

Food-Borne Origins of *Escherichia coli* Causing Extraintestinal Infections

Amee R. Manges¹ and James R. Johnson^{2,3}

¹Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, Québec, Canada; ²Infectious Diseases Section, Veterans Affairs Medical Center, and ³Department of Medicine, University of Minnesota, Minneapolis

Most human extraintestinal *Escherichia coli* infections, including those involving antimicrobial resistant strains, are caused by the members of a limited number of distinctive *E. coli* lineages, termed extraintestinal pathogenic *E. coli* (ExPEC), that have a special ability to cause disease at extraintestinal sites when they exit their usual reservoir in the host's intestinal tract. Multiple lines of evidence suggest that many of the ExPEC strains encountered in humans with urinary tract infection, sepsis, and other extraintestinal infections, especially the most extensively antimicrobial-resistant strains, may have a food animal source, and may be transmitted to humans via the food supply. This review summarizes the evidence that food-borne organisms are a significant cause of extraintestinal *E. coli* infections in humans.

Extraintestinal pathogenic *Escherichia coli* (ExPEC) strains are the cause of most community and hospital-acquired extraintestinal *E. coli* infections, including infections of the urinary tract, bloodstream, and other anatomical sites [1]. ExPEC include neonatal meningitis *E. coli* and uropathogenic *E. coli*. During the past 10 years, recognition has grown that certain important *E. coli* lineages, or clonal groups (defined as genetically closely related *E. coli* isolates), are responsible for a large fraction of human extraintestinal *E. coli* infections and that these lineages are variably antimicrobial resistant.

Molecular epidemiology studies of ExPEC from around the world have identified several potential reservoirs for ExPEC, including the human intestinal tract, plus various nonhuman reservoirs such as food animals and retail meat products, sewage and other environmental sources, and companion animals. Here

we review the evidence for food and food animal reservoirs for human ExPEC, paying specific attention to those ExPEC lineages that cause a large fraction of infections and to the public health implications and importance of food animal reservoirs for ExPEC dissemination and transmission.

FOOD-BORNE ORIGINS OF HUMAN ExPEC

Much current research effort is directed toward determining the contribution, if any, to human infections of food animal-associated ExPEC, particularly those strains that are resistant to therapeutically important antimicrobials. Based on existing evidence, poultry is the food animal source most closely linked to human ExPEC [2–9]. Poultry meat exhibits the highest overall levels of *E. coli* contamination, and these *E. coli* can be more extensively antimicrobial resistant than *E. coli* recovered from other meats [10, 11]. Poultry-associated *E. coli* also often possess virulence genes similar to those of human ExPEC, suggesting the potential to cause human disease. Contamination of pork with ExPEC has also been reported; however, fewer studies have been conducted to date [3, 8, 12–14].

Investigators of the human versus extrahuman origins of ExPEC have used both population ecology

Received 23 February 2012; accepted 7 May 2012; electronically published 21 May 2012.

Correspondence: Amee R. Manges, MPH, PhD, Department of Epidemiology, Biostatistics and Occupational Health, 1020 Pine Ave W, McGill University, Montréal, QC H3A 1A2 (amee.manges@mcgill.ca).

Clinical Infectious Diseases 2012;55(5):712–9

© The Author 2012. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/cis502

surveys and experimental pathogenesis studies to examine the host species distribution and ExPEC specificity. 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 and geographic range) have become established and account for the bulk of extraintestinal *E. coli* infections in humans and some domestic animals. More importantly, these extraintestinal disease-causing lineages are becoming increasingly multidrug resistant and, therefore, difficult to treat. Identification of sources or potential reservoirs for these important human-associated ExPEC groups could help to curb their transmission, or, at the very least, to reduce the extent of antimicrobial resistance associated with human ExPEC infections.

One hypothesis that has emerged is that some human-associated ExPEC evolved from, or are the same as, avian pathogenic *E. coli* (APEC), the cause of colibacillosis, an extraintestinal infection in poultry. Extensive genetic similarity has been documented between APEC and ExPEC strains causing disease in poultry and humans, respectively [15–20]. Experimental evidence suggests that APEC can cause disease in mammalian infection models that mimic human ExPEC infections (eg, ascending urinary tract infection [UTI]) [12, 21]; conversely, human-source ExPEC can cause disease in avian disease models [22, 23].

A possible link between human-associated ExPEC and APEC, or *E. coli* derived from poultry, especially chicken, is further supported by the commonality of antimicrobial resistance patterns and/or resistance genes among *E. coli* from these sources [2, 3, 5, 6, 9, 24], and by an epidemiologic association among women with UTI between self-reported chicken consumption and having an antimicrobial-resistant UTI pathogen [8]. Recent studies have identified highly similar extended-spectrum β -lactamase (ESBL)-producing *E. coli* strains in humans and retail chicken products [7, 9]. Likewise, APEC and human-associated ExPEC have been shown to possess overlapping virulence and antimicrobial resistance gene profiles [16, 17, 18, 20, 22, 25]. The minor genetic differences observed between the 2 source groups could be related to recent evolutionary changes associated with host specificity [26].

A likely factor underlying the observed emergence of antimicrobial-resistant *E. coli* strains resembling human ExPEC in food animals, especially poultry, is the disproportionate increase in human consumption of retail chicken during the past 30 years [27]. This has led to changes in the scale and methods of food animal production, including increased use of antimicrobial agents for growth promotion, feed efficiency, infection prevention, and treatment [28]. Multiple lines of evidence indicate that these changes have helped to select for and amplify multidrug-resistant ExPEC [29]. Resistant *E. coli*, once established in food animal reservoirs, can spread among

animals, maintaining the circulation of drug-resistant ExPEC in food animals [29].

The proposed chain of food-borne ExPEC transmission postulates that ExPEC originating from food animals or meat products subclinically colonize the human consumer's intestinal tract and reside there until circumstances favor an extraintestinal infection (eg, sexual intercourse or urinary catheter insertion). The host's own intestinal tract is the conventionally recognized source of the ExPEC that cause human infections [30, 31]. Once an incoming ExPEC strain establishes residence in the intestinal tract, it will be available to cause disease in the subsequent months [32]. The often-lengthy interval between ExPEC acquisition and disease development (if disease even occurs) makes transmission of ExPEC and antimicrobial-resistant *E. coli* from external (eg, food-source) reservoirs to humans difficult to detect.

DEFINING ExPEC LINEAGES

The labels applied to important ExPEC groups have evolved over the decades in relation to the technologies used to identify these groups. Early studies identified 10–15 O antigen-based serogroups (of the approximately 180 that occur in *E. coli*) as being associated with human extraintestinal infections [26, 33]. The addition of K and H antigen typing, resolved more highly homogeneous groups. Recent DNA-based genotyping methods such as multilocus sequence typing (MLST) have further advanced our understanding of these lineages. For consistency, we use labels that combine the group's O:K:H serotype (if known), major *E. coli* phylogenetic group of origin (A, B1, B2, or D), and sequence type (ST), as determined by MLST (for example, O25:H4-B2-ST131). MLST is widely used today to resolve ExPEC lineages because it captures evolutionary relationships among *E. coli* groups and provides consistent results that are easily comparable across laboratories [34]. Although MLST is not as highly discriminatory as certain other genotyping methods, it is useful for regional or global molecular epidemiology studies.

EMERGING ExPEC LINEAGES

We focus on specific lineages of ExPEC, characterized by MLST, that in population-based studies appear to be collectively responsible for a large fraction of human extraintestinal infections. Because many of these groups have come to attention through surveys specifically focused on ESBL-producing *E. coli*, ESBL-producing lineages are overrepresented. Evidence for food reservoirs and transmission routes are presented for each major group, and a summary is provided in Table 1.

***E. coli* O25:H4-B2-ST131**

Initially reported in 2008 as an important new pathogen [35, 36], *E. coli* O25:H4-B2-ST131 is a globally emerging lineage of *E. coli*. It is currently under intense investigation because of its extensive antimicrobial resistance profile, which often includes ESBL production, specifically of CTX-M-15, plus fluoroquinolone resistance. O25:H4-B2-ST131 has been identified primarily from human infections and has been associated with travel, possibly explaining its widespread emergence during the past decade. In surveys of human *E. coli* infections this group accounts for a large fraction of cases overall [37], and up to 88% of antimicrobial-resistant infections, depending on the specific resistance phenotype [38, 39].

Nonhuman intestinal carriage of this group has been reported for wild, companion, and food animals, although the prevalence of human colonization has tended to exceed that of nonhuman animal colonization, as recently reviewed [39, 40]. Indistinguishable *E. coli* O25:H4-B2-ST131 strains have been identified in a human UTI case and retail chicken meat sample in Canada [14]. Mora et al also demonstrated similarity by pulsed field gel electrophoresis (PFGE) and virulence gene content between 1 chicken and 1 human *E. coli* O25:H4-B2-ST131 isolate [41]. ESBL-positive *E. coli* O25:H4-B2-ST131 was also recovered from poultry farms in Spain, with human and poultry O25:H4-B2-ST131 isolates exhibiting moderate (75%) PFGE similarity [42]. Two other studies identified ESBL-positive ST131 *E. coli* among humans but not in chickens or chicken meat [7, 9]. *E. coli* ST131 has been detected in pork and UTI isolates from Denmark and Norway [43].

***E. coli* O11/O17/O77:K52:H18-D-ST69**

E. coli O11/O17/O77:K52:H18-D-ST69 (also termed CgA, for “clonal group A”), members of which express various closely related O antigens, was identified initially in an apparent outbreak of extraintestinal infections in Berkeley, California, during which it accounted for 11% of all UTIs and 52% of antimicrobial-resistant UTIs [44]. It subsequently has been identified around the world, usually as a cause of sporadic human disease [45]. This group often exhibits multidrug resistance and has been responsible for urinary tract and more severe human extraintestinal infections [38, 45–47]. Several studies have confirmed this group as a cause of about 10%–20% of all human *E. coli* infections [45, 48, 49]. 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 [49]. O11/O17/O77:K52:H18-D-ST69 has been linked to nonhuman reservoirs, primarily pork and chicken [12, 14], and possibly beef [50]. 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 food animal-source CgA *E. coli* are just as pathogenic as human-derived CgA strains [2].

***E. coli* Serotype (Various)-A-ST10**

The *E. coli* ST10 clonal complex (ie, ST10 and closely related STs), although commonly encountered as an antimicrobial-susceptible, low-virulence human intestinal colonizer, also has been associated with human infections and ESBL production, including as isolated from human clinical specimens (from hospital and community-acquired infections), meat products, and food animals [42, 51–53]. Specifically, in 1 study from the Netherlands, CTX-M-1–producing ST10 isolates were identified in human blood cultures and poultry, whereas TEM-52–producing ST10 isolates were recovered from human urine samples and poultry [7]. Likewise, a similar study from the Netherlands identified ESBL-producing *E. coli* ST10 in chicken meat, other meat types, rectal swab samples from healthy humans, and human blood cultures [9]. Moreover, a study from Canada identified multidrug-resistant ST10 isolates (albeit of limited PFGE similarity) in human clinical samples, chicken and pig feces, and retail chicken and pork meat [54].

***E. coli* Serotype (Various)-D-ST117**

E. coli ST117 is a recognized APEC lineage [18]. One study identified a human sepsis-associated O111:H4-D-ST117 ExPEC strain that resembled known APEC strains [18]. Likewise, the 2 above-mentioned studies from the Netherlands linking *E. coli* ST10 isolates from human and poultry reservoirs also identified ESBL-producing ST117 *E. coli* in these reservoirs [7, 9]. Closely related O114:H4-ST117 strains also have been identified in a human UTI case and in retail chicken meat in Canada [14].

***E. coli* O1/O2/O18:K1:H7-B2-ST95**

E. coli O1/O2/O18:K1:H7-B2-ST95, a recognized APEC clonal group [55] and prominent human pathogen, caused 6% of human extraintestinal infections in 1 study [56]. *E. coli* O1/O2/O18:K1:H7-B2-ST95 isolates with related PFGE profiles have been identified in humans and poultry [14, 17] and, separately, in honeydew melon and multiple human infections [14]. In another study, within a cluster of 108 APEC and human ExPEC isolates from serogroups O1, O2, or O18, 58% of isolates, representing diverse host species, belonged to ST95 [25]. When assessed in animal models, O18-B2-ST95 *E. coli* isolates from human neonates with meningitis could cause colisepticemia in poultry [22]; conversely, O18-B2-ST95 *E. coli* isolates

from cases of avian colibacillosis (APEC) could cause neonatal meningitis in a rat model [21]. This indicated that the APEC- and neonatal meningitis *E. coli*-associated ST95 group may have zoonotic potential.

OTHER IMPORTANT HUMAN ExPEC GROUPS WITHOUT KNOWN FOOD ANIMAL ASSOCIATIONS

E. coli O15:K52:H1-D-ST393 was first recognized during an outbreak of extraintestinal infections in 1986–1987 in London, United Kingdom [57], and has since been identified elsewhere in Europe [58, 59] and globally [60]. In the initial epidemic, O15:K52:H1 caused 26% of all extraintestinal infections during a 1-year interval [37, 57]. This group is typically multidrug resistant and has caused community-acquired extraintestinal infections of all types [57, 59, 61, 62]. No available evidence supports the existence of food animal reservoirs for O15:K52:H1-ST393, and investigations during the London outbreak failed to identify a source [63]. This group is closely related to O11/O17/O77:K52:H18-D-ST69; both groups commonly possess similar antimicrobial resistance and virulence factor patterns and appear to share a common ancestor [63, 64].

E. coli O6:H1-B2-ST73 was recently reported as a leading cause (17% overall) of human extraintestinal infections in the UK [56]. This group, like many others, is associated occasionally with ESBL production [56, 65, 66]. It may represent a long-standing, human-adapted ExPEC group, because it has caused UTIs in women from widely separated geographic areas over many years [67]. To date, no food animal reservoirs for this group have been reported.

E. coli serotype (Various)-D-ST405 is another globally disseminated, extensively antimicrobial-resistant group [35]. ST405 may be the second most common contributor to the global dissemination of CTX-M-15 after ST131 [35]. Furthermore, an ST405 *E. coli* isolate was recently encountered that produced multiple ESBLs, including QepA1, CTX-M-15, and RmtB [68]. ST405 has been associated with person-to-person transmission in 1 study [69]. Evidence for nonhuman reservoirs is still lacking, suggesting that this group also may exist exclusively among humans [67].

E. coli O75:K + :H5-B2-ST14, a historically important ampicillin-resistant group, has recently been associated with fluoroquinolone resistance in Australia [70]. Although this group recently has been identified in pet dogs, no food or food animal reservoir has yet been demonstrated [70].

Accumulating evidence indicates that certain prominent ExPEC groups can occur in nonhuman sources, including food animals and retail meat products, although the extent of this phenomenon, its importance to human health, and the strength of the evidence vary by source and *E. coli* group.

These major lineages are implicated repeatedly as causing a large proportion of human extraintestinal infections. Since many are multidrug resistant, they probably contribute significantly to the ongoing population-level increase in antimicrobial-resistant human *E. coli* infections. For example, in a recent study, just 3 clonal groups (O25:H4-B2-ST131, O15: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, and for 30% of multidrug-resistant isolates [38].

Similarities between human ExPEC and *E. coli* recovered from poultry and pigs, and from retail chicken, turkey, and pork products, suggest a possible role for a food animal reservoir. Although transmission of ExPEC has been documented between cohabiting humans and between companion animals and humans [32, 71–74], transmission of ExPEC from food animals or retail meats to humans has yet to be directly demonstrated. However, members of at least 4 of the above-mentioned high-prevalence ExPEC groups have been identified in nonhuman reservoirs, with the main such source being food animals, specifically chickens and pigs.

Additionally, the plausibility of food-borne transmission of antimicrobial-resistant *E. coli* to humans is supported 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 [75, 76]. Furthermore, volunteers fed a diet of irradiated food exhibited markedly reduced levels of antimicrobial-resistant intestinal *E. coli*, with reversion to baseline after intervention [77], implying that a conventional diet sustains the baseline prevalence of intestinal resistant *E. coli* through a steady input of food-borne resistant organisms. Thus, the available evidence, albeit indirect, strongly supports a food-borne component to the antimicrobial-resistant *E. coli* problem in humans.

The above-mentioned food-animal-associated ExPEC groups typically exhibit multidrug resistance. This probably occurs because they and other animal-associated *E. coli* are subjected to frequent or continuous selection pressure for antimicrobial resistance within the food animal reservoir, due to extensive antimicrobial use during food animal production [78]. Human antimicrobial use provides additional selection pressure once these organisms enter the human population. Thus, the global increase of antimicrobial resistance among human-associated ExPEC likely has multiple ecologic origins, with contributions from the transmission of antimicrobial resistant ExPEC from food animals, companion animals, and environmental sources to humans after amplification in these selection reservoirs, followed by further amplification in humans [79].

From a public health perspective, what can be done? Certainly, antimicrobial stewardship is important for reducing the selection pressure for antimicrobial resistance in food animals

Table 1. Antimicrobial Resistance and Food Animal Reservoir Summary for Major Human Extraintestinal Pathogenic *Escherichia coli* Groups

Human ExPEC Groups	Associated Characteristics and Food Animal Sources					
	Antimicrobial Resistance	ESBL Production	Poultry	Pork/Pigs	Beef/Cattle	No Known Food Animal Reservoir
O25:H4-B2-ST131	✓	✓	✓			
O11/O17/O77:K52:H18-D-ST69	✓		✓	✓	✓	
O15:K52:H1-D-ST393	✓					
Serotype (Various)-A-ST10 ^a	✓	✓	✓	✓		
Serotype (Various)-D-ST117	✓	✓	✓			
O1/O2/O18:K1:H7-B2-ST95	✓	✓	✓			
O6:H1-B2-ST73	✓	✓				✓
Serotype (Various)-D-ST405	✓	✓				✓
O75:K + :H5-B2-ST14	✓					✓

This table summarizes general information available on these groups from the literature. It is not exhaustive and does not distinguish the quantity or quality of the data.

Abbreviations: ESBL; extended-spectrum β -lactamase; ExPEC, extraintestinal pathogenic *Escherichia coli*.

^a Many *E. coli* ST10 strains are not ExPEC; those that are ExPEC tend to be extensively antimicrobial resistant.

and other relevant selection environments. Antimicrobial usage in food animals varies widely throughout Europe, despite the 2006 European Union antimicrobial growth promoter ban [80]. However, given the linkage of multiple resistance genes and the inescapable need for antimicrobial use in some circumstances, in humans and animals alike, stewardship may at best be 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 food production use of antimicrobials classified as very important to human medicine (eg, 3rd generation cephalosporins) [81] to reduce antimicrobial resistance, but this is not always a straightforward or successful approach (eg, the ban on fluoroquinolone use in poultry) [82]. 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 virulence properties that contribute to their ability to cause extraintestinal disease, in humans and animals alike. They also must have characteristics promoting their survival within specific reservoirs (eg, in avian hosts) and widespread dissemination among human hosts. Indeed, distinguishing between genes associated with “virulence”—versus “fitness” and versus “colonization”—can be difficult [83]. Whereas some ExPEC lineages can be traced far back in time and are well established as perennial extraintestinal pathogens [37], new ExPEC lineages continuously emerge [84]. Elucidation of the factors that make certain ExPEC groups so successful could identify good candidate vaccine targets, which could be particularly suitable for use in the animal hosts that act as reservoirs [85].

It is important to elucidate the transmission dynamics of the main recognized ExPEC groups, which are key contributors to human extraintestinal *E. coli* disease. Understanding these organisms’ reservoirs, chain of transmission, and epidemiologic associations will go a long way toward finding ways to reduce the associated disease burden. There are inherent limitations to ecologic studies comparing ExPEC from multiple sources. Determining the direction of transmission (from animals to human or vice versa) and pinpointing actual transmission events has been difficult. However, despite these limitations, the greater public health community should heed the growing body of evidence supporting food-borne transmission, and should implement policies and practices that would meaningfully limit the evolution, selection and amplification, and dissemination of antimicrobial-resistant ExPEC from food animals to humans.

Notes

Financial support. This work was supported by funds from the Canadian Institutes of Health Research (to A. R. M.) and the Office of Research and Development, Medical Research Service, Department of Veterans Affairs (to J. R. J.).

Potential conflicts of interest. A. R. M. reports receiving research funds from Pfizer. J. R. J. reports receiving research funds from Merck, Rochester Medical, and Syntiron.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Russo TA, Johnson JR. Medical and economic impact of extraintestinal infections due to *Escherichia coli*: focus on an increasingly important endemic problem. *Microbes Infect* 2003; 5:449–56.

2. Jakobsen L, Hammerum AM, Frimodt-Møller N. Detection of clonal group A *Escherichia coli* isolates from broiler chickens, broiler chicken meat, community-dwelling humans, and urinary tract infection (UTI) patients and their virulence in a mouse UTI model. *Appl Environ Microbiol* **2010**; 76:8281–4.
3. Jakobsen L, Spangholm DJ, Pedersen K, et al. Broiler chickens, broiler chicken meat, pigs and pork as sources of ExPEC related virulence genes and resistance in *Escherichia coli* isolates from community-dwelling humans and UTI patients. *Int J Food Microbiol* **2010**; 142:264–72.
4. Johnson JR, Delavari P, O'Bryan TT, Smith KE, Tatini S. Contamination of retail foods, particularly turkey, from community markets (Minnesota, 1999–2000) with antimicrobial-resistant and extraintestinal pathogenic *Escherichia coli*. *Foodborne Pathog Dis* **2005**; 2:38–49.
5. Johnson JR, Kuskowski MA, Menard M, Gajewski A, Xercavins M, Garau J. Similarity between human and chicken *Escherichia coli* isolates in relation to ciprofloxacin resistance status. *J Infect Dis* **2006**; 194:71–8.
6. Johnson TJ, Jordan D, Kariyawasam S, et al. Sequence analysis and characterization of a transferable hybrid plasmid encoding multidrug resistance and enabling zoonotic potential for extraintestinal *Escherichia coli*. *Infect Immun* **2010**; 78:1931–42.
7. Leverstein-van Hall MA, Dierikx CM, Cohen Stuart J, et al. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. *Clin Microbiol Infect* **2011**; 17:873–80.
8. Manges AR, Smith SP, Lau BJ, et al. Retail meat consumption and the acquisition of antimicrobial resistant *Escherichia coli* causing urinary tract infections: a case-control study. *Foodborne Pathog Dis* **2007**; 4:419–31.
9. Overdeest I, Willemsen I, Rijnsburger M, et al. Extended-spectrum β -lactamase genes of *Escherichia coli* in chicken meat and humans, The Netherlands. *Emerg Infect Dis* **2011**; 17:1216–22.
10. Department of Health and Human Services. NARMS Retail Meat Annual Report. Food and Drug Administration; **2010**. Available at: <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm293578.htm>. Accessed 18 March 2012.
11. Government of Canada. Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS), 2008. Guelph, Ontario: Public Health Agency of Canada; **2009**. Available at: <http://www.phac-aspc.gc.ca/cipars-picra/2008/index-eng.php>. Accessed 18 March 2012.
12. Jakobsen L, Garneau P, Bruant G, et al. Is *Escherichia coli* urinary tract infection a zoonosis? Proof of direct link with production animals and meat. *Eur J Clin Microbiol Infect Dis* **2011**; 1–9.
13. Johnson JR, Kuskowski MA, Smith K, O'Bryan TT, Tatini S. Antimicrobial-resistant and extraintestinal pathogenic *Escherichia coli* in retail foods. *J Infect Dis* **2005**; 191:1040–9.
14. Vincent C, Boerlin P, Daignault D, et al. Food reservoir for *Escherichia coli* causing urinary tract infections. *Emerg Infect Dis* **2010**; 16:88–95.
15. Johnson TJ, Logue CM, Johnson JR, et al. Associations between multidrug resistance, plasmid content, and virulence potential among extraintestinal pathogenic and commensal *Escherichia coli* from humans and poultry. *Foodborne Pathog Disease* **2012**; 9:37–46.
16. Johnson TJ, Kariyawasam S, Wannemuehler Y, et al. The genome sequence of avian pathogenic *Escherichia coli* strain O1:K1:H7 shares strong similarities with human ExPEC genomes. *J Bacteriol* **2007**; 189:4554.
17. Mora A, Lopez C, Dabhi G, et al. Extraintestinal pathogenic *Escherichia coli* O1:K1:H7/NM from human and avian origin: detection of clonal groups B2 ST95 and D ST59 with different host distribution. *BMC Microbiol* **2009**; 9:132.
18. Mora A, Lopez C, Herrera A, et al. Emerging avian pathogenic *Escherichia coli* strains belonging to clonal groups O111:H4-D-ST2085 and O111:H4-D-ST117 with high virulence-gene content and zoonotic potential. *Vet Microbiol* **2011**; 156:347–52.
19. Moulin-Schouleur M, Schouleur C, Tailliez P, et al. Common virulence factors and genetic relationships between O18:K1:H7 *Escherichia coli* isolates of human and avian origin. *J Clin Microbiol* **2006**; 44:3484–92.
20. Rodriguez-Siek KE, Giddings CW, Doetkott C, Johnson TJ, Fakhr MK, Nolan LK. Comparison of *Escherichia coli* isolates implicated in human urinary tract infection and avian colibacillosis. *Microbiology* **2005**; 151:2097–110.
21. Tivendale KA, Logue CM, Kariyawasam S, et al. Avian-pathogenic *Escherichia coli* strains are similar to neonatal meningitis *E. coli* strains and are able to cause meningitis in the rat model of human disease. *Infect Immun* **2010**; 78:3412–9.
22. Moulin-Schouleur M, Répérant M, Laurent S, et al. Extraintestinal pathogenic *Escherichia coli* strains of avian and human origin: link between phylogenetic relationships and common virulence patterns. *J Clin Microbiol* **2007**; 45:3366–76.
23. Skyberg JA, Johnson TJ, Johnson JR, Clabots C, Logue CM, Nolan LK. Acquisition of avian pathogenic *Escherichia coli* plasmids by a commensal *E. coli* isolate enhances its abilities to kill chick embryos, grow in human urine, and colonize the murine kidney. *Infect Immun* **2006**; 74:6287–92.
24. Brinas L, Moreno MA, Zarazaga M, et al. Detection of CMY-2, CTX-M-14, and SHV-12 β -Lactamases in *Escherichia coli* fecal-sample isolates from healthy chickens. *Antimicrob Agents Chemother* **2003**; 47:2056–8.
25. Johnson TJ, Wannemuehler Y, Johnson SJ, et al. Comparison of extraintestinal pathogenic *Escherichia coli* strains from human and avian sources reveals a mixed subset representing potential zoonotic pathogens. *Appl Environ Microbiol* **2008**; 74:7043–50.
26. Bettelheim KA, Ismail N, Shinbaum R, Shooter RA, Moorhouse E, Farrell W. The distribution of serotypes of *Escherichia coli* in cow-pats and other animal material compared with serotypes of *E. coli* isolated from human sources. *J Hyg (Lond)* **1976**; 76:403–6.
27. Lawrence J. Long Term Meat Production and Consumption Trends. **2006**. Available at: <http://www.thepoultrysite.com/articles/527/long-term-meat-production-and-consumption-trends>. Accessed 18 March 2012.
28. Committee on Drug Use in Food Animals, Panel on Animal Health FSAPI, National Research Council. The use of drugs in food animals: benefits and risks. Washington D.C.: National Academies Press; **1999**.
29. Aarestrup FM, Wegener HC, Collignon P. Resistance in bacteria of the food chain: epidemiology and control strategies. *Expert Rev Anti Infect Ther* **2008**; 6:733–50.
30. Caugant DA, Levin BR, Lidin-Janson G, Whittam TS, Svanborg Eden C, Selander RK. Genetic diversity and relationships among strains of *Escherichia coli* in the intestine and those causing urinary tract infections. *Prog Allergy* **1983**; 33:203–27.
31. Yamamoto S, Tsukamoto T, Terai A, Kurazono H, Takeda Y, Yoshida O. Genetic evidence supporting the fecal-perineal-urethral hypothesis in cystitis caused by *Escherichia coli*. *J Urol* **1997**; 157:1127–9.
32. Manges AR, Johnson JR, Riley LW. Intestinal population dynamics of UTI-causing *Escherichia coli* within heterosexual couples. *Curr Issues Intest Microbiol* **2004**; 5:49–57.
33. Bettelheim KA. *E. coli* in the normal flora of humans and animals. In: Sussman M, ed. *Escherichia coli: mechanisms of virulence*. Cambridge: Cambridge University Press, **1997**:85–109.
34. Maiden MC, Bygraves JA, Feil E, et al. Multilocus sequence typing: a portable approach to the identification of clones within populations of pathogenic microorganisms. *Proc Natl Acad Sci U S A* **1998**; 95:3140–5.
35. Coque TM, Novais A, Carattoli A, et al. Dissemination of clonally related *Escherichia coli* strains expressing extended-spectrum beta-lactamase CTX-M-15. *Emerg Infect Dis* **2008**; 14:195–200.
36. Nicolas-Chanoine MH, Blanco J, Leflon-Guibout V, et al. Intercontinental emergence of *Escherichia coli* clone O25:H4-ST131 producing CTX-M-15. *J Antimicrob Chemother* **2008**; 61:273–81.
37. George DB, Manges AR. A systematic review of outbreak and non-outbreak studies of extraintestinal pathogenic *Escherichia coli* causing community-acquired infections. *Epidemiol Infect* **2010**; 138:1679–90.
38. Blanco J, Mora A, Mamani R, et al. National survey of *Escherichia coli* causing extraintestinal infections reveals the spread of drug-resistant

- clonal groups O25b:H4-B2-ST131, O15:H1-D-ST393 and CGA-D-ST69 with high virulence gene content in Spain. *J Antimicrob Chemother* **2011**; 66:2011–21.
39. Rogers BA, Sidjabat HE, Paterson DL. *Escherichia coli* O25b-ST131: a pandemic, multiresistant, community-associated strain. *J Antimicrob Chemother* **2011**; 66:1–14.
 40. Platell JL, Johnson JR, Cobbold RN, Trott DJ. Multidrug-resistant extraintestinal pathogenic *Escherichia coli* of sequence type ST131 in animals and foods. *Veterinary Microbiology* **2011**; 153:99–108.
 41. Mora A, Herrera A, Mamani R, et al. Recent emergence of clonal group O25b:K1:H4-B2-ST131 ibeA strains among *Escherichia coli* poultry isolates, including CTX-M-9-producing strains, and comparison with clinical human isolates. *Appl Environ Microbiol* **2010**; 76:6991–7.
 42. Cortes P, Blanc V, Mora A, et al. Isolation and characterization of potentially pathogenic antimicrobial-resistant *Escherichia coli* strains from chicken and pig farms in Spain. *Appl Environ Microbiol* **2010**; 76:2799–805.
 43. Trobos M, Christensen H, Sunde M, et al. Characterization of sulphonamide-resistant *Escherichia coli* using comparison of sul2 gene sequences and multilocus sequence typing. *Microbiology* **2009**; 155: 831–6.
 44. Manges AR, Johnson JR, Foxman B, O'Bryan TT, Fullerton KE, Riley LW. Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group. *N Engl J Med* **2001**; 345:1007–13.
 45. Johnson JR, Murray AC, Kuskowski MA, et al. Distribution and characteristics of *Escherichia coli* clonal group A. *Emerg Infect Dis* **2005**; 11:141–5.
 46. Johnson JR, Manges AR, O'Bryan TT, Riley LW. A disseminated multidrug-resistant clonal group of uropathogenic *Escherichia coli* in pyelonephritis. *Lancet* **2002**; 359:2249–51.
 47. Manges AR, Perdreaux-Remington F, Solberg O, Riley LW. Multidrug-resistant *Escherichia coli* clonal groups causing community-acquired bloodstream infections. *J Infect* **2006**; 53:25–9.
 48. Dias RCS, Marangoni DV, Smith SP, et al. Clonal composition of *Escherichia coli* causing community-acquired urinary tract infections in the State of Rio de Janeiro, Brazil. *Microb Drug Resist* **2009**; 15:303–8.
 49. Johnson JR, Menard ME, Lauderdale TL, et al. Global distribution and epidemiologic associations of *Escherichia coli* clonal group A, 1998–2007. *Emerg Infect Dis* **2011**; 17:2001–9.
 50. Ramchandani M, Manges AR, DeRoy C, Smith SP, Johnson JR, Riley LW. Possible animal origin of human-associated, multidrug-resistant, uropathogenic *Escherichia coli*. *Clin Infect Dis* **2005**; 40:251–7.
 51. Oteo J, Diestra K, Juan C, et al. Extended-spectrum β -lactamase-producing *Escherichia coli* in Spain belong to a large variety of multilocus sequence typing types, including ST10 complex/A, ST23 complex/A and ST131/B2. *Int J Antimicrob Agents* **2009**; 34:173–6.
 52. Peirano G, van der Bij AK, Gregson DB, Pitout JDD. Molecular epidemiology over an 11-Year Period (2000 to 2010) of extended-spectrum β -lactamase-producing *Escherichia coli* causing bacteremia in a centralized Canadian region. *J Clin Microbiol* **2012**; 50:294–9.
 53. Cohen Stuart J, van den Munckhof T, Voets G, Scharringa J, Fluit A, Hall ML-V. Comparison of ESBt contamination in organic and conventional retail chicken meat. *Int J Food Microbiol* **2012**; 154:212–4.
 54. Racicot Bergeron C, Prussing C, Boerlin P, et al. Chicken as reservoir for human extraintestinal pathogenic *Escherichia coli*, Canada. *Emerg Infect Dis* **2012**; 18:415–21.
 55. Antão EM, Ewers C, Gürlebeck D, et al. Signature-tagged mutagenesis in a chicken infection model leads to the identification of a novel avian pathogenic *Escherichia coli* fimbrial adhesin. *PLoS One* **2009**; 4: e7796.
 56. Gibreel TM, Dodgson AR, Cheesbrough J, Fox AJ, Bolton FJ, Upton M. Population structure, virulence potential and antibiotic susceptibility of uropathogenic *Escherichia coli* from Northwest England. *J Antimicrob Chemother* **2012**; 67:346–56.
 57. Phillips I, King A, Rowe B, et al. Epidemic multiresistant *Escherichia coli* infection in West Lambeth Health District. *Lancet* **1988**; 8593:1038–41.
 58. Olesen B, Kolmos HJ, Orskov F, Orskov I. A comparative study of nosocomial and community-acquired strains of *Escherichia coli* causing bacteraemia in a Danish University Hospital. *J Hospital Infect* **1995**; 31:295–304.
 59. Prats G, Navarro F, Mirelis B, et al. *Escherichia coli* serotype O15:K52:H1 as a uropathogenic clone. *J Clin Microbiol* **2000**; 38:201–9.
 60. Johnson JR, Stell AL, O'Bryan TT, et al. Global molecular epidemiology of the O15:K52:H1 extraintestinal pathogenic *Escherichia coli* clonal group: evidence of distribution beyond Europe. *J Clin Epidemiol* **2002**; 40:1913–23.
 61. Neil PMO, Talboys CA, Roberts AP, Azadian BS. The rise and fall of *Escherichia coli* O15 in a London Teaching Hospital. *J Med Microbiol* **1990**; 33:23–7.
 62. Olesen B, Scheutz F, Menard M, et al. Three-decade epidemiological analysis of *Escherichia coli* O15:K52:H1. *J Clin Microbiol* **2009**; 47: 1857–62.
 63. Johnson JR, Kuskowski MA, Owens K, Gajewski A, Winokur PL. Phylogenetic origin and virulence genotype in relation to resistance to fluoroquinolones and/or extended-spectrum cephalosporins and cephamycins among *Escherichia coli* isolates from animals and humans. *J Infect Dis* **2003**; 188:759–68.
 64. Johnson JR, Owens KL, Clabots CR, Weissman SJ, Cannon SB. Phylogenetic relationships among clonal groups of extraintestinal pathogenic *Escherichia coli* as assessed by multi-locus sequence analysis. *Microbes Infect* **2006**; 8:1702–13.
 65. Fam N, Leflon-Guibout V, Fouad S, et al. CTX-M-15-producing *Escherichia coli* clinical isolates in Cairo (Egypt), including isolates of clonal complex ST10 and clones ST131, ST73, and ST405 in both community and hospital settings. *Microb Drug Resist* **2011**; 17:67–73.
 66. Suzuki S, Shibata N, Yamane K, Wachino Ji, Ito K, Arakawa Y. Change in the prevalence of extended-spectrum- β -lactamase-producing *Escherichia coli* in Japan by clonal spread. *J Antimicrob Chemother* **2009**; 63:72–9.
 67. Manges AR, Tabor H, Tellis P, Vincent C, Tellier PP. Endemic and epidemic lineages of *Escherichia coli* that cause urinary tract infections. *Emerg Infect Dis* **2008**; 14:1575–83.
 68. Tian GB, Rivera JI, Park YS, et al. Sequence type ST405 *Escherichia coli* isolate producing QepA1, CTX-M-15, and RmtB from Detroit, Michigan. *Antimicrob Agents Chemother* **2011**; 55:3966–7.
 69. Mihaila L, Wyplosz B, Clermont O, et al. Probable intrafamily transmission of a highly virulent CTX-M-3-producing *Escherichia coli* belonging to the emerging phylogenetic subgroup D2 O102-ST405 clone. *J Antimicrob Chemother* **2010**; 65:1537–9.
 70. Platell JL, Trott DJ, Johnson JR, et al. Prominence of an O75 clonal group (clonal complex 14) among non-ST131 fluoroquinolone-resistant *Escherichia coli* causing extraintestinal infections in humans and dogs in Australia [published online ahead of print 23 April 2012]. *Antimicrob Agents Chemother* **2012**.
 71. Foxman B, Zhang L, Tallman P, et al. Transmission of uropathogens between sex partners. *J Infect Dis* **1997**; 175:989–92.
 72. Johnson JR, Stell AL, Delavari P. Canine feces as a reservoir of extraintestinal pathogenic *Escherichia coli*. *Infect Immun* **2001**; 69:1306–14.
 73. Johnson JR, Clabots C. Sharing of virulent *Escherichia coli* clones among household members of a woman with acute cystitis. *Clin Infect Dis* **2006**; 43:e101–8.
 74. Johnson JR, Clabots C, Kuskowski MA. Multiple-host sharing, long-term persistence, and virulence of *Escherichia coli* clones from human and animal household members. *J Clin Microbiol* **2008**; 46:4078–82.

75. Cogan TA, Bloomfield SF, Humphrey TJ. The effectiveness of hygiene procedures for prevention of cross-contamination from chicken carcasses in the domestic kitchen. *Lett Appl Microbiol* **1999**; 29:354–8.
76. Linton AH, Howe K, Bennett PM, Richmond MH, Whiteside EJ. The colonization of the human gut by antibiotic resistant *Escherichia coli* from chickens. *J Appl Bacteriol* **1977**; 43:465–9.
77. Corpet DE. Antibiotic resistance from food. *N Engl J Med* **1988**; 318:1206–7.
78. Threlfall EJ, Ward LR, Frost JA, Willshaw GA. Spread of resistance from food animals to man—the UK experience. *Acta Vet Scand Suppl* **2000**; 93:63–8.
79. Levy SB, FitzGerald GB, Macone AB. Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. *N Engl J Med* **1976**; 295:583–8.
80. Grave K, Torren-Edo J, Mackay D. Comparison of the sales of veterinary antibacterial agents between 10 European countries. *J Antimicrob Chemother* **2010**; 65:2037–40.
81. Gilbert N. Rules tighten on use of antibiotics on farms. *Nature* **2012**; 481:125.
82. Price LB, Lackey LG, Vailes R, Silbergeld E. The persistence of fluoroquinolone-resistant *Campylobacter* in poultry production. *Environ Health Perspect* **2007**; 115:1035–9.
83. Pitout JDD. Extraintestinal pathogenic *Escherichia coli*: a combination of virulence with antibiotic resistance. *Frontiers in Microbiology* **2012**; 3:1–7.
84. Mora A, Blanco M, Lopez C, et al. Emergence of clonal groups O1: HNM-D-ST59, O15:H1-D-ST393, O20:H34/HNM-D-ST354, O25b: H4-B2-ST131 and ONT:H21,42-B1-ST101 among CTX-M-14-producing *Escherichia coli* clinical isolates in Galicia, northwest Spain. *Int J Antimicrob Agents* **2011**; 37:16–21.
85. Moriel DG, Bertoldi I, Spagnuolo A, et al. Identification of protective and broadly conserved vaccine antigens from the genome of extraintestinal pathogenic *Escherichia coli*. *Proc Natl Acad Sci U S A* **2010**; 107:9072–7.