (i) recovered from extraintestinal infections, (ii) possessing known ExPEC virulence factors, (iii) exhibiting MLST sequence types associated with extraintestinal infections, and/or (iv) exhibiting classic ExPEC-associated serogroups/serotypes in conjunction with typical ExPEC virulence factor profiles or phylogenetic group membership (e.g., groups B2 and D).

Certain major E. coli lineages have been implicated repeatedly in epidemiologic studies as the cause of a large proportion of human extraintestinal E. coli infections (Fig. 1). Many such groups are multidrug-resistant and likely contribute significantly to the ongoing population-level increase in antimicrobial-resistant human E. coli infections. Here, for consistency, we identify specific ExPEC lineages by O:K:H serotype (if known), phylo-
genetic group of origin (A, B1, B2, or D), and sequence type (ST), as determined by MLST; for example, O25:H4-B2-ST131. Several important ExPEC lineages are highlighted based on their large contribution to overall disease burden, including: O25b:H4-B2-ST131, O25a:H4(a)-D-ST648, O11/O17/O77:K52:H18-D-ST69, O15:K52:H1-D-ST393, (serotype: various)-D-ST117, O1/O2/O18:K1:H7-B2-ST93, (serotype: various)-A-ST10, (serotype: various)-D-ST405, and O75:K+:H5-B2-ST14. Since many of these groups have been identified in surveillance studies focused on extended spectrum β-lactamase (ESBL)-producing E. coli, ESBL-producing lineages tend to be overrepresented.

### IMPORTANT ExPEC LINEAGES

*E. coli* O25:H4-B2-ST131, reported first in 2008, is an important new globally emerging pathogen (3, 4). This clonal group is of major public health concern because of its typically extensive antimicrobial resistance profile, which often includes ESBL production, specifically of CTX-M-15, plus fluoroquinolone resistance, and its widespread distribution. *E. coli* O25:H4-B2-ST131 has been identified primarily from human infections and has been associated with travel, which may explain its international spread over the past decade. In surveys of human *E. coli* infections this group accounts for a large fraction of cases overall (5), and up to 88% of antimicrobial-resistant infections, depending on the specific resistance phenotype (6).

*E. coli* O11/O17/O77:K52:H18-D-ST69 (also termed CgA, for “clonal group A”) was identified initially in an apparent outbreak of extraintestinal infections in Berkeley, California, during which it accounted for 11% of all urinary tract infections (UTIs) and 52% of antimicrobial-resistant UTIs (7). It has since been identified around the world (8). This group often exhibits multidrug resistance and has been responsible for urinary tract and more severe human extraintestinal infections (8–11). Several studies found this group to cause approximately 10% to 20% of all human *E. coli* infections (8, 12, 13). A recent global survey suggested that the O11/O17/O77:K52:H18-D-ST69 group is concentrated in North America and may have emerged in the 1990s (13).

*E. coli* O15:K52:H1-D-ST393 was first recognized during an outbreak of extraintestinal infections from 1986 to 1987 in London, UK (14), and has subsequently been identified across Europe (15, 16) and globally (17). In the initial epidemic, O15:K52:H1 caused 26% of all extraintestinal infections during a 1-year interval (5, 14). This group also is typically multidrug-resistant and has caused community-acquired extraintestinal infections of all types (14, 16, 18, 19). It is closely related to O11/O17/O77:K52:H18-D-ST69; both possess similar antimicrobial resistance and virulence factor patterns and appear to share a common ancestor (20).

*E. coli* O6:H1-B2-ST73 was recently reported as a leading cause (17% overall) of human extraintestinal infections in the UK (21). This clonal group, like many others, is associated occasionally with ESBL production (21–23). It may represent a long-standing, human-adapted ExPEC group, since it has caused UTIs in women in many geographic areas and over many years (24).

*E. coli* (serotype: various)-D-ST405 is another globally disseminated, extensively antimicrobial-resistant group (3, 25–27). ST405 may be the next most important contributor after ST131 to the global dissemination of CTX-M-15 (3). Furthermore, an ST405 *E. coli* isolate was recently encountered that produced multiple ESBLs, including QepA1, CTX-M-15, and RmtB (28). ST405 also has been associated with New Delhi metallo (NDM) β-lactamases (29). ST405 has been associated with person-to-person transmission (26), but evidence for non-human reservoirs is still lacking (24).
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*E. coli* (serotype: various)-A-ST10 or *E. coli* ST10 clonal complex (i.e., ST10 and closely related STs), although typically encountered as an antimicrobial-susceptible, low-virulence human intestinal colonizer, also has been associated with human infections and ESBL production. This clonal group, members of which have caused hospital and community-acquired infections, was found to account for 7% of all human clinical *E. coli* isolates in Calgary, Alberta, Canada (30).

**OTHER NOTABLE ExPEC CLONAL GROUPS**

*E. coli* O1/O2/O18:K1:H7-B2-ST95 is both a recognized avian pathogenic *Escherichia coli* (APEC) clonal group (31) and a prominent human urinary tract and meningitis pathogen, accounting for 6% of human extraintestinal clinical isolates in one study (21). *E. coli* (serotype: various)-D-ST117 is another recognized APEC lineage that has also been identified as a cause of human UTI (32, 33). *E. coli* O75:K+::H5-B2-ST14, in the past an important ampicillin-resistant clonal group, has recently been associated with fluoroquinolone resistance in Australia (34). *E. coli* (serotype: various)-D-ST648 has been associated with human disease in China (35), Canada, and the Netherlands (36), and with NDM β-lactamases (37). Additionally, *E. coli* ST167, ST410, and ST38 have also been identified in epidemiologic studies of human extraintestinal infections; however, less information is available concerning the dissemination and reservoirs for these *E. coli* clonal groups (23, 36, 38–41). Given the wide distribution of several of these *E. coli* clonal groups, efforts to identify their reservoirs are needed.

**THE HUMAN RESERVOIR OF ExPEC**

An appropriate starting point for reviewing the sources of human ExPEC is the human intestinal tract. The human intestinal tract has long been recognized as a reservoir of *E. coli* (42). ExPEC also are members of the intestinal microbiota in a large fraction of healthy individuals (42). However, in contrast to non-ExPEC intestinal colonizers, once ExPEC gain access to other body sites they can persist and cause disease. ExPEC that cause UTIs typically follow a fecal-to-perineal/vaginal-to-urethral transmission pathway within the individual host (43, 44). ExPEC also sometimes cause sepsis by entering the bloodstream directly, via translocation across the intestinal barrier (45). Importantly, the intestinal microbiota also can serve as a reservoir of antimicrobial resistance determinants for ExPEC (46, 47). Exposure to an antimicrobial agent can temporarily increase the prevalence of antimicrobial-resistant *E. coli* in the intestine, although this increase may be short-lived for most antimicrobials (48).

Several studies have documented direct person-to-person transmission of ExPEC strains between household members and sexual contacts, in many instances with linkage to subsequent extraintestinal infections (49–53). The exchange of ExPEC between sexual partners in particular could be one explanation for the phenomenon of recurrent UTIs in some women, since the male partner (who is not treated) may remain a reservoir for re-infection of the woman. Although strain sharing among household and sexual contacts could increase the risk of future infection in a given individual, spread of ExPEC or antimicrobial-resistant *E. coli* from non-human or food reservoirs through the entire population represents a larger public health threat. Understanding how these organisms reach the human intestinal tract could lead to strategies to minimize transmission, thereby reducing the pool of antimicrobial-resistant and pathogenic *E. coli* in the gut available to cause disease.

**ENVIRONMENTAL RESERVOIRS OF ExPEC**

Surface water, rainwater, wild animals, sewage, and wastewater effluents have all been investigated as possible environmental sources of ExPEC. Sewage may contribute significantly to the environmental dissemination or circulation of ExPEC due to the presence of highly concentrated human fecal waste containing ExPEC. To study environmental reservoirs is challenging because these sources tend to contain *E. coli* from multiple sources (e.g., sewage may contain human, animal, and industrial waste). Microbial source tracking is complicated by the difficulty of assigning the *E. coli* recovered in any given environment to a particular source. Furthermore, the methods used to discriminate and describe ExPEC and other types of *E. coli* can be highly variable. In this section, water and other potential environmental sources of ExPEC are reviewed.

Survival of ExPEC during sewage treatment, leading to possible environmental contamination, has been investigated in several studies, which identified ExPEC-associated phylogenetic groups, virulence genes, and lineages among *E. coli* from sewage samples. For example, in a study of four sewage treatment plants 60% of *E. coli* sewage isolates belonged to ExPEC phylogenetic groups B2 and D and a large fraction possessed *hly*A (74%) and *iro*N (82%), while smaller...
proportions possessed P fimbrial genes *papAH, papEF, papC*, and the cytotoxic necrotizing factor 1 (*cnf1*) gene (54). Another study found a high prevalence of group D *E. coli* (37%) and quinolone resistance (56%) among *E. coli* sewage isolates (55). Both studies identified putative ExPEC isolates in the final effluent, suggesting that treated water released into the environment may contain viable ExPEC (54, 55).

Notably, two important ExPEC lineages were identified in sewage sources, including *E. coli* O25:H4-B2-ST131 (treated wastewater and river water) (56, 57) and *E. coli* O11/O17/O77:K52:H18-D-ST69 (sewage effluent) (58). It is clear that, despite sewage treatment, ExPEC persist throughout the treatment process, with their presence risking contamination of surface water (54). Investigation of the movement of ExPEC in treated sewage and other wastewater sources is needed, since these sources may participate in the environmental cycling of ExPEC clonal groups that cause disease in humans and animals.

Surveillance studies have consistently identified antimicrobial-resistant and pathogenic *E. coli* in natural bodies of water and recreational waterways (59–61). In one study, 40% of *E. coli* isolates from coastal marine sediments represented phylogenetic groups B2 and D, and most of these contained at least 1 of 11 ExPEC virulence genes (61). Hamelin et al. used a DNA microarray containing probes to 348 antimicrobial resistance genes and virulence genes from all *E. coli* pathotypes to characterize *E. coli* from recreational and river waterways. Isolates were defined as uropathogenic if positive for at least one of the following: *pap* genes, *hlyA*, *S* fimbriae-encoding genes, *chuA*, *fepC*, *cnf1*, *irp1*, *irp2*, *fyuA*, *iroN*, or *usp* (60, 62). From Lake Ontario recreational water, 73% of *E. coli* isolates were uropathogenic, with most belonging to phylotypes B2 and D, whereas from six different river, estuary, and offshore lake locations, 26% of *E. coli* were uropathogenic (60, 62). Similarly, Mühldorfer et al. found that 41% of *E. coli* isolates from surface water samples from the Elbe River in Germany contained ExPEC-associated genes (63). Finally, rainwater contamination with ExPEC, as defined based on ExPEC virulence genes, was documented for 68% of rain barrels in Australia, which was concerning since many of the barrels were used as a potable water source (64).

Wild animals, particularly wild birds, have also been investigated as an environmental source of antimicrobial-resistant and pathogenic *E. coli* (65–69). A study of ESBL-positive *E. coli* from yellow-legged gulls in France identified CTX-M-1-positive *E. coli* representing the ST23 complex and the ST533 clonal group, which previous studies associated with UTIs (65, 70–73). Additionally, *E. coli* ST648 was identified in wild birds in Germany (74). A review of ESBL-producing *E. coli* recovered from wildlife sources documented the diversity of *E. coli* colonizing different animal hosts, but highlighted the occurrence primarily in wild birds of ExPEC-associated STs, including ST69, ST131, ST405, ST10, and ST648 (75).

Thus, compelling evidence exists that ExPEC occurs in sewage and other environmental sources, including wild animals and water. However, to date such ExPEC have not been tested in established animal models of human extraintestinal disease for their potential human extraintestinal pathogenicity. This step would provide important confirmation that wild animals, sewage, and water could act as reservoirs for ExPEC capable of causing infections in humans.

**COMPANION ANIMAL RESERVOIRS OF ExPEC**

Companion animals, which develop similar types of extraintestinal infections as their human guardians, have also been identified as a reservoir of human ExPEC (76–78). Surveys of the *E. coli* causing infections in pets, and surveillance studies at veterinary hospitals, have documented the circulation of genetically related and frequently antimicrobial-resistant ExPEC in dogs, cats, and other animals that live in close contact with humans (79, 80).

Intestinal colonization by ExPEC has been demonstrated in companion animals. A study of *E. coli* from canine fecal samples identified approximately 50% of isolates as ExPEC by virulence factor genotyping and direct comparison with reference human ExPEC isolates (81). Environmental contamination with feces, and consequent transmission of fecal-source *E. coli* between dogs, in particular, likely occurs frequently. Multidrug-resistant *E. coli* isolates from rectal swabs from a population of dogs were similar (according to phylogenetic group and pulsed field gel electrophoresis [PFGE]) to the *E. coli* causing extraintestinal infections in animals (82). The ExPEC isolates were closely related, persistent, and present in multiple species, including cats, dogs, and horses (82).

Closely related or indistinguishable ExPEC strains have been recovered from humans and their companion animals, suggesting transmission in either direction. For example, in one study, an *E. coli* strain (O1:K1:H7-B2-ST95) was shared extensively (present in 45% of
samples) among household members and the family dog, and caused a UTI in the mother (83). Similarly, an E. coli O6:K2:H1-B2-ST73 strain was shared between family members and the family dog, which developed UTI due to this strain (51, 84). The human ExPEC lineages O6:K15:H31-B2-ST127 and O4:K54:H5-B2-ST493 also have been identified in dogs, cats, and humans (85). These results were confirmed using a set of E. coli recovered from dogs alone, where the canine isolates exhibited ExPEC virulence factors related to those of human reference ExPEC isolates (85, 86). Additionally, E. coli O75:K+H5-B2-ST14 was recently identified in pet dogs (34).

ESBL-producing E. coli, some from ExPEC-associated clonal groups, also have been recovered from companion animals in diverse locales. ESBL (specifically, CTX-M)-positive E. coli recovered from stray dogs in Korea included members of the ST10, ST38, ST93, and ST95 clonal groups, whereas CMY-2-positive E. coli included ST405 and ST648 (87). CTX-M-positive E. coli ST648 was recovered from companion animals in Japan (88). Closely related ESBL (CTX-M-15)-positive E. coli O25:H4-B2-ST131 isolates were identified in humans, companion animals (primarily dogs), and other animals from several European countries (89). Likewise, in Australia, 42% of fluoroquinolone-resistant human ExPEC isolates belonged to three ExPEC lineages (O25:H4-B2-ST131, O11/O17/O77:K52:H18-D-ST69 and O15:K52:H1-D-ST393), representatives of which also were identified among contemporaneous clinical isolates from companion animals (80). These findings demonstrate that the extensive clonal spread of E. coli O25:H4-B2-ST131 is not limited to humans. Another study provided strong evidence for direct transmission of an E. coli O25:H4-B2-ST131 strain among multiple companion animals within a single household (52). This strain’s PFGE profile closely resembled the PFGE profiles of E. coli O25:H4-B2-ST131 isolates from human infections from other studies, implying cross-species transmission at some point (90). Additional ExPEC strains were also shared between dogs and cats in this study, again suggesting cross-species transmission within a household (51).

These results support the hypothesis that ExPEC from companion animals and humans represent overlapping populations, with certain ExPEC lineages capable of causing infections in and/or colonizing either host group. Related to this, antimicrobial resistance among ExPEC may be further selected by antimicrobial therapy given to companion animals, leading to additional exposure of humans to antimicrobial-resistant ExPEC through routine contact with colonized companion animals.

**AVIAN PATHOGENIC E. COLI AND HUMAN EXTRAINTESTINAL E. COLI**

Evidence is increasing that some human-associated ExPEC are related to APEC, the cause of colibacillosis, an extraintestinal infection of poultry. Considerable genetic similarity has been demonstrated between APEC isolates from infected poultry and ExPEC isolates from infected humans (32, 91–95). For example, a human sepsis-associated O111:H4-D-ST117 ExPEC strain was closely related to known APEC strains by PFGE, virulence factor profiling and phylotyping (32). A population-level association between human ExPEC and APEC (or E. coli derived from poultry) is suggested by these groups’ overlapping antimicrobial resistance patterns, resistance genes, and virulence factors (32, 70, 72, 83, 91, 93, 95–100). As for experimental evidence of cross-species pathogenicity, several studies have demonstrated that APEC can cause disease in mammalian models of human ExPEC infections (e.g., the mouse model of ascending UTI) (101, 102), and human-source ExPEC can cause disease in certain avian disease models (72, 103).

**FOODBORNE RESERVOIRS OF HUMAN ExPEC**

Foodborne transmission of food animal or retail meat-associated ExPEC has been the topic of many recent investigations, with poultry and poultry products receiving the most attention (83, 97, 98, 100, 104–106). A review of outbreaks of ExPEC-related infections identified a sizable number of community-wide clusters (5). Although the sources of the outbreaks were not identified, these E. coli infection clusters typically result from point-source dissemination and food or waterborne transmission. The proposed chain of foodborne ExPEC transmission involves ExPEC from food animals or meat products subclinically colonizing the human consumer’s intestinal tract after ingestion of undercooked meat or cross-contamination in the kitchen during food handling. Once an incoming ExPEC strain has established residence in the human intestinal tract, it persists there until circumstances favor an extraintestinal infection, e.g., sexual intercourse or urinary catheter insertion (53). The often-lengthy interval between ExPEC acquisition and disease development, if disease ever occurs, makes transmission of ExPEC and antimicrobial-resistant E. coli from external reservoirs (e.g., foods) to humans very difficult to detect. However, although direct transmission has not been demonstrated, abundant circumstantial evidence links E. coli recovered from food...
animal sources to human ExPEC isolates. The most troubling aspect of these observations is the extensive antimicrobial resistance of *E. coli* isolates from food animals, particularly chickens (107, 108).

One likely contributing factor to the emergence of antimicrobial-resistant *E. coli* in food animals, especially poultry, is the large increase in human consumption of retail chicken over the past 30 years (109). This has led to changes in the scale and methods of food animal production, including increased use of antimicrobial agents for growth promotion, infection prevention, and treatment (110), which likely has selected for and amplified multidrug-resistant ExPEC in the food animal reservoir (111). Resistant *E. coli*, once established in food animals, can spread among animals and the local environment, maintaining the circulation of antimicrobial-resistant ExPEC within the herd, flock, or production facility (111).

The plausibility of foodborne transmission of antimicrobial-resistant *E. coli* to humans is strengthened by the finding that antimicrobial-resistant *E. coli* from chicken carcasses widely contaminate the kitchen during meal preparation and can appear in the intestinal tract of individuals who prepare food dishes from the carcasses (112, 113). Furthermore, volunteers fed a diet of irradiated food exhibited markedly reduced levels of antimicrobial-resistant intestinal *E. coli*, with reversion to baseline post-intervention (114), implying that a conventional diet sustains a certain prevalence of intestinal resistant *E. coli* through a steady input of resistant strains. Thus, the available evidence, albeit indirect, strongly supports a foodborne component to the antimicrobial-resistant *E. coli* problem in humans.

**Poultry Sources**

Based on existing evidence, poultry is the food animal source most closely linked to human ExPEC (83, 97–100, 104–106). In women, UTI caused by antimicrobial-resistant ExPEC has been epidemiologically linked with high levels of self-reported chicken consumption (106). Among different meat types, poultry generally exhibits the highest overall levels of *E. coli* contamination, and poultry-associated *E. coli* tend to be more extensively antimicrobial-resistant than those from other meats (107, 108). Poultry-associated *E. coli* also often possess virulence genes characteristic of human ExPEC, suggesting a potential to cause human disease.

A 2006 study by the U.S. National Antimicrobial Resistance Monitoring Systems (NARMS) identified 200 ExPEC isolates among 1,275 *E. coli* isolates from retail meat samples. The proportion of isolates representing ExPEC varied by meat type, being highest in ground turkey (23.5%), followed by chicken breast meat (20.2%), pork chops (8.3%), and ground beef (3.4%) (115). More than half of these isolates belonged to serogroups associated with human extraintestinal infections. Serogroup O25 (17.9%) was the most common among chicken isolates, while serogroup O2 (36.2%) was most common among turkey isolates. Furthermore, 42% of retail meat ExPEC isolates represented ExPEC-associated phylogenetic groups B2 (25%) and D (23%) (115). These findings confirmed those of an earlier study from 2002 to 2004 involving NARMS isolates, which additionally showed that isolates from different meat types were genetically distinct, suggesting that they originated from the respective animal species (116). Importantly, however, susceptible and resistant isolates from a given meat type did not differ genetically, suggesting that the resistant isolates emerged from susceptible isolates within the different food animal hosts, possibly from on-farm antimicrobial use (116).

Specific ExPEC lineages have been found in poultry and poultry meat sources. Indistinguishable *E. coli* O25:H4-B2-ST131 strains were identified in a human UTI case and retail chicken meat sample in Canada (33). Mora et al. also demonstrated similarity by PFGE and virulence gene content between one chicken and one human CTX-M-9-positive *E. coli* O25:H4-B2-ST131 isolate (117). ESBL-positive *E. coli* O25:H4-B2-ST131 was also recovered from poultry farms in Spain, where human and poultry-source O25:H4-B2-ST131 isolates exhibited moderate (75%) PFGE similarity (118). Several other studies identified antimicrobial susceptible ST131 isolates in chickens and/or chicken meat (100, 105, 119, 120).

O11/O17/O77:K52:H18-D-ST69 likewise has been linked to non-human reservoirs, primarily chicken (33, 101). Moreover, in an experimental study, CgA *E. coli* isolates recovered in Denmark from human infections and retail chicken meat were equally able to cause UTI in a mouse model, suggesting that poultry-source CgA *E. coli* are just as pathogenic for mammals as are human-derived CgA strains (97).

A recent study from the Netherlands identified *E. coli* (serotype: various)-A-ST10 producing CTX-M-1 ESBL in human blood cultures and poultry, whereas TEM-52-producing ST10 isolates were recovered from human urine samples and poultry (105). A similar study from the Netherlands also identified ESBL-producing *E. coli* ST10 in chicken meat, other meat types, rectal swabs from healthy humans, and human blood cultures (100). A study from Canada identified multidrug-resistant
ST10 isolates (albeit of limited PFGE similarity) in human clinical samples, chicken feces, and retail chicken meat (121).

E. coli O1/O2/O18:K1:H7-B2-ST95 isolates with related PFGE profiles have been identified in humans and poultry (33, 92) and, separately, in honeydew melon and multiple human infections (33). In another study, 58% of 108 APEC and human ExPEC isolates from serogroups O1, O2, or O18, representing diverse host species, belonged to ST95 (70). When assessed in animal models, O18-B2-ST95 E. coli isolates from human neonates with meningitis could cause colisepticemia in poultry (72); conversely, O18-B2-ST95 E. coli isolates from cases of avian colibacillosis (APEC) could cause neonatal meningitis in a rat model (102). This indicates that the APEC and NMEC-associated ST95 group may have zoonotic potential.

ESBL-producing ST117 isolates were also identified in human and poultry reservoirs (100, 105), and genetically closely related O114:H4-ST117 strains, as assessed by PFGE, were identified in a human UTI case and retail chicken meat in Canada (33). CTX-M-32-positive O25a:H4-D-ST648 isolates, one from a human infection and one from a poultry source, exhibited closely related PFGE profiles (118). Additionally, human clinical and turkey meat samples containing E. coli ST410 were identified in Spain (122).

**Pork and Pig Sources**

Contamination of pork products with ExPEC has also been reported; however, fewer studies have been conducted to date (33, 98, 123–126). One epidemiologic study found that women experiencing a drug-resistant UTI were more likely to report frequent pork consumption (106). In another study, E. coli recovered from pigs tended to be from phylogenetic groups A and B1 and exhibited lower overall numbers of virulence genes compared with poultry isolates (118).

E. coli ST131 was detected among pork and UTI isolates in one study from Denmark and Norway (127). Additionally, O11/O17/O77:K52:H18-D-ST69 has been linked to pork (33, 123). Multidrug-resistant and possibly related (by PFGE) ST10 isolates have been identified in human clinical samples, pig feces, and retail pork meat (121), whereas in another study O2:H(non-motile)-A-ST10 isolates were identified in pigs (118).

**Beef and Cattle Sources**

The evidence for a beef cattle reservoir for human ExPEC is fairly weak. In general, the prevalence of E. coli resembling ExPEC is low in beef cattle sources (115, 128). One study identified a single cow isolate that was similar by PFGE to a human O11/O17/O77:K52:H18-D-ST69 isolate (129). The reason for limited colonization of healthy beef cattle with ExPEC, compared with their extensive colonization with E. coli such as shiga-toxin producing E. coli (130), is unknown.

**PUBLIC HEALTH PERSPECTIVES**

Investigators of the human versus extra-human origins of ExPEC have used both population ecology surveys and experimental pathogenesis studies to examine host species distribution and specificity of different ExPEC types. What has emerged is a picture of a large and complex group of E. coli variants, within which a small number of highly successful lineages (in terms of virulence, prevalence, and geographic range) have become established and account for the bulk of extraintestinal E. coli infections in humans and some domestic animals. The importance of these lineages is highlighted in one recent study in which just three clonal groups (O25:H4-B2-ST131, O15:K52:H1-D-ST393, and O11/O17/O77:K52:H18-D-ST69) accounted for 19% of 500 consecutive extraintestinal E. coli isolates in 5 hospitals in Spain in February 2009, and for 30% of multidrug-resistant isolates (9). ST131 E. coli alone was estimated to cause approximately 17% of extraintestinal infections in the source populations of another surveillance program (131). More importantly, these extraintestinal disease-causing lineages are becoming increasingly multidrug-resistant. Identification of the reservoirs and transmission pathways for these important human-associated ExPEC groups conceivably could help to curb their transmission and to reduce their extent of antimicrobial resistance, thereby leading to fewer and easier to treat human ExPEC infections.

It is increasingly clear that certain prominent ExPEC groups can occur in non-human sources, including food animals and meat products, although the extent of this phenomenon, its importance to human health, and the strength of the supporting evidence vary by source and E. coli group. The strongest evidence for a food animal reservoir and foodborne transmission of human ExPEC exists for poultry and pigs, where genetically similar ExPEC have been recovered from retail chicken, turkey, and pork products and human infections. Although transmission of ExPEC from food animals or retail meats to humans has yet to be directly demonstrated, transmission of ExPEC has been documented between cohabiting humans, and between companion animals and humans (49, 51–53, 85).
Development and amplification of multidrug resistance in animal-associated *E. coli* is likely facilitated by the frequent or continuous selection pressure provided by antimicrobial use during food animal production and veterinary medicine (132). Antimicrobial use in human clinical medicine provides additional selection pressure once such organisms enter the human population. Thus, the global increase of antimicrobial resistance among human-associated ExPEC likely has multiple ecological origins, with important inputs from the transmission of antimicrobial-resistant ExPEC from food animals, companion animals, and environmental sources to humans. Each of these ExPEC reservoirs provides an environment for amplification, followed by further amplification in humans, then possible transmission back to these reservoirs, in a continuous feedback loop (133).

Certainly, antimicrobial stewardship is important for reducing the selection pressure for antimicrobial resistance in food animals and other environments sources. Antimicrobial usage in food animals varies widely throughout Europe, despite the 2006 European Union antimicrobial growth promoter ban (134). However, given the linkage of antimicrobial resistance genes and the unavoidable need for antimicrobial use for therapy and prophylaxis in some cases, in humans and animals alike, stewardship is at best a harm reduction strategy, slowing rather than preventing further emergence and spread of resistant *E. coli*. Recent efforts have focused on eliminating or reducing the use in food animals of antimicrobials classified as very important to human medicine (e.g., extended-spectrum cephalosporins) (135), to reduce antimicrobial resistance; however, this is not always been readily accomplished (e.g., the U.S. Food and Drug Administration’s delayed ban on fluoroquinolone use in poultry) (136). Reducing *E. coli* contamination levels on meat products is another possible intervention.

Another preventive approach deserving consideration is vaccines. Food animal-associated ExPEC lineages possess specific traits that allow them to cause extraintestinal disease, to survive within specific reservoirs (e.g., in avian hosts), and to disseminate widely among human hosts. Elucidation of such factors is essential for identifying good vaccine targets. Vaccines could be additionally effective as a public health intervention if directed toward the animal hosts that act as reservoirs (137).

Ecologic studies comparing ExPEC from multiple sources have inherent limitations, including the difficulty of determining direction of transmission (from animals to human or vice versa) and pinpointing actual transmission events. Nonetheless, the public health community should heed the growing body of evidence supporting foodborne transmission of ExPEC with human pathogenic potential and should move toward implementing policies and practices that would limit the evolution, selection/amplification, and dissemination of antimicrobial-resistant ExPEC from food animals and other reservoirs to humans.

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