Human and Avian Extraintestinal Pathogenic *Escherichia coli*: Infections, Zoonotic Risks, and Antibiotic Resistance Trends

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Abstract

Extraintestinal pathogenic *Escherichia coli* (ExPEC) constitutes ongoing health concerns for women, newborns, elderly, and immunocompromised individuals due to increased numbers of urinary tract infections (UTIs), newborn meningitis, abdominal sepsis, and septicemia. *E. coli* remains the leading cause of UTIs, with recent investigations reporting the emergence of *E. coli* as the predominant cause of nosocomial and neonatal sepsis infections. This shift from the traditional Gram-positive bacterial causes of nosocomial and neonatal sepsis infections could be attributed to the use of intrapartum chemoprophylaxis against Gram-positive bacteria and the appearance of antibiotic (ATB) resistance in *E. coli*. While ExPEC strains cause significant healthcare concerns, these bacteria also infect chickens and cause the poultry industry economic losses due to costs of containment, mortality, and disposal of carcasses. To circumvent ExPEC-related costs, ATBs are commonly used in the poultry industry to prevent/treat microbial infections and promote growth and performance. In an unfortunate linkage, chicken products are suspected to be a source of foodborne ExPEC infections and ATB resistance in humans. Therefore, the emergence of multidrug resistance (MDR) (resistance to three or more classes of antimicrobial agents) among avian *E. coli* has created major economic and health concerns, affecting both human healthcare and poultry industries. Increased numbers of immunocompromised individuals, including the elderly, coupled with MDR among ExPEC strains, will continue to challenge the treatment of ExPEC infections and likely lead to increased treatment costs. With ongoing complications due to emerging ATB resistance, novel treatment strategies are necessary to control ExPEC infections. Recognizing and treating the zoonotic risk posed by ExPEC would greatly enhance food safety and positively impact human health.
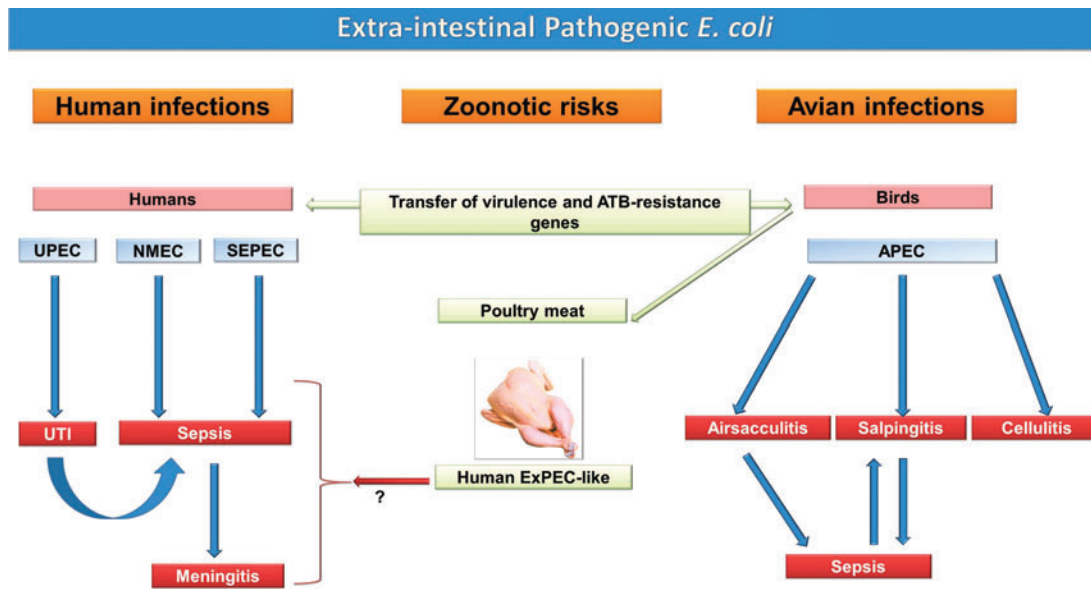
Introduction

THE NUMBER OF EXTRAINTESTINAL pathogenic *Escherichia coli* (ExPEC) infections with higher case fatality rates are dramatically increasing worldwide, leading to a tremendous burden on public health (Pitout, 2012). In addition to causing human diseases, ExPEC strains are responsible for significant economic losses in animal production, particularly within the poultry industry (Barnes *et al.*, 2003), one of the fastest growing industries in the United States and worldwide.

Recently, numerous studies have highlighted similarities between human and avian ExPEC, particularly in their virulence genes, suggesting that poultry products could serve as a source of ExPEC that causes sepsis infections in humans (Manges and Johnson, 2012) (Fig. 1). Since poultry meat exhibits the highest overall levels of *E. coli* contamination, and *E. coli* strains isolated from poultry are often more extensively multidrug resistant (MDR) than *E. coli* recovered from other meats (Manges and Johnson, 2012), the increased poultry meat consumption worldwide could have contributed to the appearance of antibiotic (ATB) resistance in ExPEC and the emergence of ExPEC infections in humans (Pitout, 2012). Global trades and travels also contribute to the worldwide spread of these infections (van der Bij and Pitout, 2012), thus making it difficult to implement infection-control measures.

Although ExPEC infections have previously been easily treatable with ATB therapy, traditional treatment regimens are currently challenged by the appearance of ATB-resistant strains. Developing alternative strategies to prevent/eliminate these ExPEC infections requires fully understanding the virulence and zoonotic risk, as well as the constant epidemiological surveillance of ATB-resistance trends of these bacteria in both humans and animals. The goal of this review is to summarize the importance of ExPEC infections in humans and chickens, their zoonotic risks, and the current trends in ExPEC ATB resistance.

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FIG. 1. Avian and human extraintestinal pathogenic *Escherichia coli* (ExPEC), their infections, and zoonotic potential. The schematic diagram illustrates the major ExPEC pathotypes and their infections in humans and birds. ExPEC can cause localized infections that can become systemic (urinary tract infection [UTI] in humans and airsacculitis in birds), a systemic infection that localizes (meningitis), both a local and systemic infection (salpingitis in birds), or localized only (cellulitis in birds). The diagram also shows the potential of poultry and their products to transfer antibiotic (ATB) resistance and ExPEC to humans and cause zoonotic diseases. UPEC, uropathogenic *Escherichia coli*; NMEC, neonatal meningitis *E. coli*; SEPEC, sepsis *E. coli*; APEC, avian pathogenic *E. coli*. Color images available online at www.liebertpub.com/fpd

General Characteristics of ExPEC

ExPEC strains have acquired specific virulence attributes that confer an ability to survive in different niches outside of their normal intestinal habitat in both mammals and birds. ExPEC are phylogenetically distinct from commensal and intestinal pathogenic *E. coli*. There are four main phylogenetic groups of *E. coli*: A, B1, B2, and D. ExPEC strains belong mainly to group B2, with some located in group D (Smith *et al.*, 2007). Phylogenic group B2 is the most predominant and the most virulent in most cases of ExPEC infections. ExPEC possess virulence factors required for extraintestinal infections (Smith *et al.*, 2007), with some virulence factors more specific to certain ExPEC groups, such as Tsh and ColV plasmids in avian pathogenic *E. coli* (APEC), K1 capsule in neonatal meningitis *E. coli* (NMEC), and Sat and Usp in uropathogenic *E. coli* (UPEC) (Table 1). This provides strong evidence that certain genetic backgrounds are required for the acquisition and expression of certain virulence factors.

ExPEC are generally very diverse, with few common virulence factors between them (Mokady *et al.*, 2005). These findings imply that strains utilize different factors for similar roles during various stages of the infection process (Mellata *et al.*, 2003; Mokady *et al.*, 2005). However, other virulence factors that have not yet been identified in ExPEC and host–pathogen interaction could have a significant role in the pathogenesis of these bacteria. This assortment of virulence genes is apparently made possible by a variety of genetic factors contributing to genome plasticity, including plasmids (Mellata *et al.*, 2010).

Early research studies of ExPEC did not establish a link between *E. coli* causing disease in humans and birds. Thus,

human ExPEC and APEC were investigated separately, as two different groups, with regard to virulence and respective hosts. Meanwhile, the virulence of APEC has been underestimated, with APEC considered an opportunistic pathogen, causing only secondary infections that are predisposed by biological and environmental stresses (Barnes *et al.*, 2003). More recently, the virulence status of APEC has been reassigned by studies demonstrating significant differences in the distribution of virulence factors among *E. coli* strains isolated from chickens with colibacillosis and those from feces of healthy chickens (Johnson *et al.*, 2012; Schouler *et al.*, 2012). Genotypic and phylogenic comparison of *E. coli* from clinical cases of colibacillosis with avian fecal *E. coli* (Ewers *et al.*, 2005; Johnson *et al.*, 2008a; Schouler *et al.*, 2012), as well as with human pathogenic *E. coli* strains (Ewers *et al.*, 2005), using a large number of isolates, has identified characteristic virulence traits that could predict the APEC subgroup. The implication of many of these virulence factors in the avian pathogenesis using experimental infection models (Dziva, 2010), and the *in vivo* expression of multiple virulence factors associated with APEC confirm their importance in the infection process in chickens (Dozois *et al.*, 2003; Tuntufye *et al.*, 2012; Dziva *et al.*, 2013).

Contrary to human ExPEC, which have been categorized into different subpathotypes based on their ability to cause different disease syndromes and virulence genes, APEC is commonly designated as a single, heterogeneous population (Fig. 1). However, lately, some studies have suggested that APEC could also be subdivided into multiple subtypes based on their pathology and virulence factors (Maturana *et al.*, 2011; Olsen *et al.*, 2011; Pires-Dos-Santos *et al.*, 2013), and their infections can lead to diverse pathogenic phenotypes and

TABLE 1. TRAITS DETERMINED TO BE ASSOCIATED WITH VIRULENCE OF EXTRAINTESTINAL PATHOGENIC *ESCHERICHIA COLI* (ExPEC) SUBGROUPS (BIEN *ET AL.*, 2012; BONACORSI AND BINGEN, 2005; DZIVA AND STEVENS, 2008; JOHNSON AND RUSSO, 2005; KIM, 2012)

ExPEC	Serogroups	Phylo-genetic group	Virulence factors[a]				
			Adhesins/ fimbriae	Iron uptake	Toxins	Protectins/ invasins	Others
APEC	O1, O2, O78, O18	A, B1, B2, D	Type 1 P AC/1 Stg curli	Aerobactin Salmochelin	VAT-PAI ECVF	K1 capsule LPS O78 TraT Iss IbeA, IbeB	ColV plasmid Tsh
UPEC	O1, O2, O4, O6, O18, O75	B2, D	Type 1 P Dr Afa S F1C Iha	Aerobactin Salmochelin Hma ChuA IreA	CNF1 HlyA Sat CDT Sat	K 1 capsule TraT OmpT	Sat Flagellin Usp
NMEC	O18, O7, O16, O1, O45	B2, D	Type 1 S fimbriae	Salmochelin Enterobactin	CNF1	K1 capsule O-LPS Ibe proteins AslA OmpA	NlpI flagellin
SEPEC[a]	O1, O2, O4, O6, O18, O45, O83	B2, D	Type 1 P S Curli	Salmochelin Yersiniabactin Hma ChuA	HlyA	K1 capsule Iss TraT O-LPS	ColV plasmid NanA

[a]Only factors tested *in vitro* and/or *in vivo* for their virulence association are presented; SEPEC include subsets of other ExPEC (such as UPEC, NMEC) groups that reach or enter the bloodstream.
APEC, avian pathogenic *E. coli*; UPEC, uropathogenic *E. coli*; NMEC, neonatal meningitis *E. coli*; SEPEC, sepsis *E. coli*.

pathological symptoms in chickens, including airsacculitis, salpingitis, and cellulitis (Fig. 1) (Barnes *et al.*, 2003).

Genetic traits that define APEC are not completely elucidated. Similar to human ExPEC, APEC strains can be genetically very diverse and have a distinct repertoire of virulence genes. In order to develop diagnostic tools, many studies have attempted to define patterns of APEC virulence genes, such as those carried on colicin V plasmids (*iss*, *tsh*, *iucC*, *cvi*, *iutA*, *hylA*, *iss*, *iroN*, and *ompT*) (Johnson *et al.*, 2008a), toxin genes (*astA*, *vat*), iron acquisition system genes (*irp2* and *iucD*), adhesin genes (*papC* and *tsh*), and the ColV genes (*cva-cvi*) (Ewers *et al.*, 2005). Schouler *et al.* (Schouler *et al.*, 2012) determined that detection of four associated virulence genes, including two iron acquisition systems (*iutA*, *sitA*), fimbriae P (F11), sugar metabolism (*frz*$_{orf4}$), O-antigen O78, and T6SS (*aec26*, *aec4*), would identify 70.2% of APEC strains and should be used for diagnostic purposes.

Far too often, avian isolates are considered as APEC based solely on their polymerase chain reaction–detected genotypic profile. However, this is a misleading strategy since avian isolates should only be characterized as APEC if their virulence has been confirmed in animal models validated for avian colibacillosis (Dziva, 2010). Another common misconception about avian *E. coli* isolates is the assumption that intestinal isolates are nonpathogenic. Comparable to human ExPEC (Smith *et al.*, 2007), *E. coli* that cause extraintestinal infections in chickens often originate from the intestines, where they can have a commensal lifestyle similar to nonpathogenic *E. coli* (Ewers *et al.*, 2009), and cause a number of diseases at extraintestinal sites.

ExPEC infections in humans: Impact on health

ExPEC strains are responsible for a diverse spectrum of invasive infections in humans (Smith *et al.*, 2007). These strains include sepsis *E. coli*, UPEC, and NMEC, which are etiologic agents of sepsis, urinary tract infection (UTI), and neonatal meningitis, respectively (Fig. 1).

E. coli Sepsis

ExPEC constitutes an increasing problem for human medicine, as it represents the leading cause of bloodstream infections in nursing homes, hospitals, and young children, especially newborns. Sepsis infections are a major cause of mortality, morbidity, and increased healthcare costs worldwide. In the United States, it is the seventh and 10th leading cause of death in infants and children (<5-year-old) and the elderly (>55-year-old), respectively (Anonymous, 2012). Additionally, in the United States, over 8 million people contract ExPEC infections each year, with associated healthcare costs of approximately $2 billion (Russo and Johnson, 2003). In 2001, severe sepsis due to *E. coli* caused 40,000 deaths (Russo and Johnson, 2003), which is more than 500 times the number of deaths caused by *E. coli* O157:H7 (Rangel *et al.*, 2005).

E. coli is responsible for approximately 30% of the total number of sepsis cases, especially in the elderly (Russo and Johnson, 2003). The yearly incidence rate (per 100,000 individuals) of *E. coli* sepsis was estimated at 40.5 in Minnesota, USA (2003–2005) (Uslan *et al.*, 2007), 30.3 in Calgary, Canada (2000–2006) (Laupland *et al.*, 2008), 30.0 in Finland (1995–

2002) (Skogberg *et al.*, 2008), 32.0 in North Jutland County, Denmark (1981–1994) (Madsen *et al.*, 1999), and 28.0 in Canberra, Australia (2000–2004) (Kennedy *et al.*, 2008). *E. coli* is the first and second cause of community- and hospital-acquired sepsis infections, respectively (Diekema *et al.*, 2003; Laupland *et al.*, 2007) and the most common cause of community-onset sepsis infections in the elderly (≥65 years), accounting for 150 cases/100,000 persons/year in the United States (Jackson *et al.*, 2005). Importantly, these numbers are increasing.

According to recent surveillance studies from Australia and European countries, *E. coli* has not only emerged as the most prevalent agent of most extraintestinal infections, but has also increased dramatically over time (Schlackow *et al.*, 2012). This trend is particularly evident among the elderly. As examples, *E. coli* sepsis cases have increased by 33% from 2004 to 2008 in the United Kingdom (Wilson *et al.*, 2011), by over 54.8% from 2001 to 2009 in Europe (de Kraker *et al.*, 2011), and from 14.2% in 2001 to 27.3% in 2009 in Australia (Aung *et al.*, 2012). This increase could be driven by an increase in ATB-resistant isolates (Schlackow *et al.*, 2012).

Sepsis *E. coli* are also associated with some specific human diseases such as nosocomial pneumonia and surgical site infections (SSI) (Smith *et al.*, 2007). In addition, severe sepsis, mostly caused by *E. coli*, is associated with cases related to transrectal ultrasound-guided prostate biopsy, with most of the organisms being resistant to multiple ATBs (Williamson *et al.*, 2012).

E. coli UTI

UTI are among the most common bacterial infections in adults, with incidence rates four times higher in women than in men (Griebling, 2007), and approximately 25% of these women having recurrence within 6 to 12 months. Individuals particularly susceptible to UTI infections include pregnant and postmenopausal women, patients undergoing urethral catheterization, and persons with diabetes (Griebling, 2007).

The urinary tract is considered one of the most common sites of ExPEC infections. *E. coli* accounts for 70–90% and 50% of community- and hospital-acquired UTIs, respectively (Pitout, 2012). Catheter-associated UTIs in U.S. hospitals and nursing homes account for more than 1 million of the ExPEC infections reported each year (Smith *et al.*, 2007).

The presence of *E. coli* in the vaginal flora of nonpregnant (9–28%) and pregnant (24–31%) women is associated with UTIs, obstetric and neonatal complications, very-low-birth-weight infants, early-onset neonatal septicemia, and meningitis (Obata-Yasuoka *et al.*, 2002).

Using multiple virulence attributes (Table 1), UPEC colonize the perineum, overcome the natural host defenses, traverse the urethra, and then infect the bladder, causing cystitis. Some *E. coli* can infect the kidneys (pyelonephritis), which can result in organ damage (Bien *et al.*, 2012). In some cases of severe pyelonephritis, UPEC can gain access to the bloodstream, causing sepsis (Fig. 1) and sometimes death (Al-Hasan *et al.*, 2010).

E. coli Neonatal Meningitis

Because their immune system is immature, newborns are particularly susceptible to ExPEC infections that are acquired

shortly before, during, and after delivery. Neonatal sepsis is considered one of the five leading neonatal infections worldwide (Bonacorsi and Bingen, 2005). Mortality from neonatal sepsis/meningitis is estimated to be 10% in developed countries and 40–58% in developing countries (Furyk et al., 2011). In the United States, Group B Streptococcus (GBS) and E. coli are the most common etiologic agents of these diseases, with high incidence in African American preterm infants (Stoll et al., 2011; Weston et al., 2011). Contrary to GBS that affects mostly full-term births (73%), E. coli primarily affects preterm babies (45–81%) (Gaschignard et al., 2011; Stoll et al., 2011) and is the cause of high mortality and morbidity (Gaschignard et al., 2011; Weston et al., 2011). Most infant survivors had sequelae including hydrocephalus, seizures, mental retardation, cerebral palsy, and hearing loss (Klinger et al., 2000). In early-onset infection, E. coli is acquired from the maternal genital tract in utero or during passage through the birth canal. In contrast, in late-onset infection, infants can acquire E. coli from different sources including their mother, the hospital, or from community contacts (Raymond et al., 2008).

NMEC use a set of virulence factors for adhesion, invasion, and fitness (Table 1) to cause neonatal meningitis (Kim, 2012), with 80% of them possessing the capsule K1. The different steps of NMEC infection include growth in blood (bacteremia) (Fig. 1), adhesion and invasion of human brain microvascular endothelial cells, and traversal of the blood–brain barrier to cause inflammation in the central nervous system, resulting in meningitis (Kim, 2012).

ExPEC Infections in Poultry: Impact on Poultry Industry

Bacterial infections due to APEC, a subgroup of ExPEC (Fig. 1), are responsible for significant, worldwide economic losses for the poultry farms (Barnes et al., 2003), which is considered one of the most important industries in many countries, including the United States, Brazil, and China. APEC strains cause multiple systemic infections in birds, commonly referred to as avian colibacillosis (Fig. 1).

While the intestines and the environment serve as reservoirs for APEC (Ewers et al., 2009), the clinical outcome of APEC infection in birds depends on the bacterial strain, the host, the route of infection, and predisposing environmental factors. Similar to most other pathogens, APEC strains take advantage of host weaknesses to cause infections in chickens, turkeys, and other avian species. APEC infection can lead to septicemia, fibrinous lesions of internal organs (airsacculitis, pericarditis, perihepatitis), and death. APEC strains also cause local infections in birds, such as cellulitis, salpingitis, synovitis, and omphalitis (Barnes et al., 2003). The main clinical signs associated with most of these infections are depression, fever, yellowish or greenish droppings, and lesions of internal organs. E. coli infections lead to a 1–10% mortality rate in chickens, with even higher mortality rates in broilers (Zanella et al., 2000; Omer et al., 2010) and commercial organic chickens (Stokholm et al., 2010).

The financial losses due to APEC infections in chickens are due to the cost of treatment, mortality, lost production time, containment, and carcass condemnations (Barnes et al., 2003). An estimated 36–43% of broiler carcasses condemned at processing had lesions consistent with E. coli septicemia (Hasan et al., 2011; Yogaratnam, 1995). In Europe, E. coli was considered the major cause of infection condemnation of processed chickens, particularly egg layers, in the poultry industry (Vandekerchove et al., 2004). In young chicks, omphalitis and yolk sac infection, which can lead to septicemia, are the most common causes for first-week mortality in egg layers, and E. coli has been associated with 53.5% of these cases (Olsen et al., 2012a).

Respiratory Infections

Airsacculitis is the most common form of colibacillosis. It starts as a result of inhalation of fecal-contaminated dusts. E. coli colonize avian air sacs, which are particularly vulnerable to colonization and invasion by bacteria because of their lack of resident macrophages (Stearns et al., 1987). Airsacculitis is frequently followed by a generalized infection (perihepatitis, pericarditis, and septicemia) (Fig. 1). Sites of entry of APEC into the bloodstream are determined to be the gas-exchange region of the lung and the air sacs (Pourbakhsh et al., 1997).

Salpingitis

Salpingitis, an inflammation of the oviduct in layers and broiler breeders, is mainly caused by E. coli (Jordan et al., 2005). This form of avian colibacillosis is the result of either an ascending infection of the oviduct from the cloaca or as part of a systemic infection (Fig. 1) (Ozaki and Murase, 2009). Early infection may be asymptomatic, but could result in reduced egg production and increased embryonic mortality in the hatchery. According to Monroy et al. (Monroy et al., 2005), the susceptibility of adult hens to salpingitis could be related to changes initiated during their sexual maturation period, such as cytodifferentiation of the oviduct, proteins secreted, and mucus that could favor E. coli adherence. Moreover, injuries caused by cloacal cannibalism or vent pecking could also predispose birds to infections (Fossum et al., 2009).

Cellulitis

Cellulitis in chickens, characterized as a subcutaneous inflammation in the lower abdomen and thigh, is commonly caused by E. coli (Barnes et al., 2003). At the histological level, the microscopic lesions of cellulitis include the thickening of the dermis, slight hyperkeratosis, hyperplasia of the epidermis, neovascularization, and infiltration of mononuclear cells and heterophils (Messier et al., 1993). Cellulitis-affected birds do not exhibit clinical symptoms commonly associated with colisepticemia, and the infection is often detected at slaughter, which results in carcass condemnation at processing (Barnes et al., 2003). Cellulitis in chickens occurs with frequencies estimated to range between 0.197% and 6.04% (Schrader et al., 2004). The development of this infection is associated with skin surface injuries, often caused by close contact among birds and litter quality (Xavier et al., 2010). Cellulitis has been successfully reproduced in laboratory chicken models, by subcutaneous injection and by contaminating dermal scratches (Norton et al., 1997). Peighambari et al. (Peighambari et al., 1995) showed that E. coli isolated from cellulitis lesions were more likely to induce cellulitis lesions in experimentally infected 4-week-old birds than strains of noncellulitis origin. The development of cellulitis lesions in broilers could be due to the weakness of their innate immune response, specifically their heterophils (Olkowski et al., 2005).

Zoonotic Potential of ExPEC

In recent years, much attention has been directed toward controlling zoonotic infections, which remain a major worldwide health concern. Meat and eggs are known to be a source of human pathogens such as *Campylobacter*, *Listeria*, and *Salmonella*, which frequently leads to a food recall of the suspected contaminated products (Greger, 2007). Recent studies on the zoonotic risk of ExPEC have prompted the Centers for Disease Control and Prevention to release information reports to caution the public on the zoonotic potential of ExPEC and their eventual transmission through chicken meat (Vincent *et al.*, 2010; Bergeron *et al.*, 2012). The zoonotic risk of APEC isolates was initially related to the fact that some human and avian ExPEC have similar phylogenic backgrounds and share some virulence genes (Manges and Johnson, 2012). The sequencing of the genome of the APEC strain O1:K1:H7 revealed that it is highly similar to human UPEC and NMEC (Johnson *et al.*, 2007). Interestingly, a comparison of a large number of ExPEC from human and chicken diseases for their phylogenetic background and the presence of virulence-associated genes has shown that although most isolates fall into genetically distinct pathotype groups (APEC, NMEC, and UPEC), with distinguishable characteristics, the study identified a genotyping cluster that includes ExPEC with overlapping traits and was considered potentially zoonotic (Johnson *et al.*, 2008b).

The role of poultry as a source of human ExPEC (Fig. 1) is suggested by multiple epidemiological studies that reveal the presence of avian ExPEC in both the intestines of healthy poultry and poultry meat from retail markets, strains that are often genetically similar to those found to be responsible for human infections (Manges and Johnson, 2012). Johnson *et al.* (Johnson *et al.*, 2005) demonstrated that 92% (180/195) of poultry meat samples tested were contaminated with *E. coli*, with 46% (83/180) of strains having virulence factors associated with ExPEC and 15.6% (28/180) identified as UPEC.

However, according to recent reports, not all ExPEC strains have zoonotic potential. A subset of ExPEC strains from specific clonal groups, including ST95 and ST23, could have a broad host range distribution and cause diseases in both humans and chickens (Mora *et al.*, 2009; Tivendale *et al.*, 2010).

The claims that ExPEC have zoonotic potential are reinforced by the experimental evidence on the ability of human ExPEC to cause diseases in chicken models for colibacillosis and avian ExPEC to cause infections in animal models of human infections (Zhao *et al.*, 2009; Tivendale *et al.*, 2010). Zhao *et al.* (Zhao *et al.*, 2009) have determined that UPEC and APEC strains sharing the same virulence gene profiles caused lesions of colibacillosis in chickens and showed the same tendency of gene expression, including iron acquisition, in a murine model of human UTI.

The correlation between *E. coli* UTI in humans and poultry meat consumption is strongly reinforced by recent investigations that have shown that *E. coli* B2 isolated from meat and intestines of healthy chickens are able to cause infection in a murine model of human UTI (Jakobsen *et al.*, 2010). Moreover, B2 *E. coli* from UTI patients, poultry meat, and healthy chickens exhibiting high virulence genotypes were clonally related and were virulent in a mouse model of UTI (Jakobsen *et al.*, 2012).

The zoonotic risk of ExPEC appears to be mainly related to their large plasmids. Growing evidence shows that APEC plasmids could be a source of virulence genes for other ExPEC strains (Johnson *et al.*, 2012; Olsen *et al.*, 2012b). Studies have shown that UPEC and APEC isolates have certain genes in common that are associated with large transmissible plasmids of APEC (Rodriguez-Siek *et al.*, 2005). Some virulence genes associated with APEC plasmids (aerobactin, salmochelin, and *sit* operons) also occur on plasmids of UPEC (Ewers *et al.*, 2007). Additionally, APEC and NMEC have virulence genes of ColV plasmids in common (Johnson *et al.*, 2008b), and APEC plasmids in *E. coli* can contribute to the pathogenicity of urinary infection in mice (Skyberg *et al.*, 2006) and meningitis in rats (Johnson *et al.*, 2010).

ATB Resistance in ExPEC: Impact on Human Health

MDR-resistant ExPEC infections prolong hospital stays and exhibit higher mortality rates (Gastmeier *et al.*, 2012). Until the late 1990s, ExPEC were highly susceptible to most widely used ATBs, such as ampicillin and trimethoprim-sulfamethoxazole (SXT). Yet, over the past decade, ExPEC emerged as an important reservoir of resistance to first-line ATBs, including cephalosporins, fluoroquinolones, and SXT (Table 2) (Pitout, 2012). For example, UPEC are often resistant to fluoroquinolones and SXT (Table 2), which are considered the drugs of choice for uncomplicated cystitis by the international clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women, (Gupta *et al.*, 2011). In Turkey, the extensive use of SXT to treat UTI in the early 1980s has led to an increase of resistance to SXT in *E. coli* to above 50%, in the period of a decade. Subsequently, treatment shifted to quinolones due to treatment failures and has since generated an increase in resistance to quinolones (Karaca *et al.*, 2005). In the United States, resistance of urinary *E. coli* to SXT exceeded 20% in 2010, and this ATB may no longer be acceptable for UTI treatment in this country (Sanchez *et al.*, 2011). MDR resistance among UPEC has been reported from different regions of the globe (Table 2), and the rate of ATB resistance is higher in *E. coli* from recurrent UTIs (Schmiemann *et al.*, 2012). The appearance and increase of ATB resistance among ExPEC strains complicate the therapeutic management of ExPEC infections (Smith *et al.*, 2007) and has led to the increased use of last-resort antimicrobial drugs, such as carbapenems, and the appearance of the resistance to these ATBs in ExPEC (Table 2).

In 2007, 15,183 episodes of third-generation cephalosporin-resistant *E. coli* were associated with 2712 deaths and 120,065 extra hospital days in Europe (de Kraker *et al.*, 2011). Based on prevailing trends, the number of sepsis cases caused by these *E. coli* is likely to rapidly increase, potentially outnumbering the number of methicillin-resistant *Staphylococcus aureus* (MRSA) sepsis cases in the near future (de Kraker *et al.*, 2011).

Although the introduction of intrapartum ATB prophylaxis has reduced cases of neonatal GBS infection in the United States, it may also have resulted in a shift of pathogens and their resistance to ATBs, shifting to an increased incidence of Gram-negative bacteria, including *E. coli* (Furyk *et al.*, 2011). In premature infants, an increased trend in the incidence of early-onset neonatal sepsis caused by ATB-resistant *E. coli* is observed (Bizzarro *et al.*, 2008). Of particular concern is the recent apparition of NMEC producing cefotaxime (CTX)-M-type or TEM-type extended-spectrum β-lactamases (Table 2).

ExPEC producing ''newer β-lactamases,'' such as plasmid-mediated among class C cephalosporinases

TABLE 2. SELECTED WORLDWIDE REPORTS ON PHENOTYPE AND GENOTYPE OF ANTIBIOTIC RESISTANCE IN HUMAN AND AVIAN EXTRAINTESTINAL PATHOGENIC *ESCHERICHIA COLI* (ExPEC) ISOLATES

Country (reference)	ExPEC group (period of isolation)	Selection criteria	Antibiotic resistance[a]									
			β-lactams		Aminoglycosides		Macrolides		Fluoro/Quinolones		Others	
			Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)
Cambodia (Vlieghe et al., 2013)	SEPEC (07/2007–03/2010)	None	ESBL (+) (47.7) AMC (49) AMP (94) CAZ (36) CEP (46) CTX (51.5) PIT (9)	NT	AMK (3.8) GEN (56.2)	NT	NT	NT	CIP (65.4)	NT	SXT (95.4) COL (0.8)	NT
India (Haque et al., 2012)	SEPEC (NR)	ESBL-producing	ESBL (+) (7.3) AMP (100) CEP (100) CFZ (100) CLX (100) COX (100) CRO (100) CTX (100) MEM (9.7) PN (100)	bla_{TEM} (3/3) bla_{CTX-M} (3/3) bla_{SHV} (0/3)	AMK (43.9) GEN (43.9) TOB (51)	NT	NT	NT	CIP (100) GAT (31.7) NAL (100)	NT	SXT (100) TET (95.1)	NT
India (Hussain et al., 2012)	UPEC (NR)	ESBL-producing ST131 genotype	ESBL(+) (23)	$bla_{CTX-M15-O26b}$ (16/16) bla_{TEM-1} (8/16) bla_{OXA-1} (11/16)	GEN (69)	NT	NT		CIP (81)	$aac(6')$-Ib-cr (12/16) $qnrA$ (0/16) $qnrB$ (0/16) $qnrS$ (0/16)	CMP (6) SXT (69) TET (94)	$tet(A)$ (15/16) $sul1$ (13/16) $sul1$ (10/16) $str(A)$ (16/16) $str(B)$ (5/16) $dfrA12$-$aadA2$ (2/16) $dfrA17$-$aadA5$ (6/16)
China (Qin et al., 2013)	UPEC (01/2008–12/2010)	None	ESBL(+) (53) CEP (21) CFZ (79) CTX (57) CXM (61) PIP (86) PIT (9)	$bla_{CTX-M-1}$ (21/36) $bla_{CTX-M-9}$ (15/36) Unknown (1/36)	AMK (10) GEN (57)	NT	NT	NT	CIP (69)	NT	NIT (1)	NT
China (Sun et al., 2012)	APEC (03/2003–10/2010)	None	NT	Bla_{TEM-1} (17/224) $bla_{CTX-M-24}$ (16/17) $bla_{CTX-M-14}$ (1/17)	AMK (43.8) GEN (51.8) KAN (55.8) NEO (47.3) STR (84.4)	$rmtB$ (26/224)	NT	NT	NT	NT	NT	$fosA3$ (17/224)

(continued)

TABLE 2. (CONTINUED)

Country (reference)	ExPEC group (period of isolation)	Selection criteria	Antibiotic resistance[a]									
			β-lactams		Aminoglycosides		Macrolides		Fluoro/Quinolones		Others	
			Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)
Japan (Asai et al., 2011)	APEC (2001–2006)	CFZ-resistance	CFZ (32.6)	$bla_{CTX-M-25}$ (4/29) bla_{SHV-2} (3/29) $bla_{CTX-M-15/TEM-1}$ (1/29) $bla_{CTX-M-2}$ (1/29) bla_{CMY-2} (10/29) bla_{TEM-1} (7/29) unknown (2/29)	NT	NT	NT	NT	NT	NT	NT	NT
Nigeria (Iroha et al., 2012)	UPEC (NR)	ESBL-producing	ESBL (+) (100) AMP (NR) ATM (NR) CAZ (NR) CTX (NR)	$bla_{CTX-M-1}$ (44/44) $bla_{CTX-M-15}$ (3/3) bla_{TEM} (41/44) bla_{OXA-1} (41/44)	GEN (NR) KAN (NR) TOB (NR)	NT	NT	NT	NT	$aac(6')\text{-}Ib\text{-}cr$ (43/44)	CMP (NR) DOX (NR) SXT (NR) TMP (NR)	NT
Italy (Giufre et al., 2012)	UPEC (01/2009–12/2009)	CIP-resistance	ESBL (+) (14.4) AMP (86.20) CFX+CZC (26.4)	$bla_{CTX-M-15}$ (20/27) $bla_{CTX-M-15/SHV-12}$ (1/27) $bla_{CTX-M-1}$ (2/27) bla_{TEM-20} (1/27) bla_{TEM-52} (1/27) bla_{SHV-12} (1/27) unknown (1/27)	GEN (27.6)	NT	NT	NT	CIP (46.5)	NT	SXT (61)	NT
	SEPEC (01/2009-12/2009)	CIP-resistance	ESBL(+) (23.3) AMP (100) CFX+CZC (41.7)	$bla_{CTX-M-15}$ (19/27) $bla_{CTX-M-27}$ (1/27)	GEN (16.7)	NT	NT	NT	CIP (53.3)	NT	SXT (48)	NT
Germany (Heideking et al., 2013)	NMEC (01/2009–12/2010)	None	AMP (44.9) CTX (3.8) CZC (4.4) PIP (27.9)	$bla_{CTX-M-15/TEM-1}$ (1/6) $bla_{CTX-M-14/TEM-1}$ (1/6) $bla_{CTX-M-1}$ (1/6) $bla_{CTX-M-3}$ (1/6) bla_{TEM-52} (2/6)	GEN (4.4)	NT	NT	NT	CIP (4.4)	NT	SXT (19) TET (30.4)	NT
Netherland (van der Bij et al., 2011)	SEPEC (2008–2009)	ESBL-producing	ESBL(+) (4.9) AMC (90) PIT (61)	$bla_{CTX-M-15}$ (22/41) $bla_{CTX-M-14}$ (6/41) $bla_{CTX-M-2}$ (2/41) $bla_{CTX-M-3}$ (2/41) $bla_{CTX-M-9}$ (1/41) $bla_{CTX-M-27}$ (1/41) $bla_{CTX-M-1}$ (1/41) bla_{SHV-5} (2/41) bla_{SHV-12} (3/41) bla_{TEM-52} (1/41)	AMK (24) GEN (32) TOB (51)	NT	NT	NT	CIP (63)	NT	SXT (90)	NT

(continued)

TABLE 2. (CONTINUED)

Country (reference)	ExPEC group (period of isolation)	Selection criteria	β-lactams Phenotype (%)	β-lactams Genes (N+/N tested)	Aminoglycosides Phenotype (%)	Aminoglycosides Genes (N+/N tested)	Macrolides Phenotype (%)	Macrolides Genes (N+/N tested)	Fluoro/Quinolones Phenotype (%)	Fluoro/Quinolones Genes (N+/N tested)	Others Phenotype (%)	Others Genes (N+/N tested)
France (Courpon-Claudinon et al., 2011)	SEPEC (2005)	None	ESBL(+) (1.8) AmpC (+) (1.7)	$bla_{CTX-M-1}$ (2/41) $bla_{CTX-M-9}$ (1/41) $bla_{CTX-M-14}$ (6/41) $bla_{CTX-M-15}$ (3/41) $bla_{CTX-M-15/\ OXA-1}$ (6/41) bla_{TEM-52} (1/41) bla_{CMY-2} (1/41) bla_{AmpC} (13/41) $bla_{AmpC/CMY-2}$ (4/41) bla_{OXA-1} (4/41)	AMK (1.3) GEN (4.5)	NT	NT	NT	CIP (11.9)	NT	SXT (29.8)	NT
Spain (Guiral et al., 2012)	NMEC (1995–2008)	None	AMC (21) AMP (55.5) CAZ (6.5) CEP (5) CFX (6.5) CFZ (13) CPO (1.6) CTX (6.5) MEZ (62.3) PIP (20.3) PIT (6.6) SAM (46)	bla_{TEM-1} (35/42) bla_{SHV-1} (1/42) bla_{CARB} (1/42) $bla_{CTX-M-14}$ (1/42) $bla_{CTX-M-15}$ (1/42) bla_{AmpC} (1/42) unknown (2/42)	GEN (13) TOB (14.8)				CIP (6.6) LVX (3.3) MXF (8.2)	aac(3)-IV (2/8) aac(3)-II (6/8) qnrS (1/11)	CMP (24.6) SXT (32.8) TET (35.4)	catA2 (11/15) cmlA (2/15) floR (1/15) tetA (15/29) tetB (8/29) tetC (2/29) tetD (2/29) tetE (1/29) tetG (3/29) dfrAla (10/20) dfrB (0/20) dfrA12 (2/20) dfrA17 (3/20) sulI (2/22) sulII (18/22) sulIII (1/22)
Mexico (Rodriguez-Bano et al., 2012)	SEPEC (09/2004– 01/2006) SEPEC+UPEC (2007–2011)	ESBL-producing	AMC (38) CAZ (37) CEP (65) CTX (96) PIT (8)	bla_{CTX-M9} (122/191) bla_{CTX-M1} (42/191) bla_{SHV} (33/191) bla_{TEM} (1/191)	AMK (2) GEN (20) TOB (18)	NT	NT	NT	CIP (68)	NT	SXT (60)	NT

Antibiotic resistance[a]

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(continued)

TABLE 2. (CONTINUED)

Country (reference)	ExPEC group (period of isolation)	Selection criteria	Antibiotic resistance[a]									
			β-lactams		Aminoglycosides		Macrolides		Fluoro/Quinolones		Others	
			Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)
Canada (Denisuik et al., 2013)	ESBL-producing		ESBL(+) (4.2) AMC (3.9) CAZ (56.2) CEP (21.9) CFZ (100) COX (8.2) CRO (97) ETP (1.3) PIT (2.2)	$bla_{CTX-M-15}$ (21/231) $bla_{CTX-M-15}$/TEM-1 (18/231) $bla_{CTX-M-15}$/OXA-1 (84/231) $bla_{CTX-M-15}$/TEM-1/OXA-1 (30/231) $bla_{CTX-M-14}$ (15/231) $bla_{CTX-M-14}$/TEM-1 (28/231) $bla_{CTX-M-14}$/OXA-1 (2/231) $bla_{CTX-M-27}$ (13/231) $bla_{CTX-M-27}$/TEM-1 (2/231) $bla_{CTX-M-24}$ (1/231) $bla_{CTX-M-24}$/TEM-1 (1/231) $bla_{CTX-M-3}$/TEM-1 (1/231) $bla_{CTX-M-3}$/TEM-1/OXA-1 (1/231) $bla_{CTX-M-65}$ (1/231) bla_{SHV-12} (1/231) bla_{SHV-12}/TEM-1 (3/231) bla_{SHV-2a} (3/231) bla_{TEM-12} (1/231) unknown (2/231) unknown/TEM-1 (3/231)	AMK (0.4) GEN (48.5)	NT	NT	NT	CIP (88.3)	NT	COL (0.4) SXT (70.1)	NT
	AmpC-producing		AmpC (+) (2.6) AMC (49.6) CAZ (51.4) CEP (2.3) CFZ (95.7) COX (100) CRO (57.4) PIT (1.7)	Bla_{CMY-2} (64/115) Bla_{FOX-5} (1/115)	AMK (1.7) GEN (16.5)	NT	NT	NT	CIP (37.4)	NT	SXT (33.9)	NT

(continued)

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TABLE 2. (CONTINUED)

Country (reference)	ExPEC group (period of isolation)	Selection criteria	Antibiotic resistance[a]									
			β-lactams		Aminoglycosides		Macrolides		Fluoro/Quinolones		Others	
			Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)	Phenotype (%)	Genes (N+/N tested)
USA (Peirano et al., 2010)	UPEC/ SEPEC (2008)	ESBL-producing	PIT (6.7)	$bla_{TM-1}/OXA-1/CTX-M-15$ (9/30), $bla_{TM-1}/CTX-M-15$ (3/30), $bla_{OXA-1}/CTX-M-15$ (3/30), $bla_{TM-1}/CTX-M-14$ (2/30), $bla_{CTX-M-15}$ (7/30), $bla_{CTX-M-14}$ (1/30), bla_{SHV-2} (4/30)	AMK (20) GEN (33.33) TOB (50)	NT	NT	NT	CIP (93)	$aac(6')$-Ib-cr (16/30)	NIT (10) SXT (56.7)	NT
USA (Adams-Sapper et al., 2013)	SEPEC (07/2007– 09/2010)	None	CTX (12) ATM (12)	$bla_{CTX-M-15}$ (15/246), $bla_{CTX-M-1}$ (3/246), $bla_{CTX-M-14}$ (6/246), $bla_{CTX-M-14}/CTX-M-15$ (6/246), bla_{TM-1} (8/246), bla_{OXA-1} (15/246), bla_{KPC-2} (2/246)	NT	NT	NT	NT	CIP/LVX/ MXF (27)	NT	SXT (44)	NT

N, number of isolates; NT, not tested; NR, not reported; SEPEC, sepsis *E. coli*; UPEC, uropathogenic *E. coli*; APEC, avian pathogenic *E. coli*; NMEC, neonatal meningitis *E. coli*.
[a] AMC, amoxicillin/clavulanic acid; AMK, Amikacin; AMP, ampicillin; ATM, aztreonam; CARB, carbenicillin; CAZ, ceftazidime; CEP, cefepime; CFZ, cefazolin; CFX, cefotaxime; CIP, ciprofloxacin; CLX, clinafloxacin; CMP, chloramphenicol; COL, colistin; COX, cefoxitin; CPO, cefpodoxime; CRO, ceftriaxone; CTX, cefotaxime; CXM, cefuroxime; CZC, ceftazidime+clavulanic acid; DOX, doxycycline; ETP, ertapenem; ESBL, extended-spectrum β-lactamases; GAT, gatifloxacin; GEN, gentamicin; KAN, kanamycin; LVX, levofloxacin; MEM, meropenem; MEZ, mezlocillin; MXF, moxifloxacin; NAL, nalidixic acid; NIT, nitrofurantoin; NEO, neomycin; OXA, oxacillin; PIP, piperacillin; PIT, piperacillin/tazobactam; PN, penicillin; SAM, ampicillin–sulbactam; STR, streptomycin; SXT, sulfamethoxazole/trimethoprim; TET, tetracycline; TOB, tobramycin; TMP, trimethoprim.

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(AmpC) *β*-lactamases (e.g., cephamycinase [CMY] types), extended-spectrum *β*-lactamases (ESBLs) (e.g., TEM-, sulf-hydryl variable [SHV]-, CTX-M-, oxacillin-types), and carbapenemases (e.g., imipenem-, Verona integron-encoded metallo-*β*-lactamase [VIM]-, New Delhi metallo-*β*-lactamase [NDM]-types), are widespread (Table 2) (Pitout, 2012). The most prevalent is CTX-M-15, which is the most associated with human ExPEC isolates, especially UPEC, in many regions of the world (Table 2), with many belonging to specific clones. However, it has been speculated that certain sequence types (ST38, ST131, ST405, and ST648) could have contributed to their worldwide distribution (Pitout, 2012). A recent study monitoring ATB-resistance trends among human sepsis Enterobacteriaceae, mainly sepsis *E. coli* (63.4%, 443/699), from multiple countries of the Asian Pacific region during the period 2008–2009 (Sheng *et al.*, 2013), has determined that geographic genetic distribution of ESBLs, AmpCs, and carbapenemases was variable. The most dominant among ESBLs were CTX-M-14 (China, South Korea, and Taiwan), CTX-M-15 (India, Malaysia, the Philippines, and Singapore), and SHV-12 (Taiwan and the Philippines). Among AmpCs were CMY-2 (India, Taiwan, South Korea, and Vietnam), Dhahran Hospital in Saudi Arabia (DHA) (Philippines and Singapore), AmpC type (ACT)–Miriam Hospital in Providence, RI (MIR) (New Zealand and South Korea), and DHA-1 (Taiwan). Finally in this study, carbapenemases (mostly NDM-1) were exclusively detected in India.

A recent Canadian epidemiology study that covered a 5-year period (2007–2011) has shown a significant national increase in the proportion of ESBL- and AmpC-producing isolates among human ExPEC and identified carbapenemase-producing isolates (Denisuik *et al.*, 2013). The emergence and widespread dissemination of CTX-M-15, CMY-1, and NDM-producing *E. coli* is especially alarming as they often confer resistance to multiple other antibiotic classes, leaving few or no other treatment options (Table 2).

Clinicians are aware that the increase in ATB resistance is a great concern for public health as well as the economy. Treatment failures due to ATB resistance increase the cost of care and result in prolonged morbidity for patients. As the proportion of elderly and immunocompromised patients increases, the number of ExPEC infections will likely increase, while associated ATB resistance will make treatment strategies more challenging (Pitout, 2012). Therefore, the prevention of ExPEC infections is a pressing concern, and vaccines are necessary to manage ExPEC infections in the future.

Because of the significance of colibacillosis in the worldwide poultry industry, ATB treatments with tetracyclines, fluoroquinolones, and sulfonamides are primarily used to target *E. coli*, thus explaining the high level of resistance of avian *E. coli* to these ATBs (Zhao *et al.*, 2005). In the United States, MDR resistance was found in 92% (87/95) of APEC isolates from northern Georgia (Zhao *et al.*, 2005). Studies performed in China have shown that 80% of the 71 *E. coli* strains isolated from the livers of deceased chickens from 10 different poultry farms were resistant to eight or more ATBs, including fluoroquinolones, and all of them were resistant to nalidixic acid and tetracycline (Yang *et al.*, 2004). The Li *et al.* (Li *et al.*, 2007) study found comparable results, whereby 100% of APEC isolates tested were resistant to tetracycline and trimethoprim/sulfonamide, and 79–83% of the isolates

exhibited resistance to chloramphenicol, ampicillin, ciprofloxacin, and enrofloxacin.

ESBL genes have also been detected in APEC and fecal *E. coli* of healthy poultry (Asai *et al.*, 2011; Bortolaia *et al.*, 2010). The emergence of ESBL genes in poultry could be associated with the use of third-generation cephalosporins in chickens, particularly ceftiofur, which is injected into eggs to control *E. coli* omphalitis in broiler chickens (Dutil *et al.*, 2010). However, this assumption would not be the only explanation, as ESBL-producing *E. coli* were also detected in birds that were not treated with cephalosporins (Bortolaia *et al.*, 2010). Additionally, recent reports have detected ESBL-producing *E. coli* in both the environment and wildlife, especially birds (Guenther *et al.*, 2011). This could show the ability of ESBL-producing *E. coli* to transfer from one ecosystem to another and highlight the importance of life vectors in dissemination of these resistance genes to different environments.

Bacteria found in the poultry environment are important reservoirs for ATB resistance (Nandi *et al.*, 2004). The presence of ATB-resistant bacteria in poultry can lead to the contamination of poultry products, which could increase the risk of the transfer of these bacteria or their ATB genes to humans. In fact, a recent study determined that women who were infected with MDR-resistant *E. coli* reported more frequent chicken consumption (Manges *et al.*, 2007).

As the poultry industry has developed, ATBs have been used extensively for disease prevention and treatment. With the exception of the European Union, ATBs are administered in poultry feed or drinking water for growth promotion. Although ATBs have contributed to poultry health and welfare for several decades, extensive use and misuse has generated worldwide concern about the development of ATB resistance and transfer to humans and the environment.

It was speculated that ATB-resistant human ExPEC likely originated from poultry through both direct contact with birds and the consumption of poultry products (Fig. 1) (Manges and Johnson, 2012). According to a recent study in the Netherlands, retail chicken meat has the highest rate of ESBL-contamination compared to other meats and involves many of the same ESBL genes present in colonized and infected humans (Overdevest *et al.*, 2011). Identification of a major multilocus sequence–type clone associated with ciprofloxacin resistance/multiresistance in both human and avian *E. coli* isolates confirms the zoonotic risk of avian isolates (Giufre *et al.*, 2012). These ATB-resistance genes in *E. coli* may be transferred vertically to other species of bacteria. In fact, most *Salmonella* Kentucky avian isolates have acquired resistance to streptomycin and tetracycline through acquisition of an APEC-like plasmid, which could be responsible for their emergence as a dominant serovar in chickens (Fricke *et al.*, 2009).

Conclusions

ExPEC is a leading cause of infections in both humans and poultry. ATB use in the poultry industry and increases in poultry product consumption could have caused the emergence, dissemination, and persistence of ATB resistance, which is a serious health concern for both animals and humans. Due to the variability and adaptability of ExPEC, constant surveillance of their epidemiology in both humans and chickens is required and rigorous controls of their contaminants are needed.

Disclosure Statement

No competing financial interests exist.

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