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Prevalence of extended-spectrum β -lactamases in the local farm environment and livestock: challenges to mitigate antimicrobial resistance

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ABSTRACT

The effectiveness of antibiotics has been challenged by the increasing frequency of antimicrobial resistance (AR), which has emerged as a major threat to global health. Despite the negative impact of AR on health, there are few effective strategies for reducing AR in food-producing animals. Of the antimicrobial resistant microorganisms (ARMs), extended-spectrum β -lactamases (ESBLs)-producing *Enterobacteriaceae* are an emerging global threat due to their increasing prevalence in livestock, even in animals raised without antibiotics. Many reviews are available for the positive selection of AR associated with antibiotic use in livestock, but less attention has been given to how other factors including soil, water, manure, wildlife, and farm workers, are associated with the emergence of ESBL-producing bacteria. Understanding of antibiotic resistance genes and bacteria transfer at the interfaces of livestock and other potential reservoirs will provide insights for the development of mitigation strategies for AR.

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Introduction

Antimicrobial resistance (AR) is defined as “the resistance of a microorganism to an antimicrobial drug to which it was previously sensitive so that the standard treatments become ineffective and infections persist and may spread to others” (Demerec 1948; Alanis 2005). AR is one of the fundamental challenges affecting public health, claiming 23,000 estimated deaths annually and an approximate \$55 billion/year in overall societal costs in the United States (US) alone (CDC 2013; Demirjian et al. 2015). The World Health Organisation (WHO) published a list of the most critical antimicrobial resistant microorganisms (ARMs) against which new antibiotics need to be developed urgently (WHO 2017). Among the ‘Highest Priority’ pathogens, extended-spectrum β -lactamases (ESBLs)-producing *Enterobacteriaceae* were identified as an emerging global threat due to their increasing prevalence in

livestock in recent years after being mainly identified in human medicine in the past (Enoch et al. 2012; Reuland et al. 2013).

ESBLs can hydrolyse expanded-spectrum cephalosporins, including cefotaxime, ceftriaxone, ceftazidime, or cefepime and monobactams. More than 1,000 ESBL variants are known, including SHV, TEM, OXA, and CTX-M types, with more expected to be identified in the future (Allen et al. 2010; Jia et al. 2017). During the 1990s, the TEM- and SHV- β -lactamase families carried by *Klebsiella pneumoniae* and *Escherichia coli* were the main members of ESBLs (Coque et al. 2008). In recent years, the geographical distribution of ESBL-producing bacteria has increased dramatically, and ESBLs have been identified in other bacteria including *K. pneumoniae*, *E. coli*, *Acinetobacter calcoaceticus*, *Agrobacterium tumefaciens*, *Ochrobactrum* spp., and *Pseudomonas pleoglossicida*, encoding *bla*_{SHV}, *bla*_{CMY}, *bla*_{VEB}, *bla*_{OXA-2},

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*bla*_{TEM}, and *bla*_{CTX-M} genes (Zhou et al. 2015; Mir et al. 2016). In particular, the incidence of CTX-M type ESBLs has increased significantly during the past decade. A prototype of CTX-M type ESBLs has been found to originate from environmental bacteria *Kluyvera* species (Bevan et al. 2017). Most ESBL-producing bacteria encode the ESBL genes on plasmids facilitating the rapid spread through horizontal gene transfer (HGT) between bacteria, but recent findings indicate that the *bla*_{CTX-M} genes are also encoded in chromosomal DNA (Teng et al. 2019).

The emergence of ESBL-producing bacteria in animals

The prevalence of ESBL-producing bacteria in swine farms has been reported to range from approximately 10% to 45%, and *E. coli* was the major ESBL producer (Geser et al. 2011; Randall et al. 2014; Li et al. 2015; Sabia et al. 2017; Liu et al. 2018). The most prevalent ESBL gene type at swine farms was *bla*_{CTX-M}, while other β -lactamase genes such as *bla*_{CMY-2}, *bla*_{TEM}, *bla*_{SHV}, *bla*_{OXA}, *bla*_{KPC}, and *bla*_{DHA} were also identified (Dahms et al. 2015; Shin et al. 2017; Chah et al. 2018; Liu et al. 2018). Recently, the *mcr-1* gene, which was first identified in China (Liu et al. 2016), was identified along with ESBL genes in the plasmid DNA in swine farms (Shafiq et al. 2019). *E. coli* isolates from cloacal and nasal swabs of swine in China were investigated, and 39.59% (78/197) of the *E. coli* isolates carried both *mcr-1* and ESBL genes (*bla*_{CTX-M}, *bla*_{SHV}, and *bla*_{TEM}) (Shafiq et al. 2019). Similarly, nine isolates out of 24 ESBL-producing *E. coli* from the rectal swabs of swine on farms and slaughterhouse were positive with *mcr-1* gene (Malhotra-Kumar et al. 2016). Ji et al. reported 14% (4/28) prevalence of ESBL-producing *E. coli* encoding *mcr-1* gene as well (Ji et al. 2019).

In the case of poultry, there are many studies investigating the occurrence of ESBL-producing bacteria, particularly in the entire broiler production pyramid (Nilsson et al. 2014; Zurfluh et al. 2014; Apostolakos et al. 2019; Dame-Korevaar et al. 2019; Oikarainen et al. 2019). The prevalence of ESBL-producing bacteria is different depending on the levels of broiler production pyramid. For instance, a high prevalence of ESBL and plasmid mediated AmpC-type cephalosporinase-producing *E. coli* was found in broiler parent flocks (92.5%, 95%CI 72.1–98.3%), which decreased to 20% (95%CI 12.9–29.6%) during the laying period (Apostolakos et al. 2019). The prevalence increased again to 69.2% (95%CI 53.6–81.3%) at the start of the production cycle in the fattening broilers, then dropped to 54.2% (95%CI

38.9–68.6%) in the last sampling right before slaughter (Apostolakos et al. 2019). Similarly, in Denmark, broiler parent flocks showed higher prevalence of ESBL-producing *E. coli* than broiler flocks (93.0 and 27.0%, respectively) (Agerso et al. 2014). In addition, broiler production practices (i.e., conventional or organic farms) can affect the prevalence of multi-drug resistant *E. coli* on eggshells (95% in conventional barns and 30% in organic farms, $p < 0.05$) (Dame-Korevaar et al. 2019) and chicken meats (100% on conventional and 84% on organic samples, $p < 0.001$) (Cohen Stuart et al. 2012). The majority of ESBL-producing bacteria in poultry farms was *E. coli* and *Salmonella* spp., and CTX-M was the most predominant ESBLs, while SHV and TEM were also reported (Saliu et al. 2017).

Cattle also appear to be an important reservoir of ESBL-producing bacteria among food-producing animals, with the increasing detection of these bacteria in cattle (Mir et al. 2018; Tymensen et al. 2018). ESBL-producing bacteria have been isolated from cattle in the US, Germany, France, and Asian countries including China, Japan, and Korea (Duan et al. 2006; Moon et al. 2007; Hiroi et al. 2012; Zheng et al. 2012; Schmid et al. 2013; Haenni et al. 2014; Mir et al. 2018). For example, in Switzerland, two independent studies showed 17.1% and 8.4% prevalence of ESBL-producing bacteria in the gastrointestinal tract of healthy cattle at abattoirs, primarily *E. coli* (Geser et al. 2011). In Taiwan, 42.2% of *E. coli* isolates from beef carcasses produced ESBLs, with *bla*_{CTX-M-1} and *bla*_{CTX-M-9} as the most commonly identified ESBL genotypes (Chen et al. 2017).

Recent findings propose another pillar of ESBL emergence. Beef cattle raised without antibiotics on pasture had a 15.8% prevalence of cefotaxime resistant bacteria (CRB) (Mir et al. 2016). Cefotaxime is frequently used to select ESBL-producing bacteria due to its strong antimicrobial activity against non-ESBL-producing bacteria (Eliopoulos and Bush 2001). All CRB isolates contained *bla*_{CTX-M} genes as the predominant ESBL gene, and over 70% of the isolates carried more than two ESBL genes and 35% harboured more than three ESBL genes such as *bla*_{SHV} (13%), *bla*_{OXA-2} (39%), and *bla*_{VEB} (30%) (Mir et al. 2016). Mir et al. (2018) also showed that the majority of the cattle (92%) during the first year of life had become colonised by CRB at least once (Mir et al. 2018). Cattle raised in cow/calf operation systems on pasture with limited use of antibiotics to occasional treatment carried CRB, although the prevalence was relatively low, 47.4%, compared to the prevalence of CRB in feedlot (83%) (Noyes et al. 2016; Markland et al. 2019). Furthermore, genetically similar ESBL-producing *E. coli* have been isolated in various hosts around the

world (Teng et al. 2019). These observations suggest that AR in livestock can arise through various environmental pathways, even in the absence of anthropogenic antibiotic use (Li et al. 2015; Mir et al. 2016). There have been a number of reviews that have looked at the positive correlation between antibiotic use in livestock and the emergence of ARMs (Oliver et al. 2011; Landers et al. 2012; Andersson and Hughes 2014; Tang et al. 2017), while reviews on environmental factors adjacent to pastures and grazing area (e.g., the interface of wildlife and livestock, soil, and surface water) are limited. In this review, we focus on

occurrence and transmission of ESBL-producing bacteria at the interface of food-producing animals, especially cattle, and the surrounding environment (Table 1).

Potential sources of ESBL-producing bacteria in the environment

Soil

The soil has various natural antimicrobials, and the antibiotic residues in soil contaminated from animal manure, wastewater, and other sources, may serve as

Table 1. Reported occurrences of ESBL-producing bacteria in livestock-related environmental niches.

Source	Effects	Reference
Soil		
Soil near farm	18.3% of ESBLs (22/120) in soil located cattle farms	(Hartmann et al. 2012)
Intensive, extensive and organic soils	A positive correlation between AR and intensive soil	(Jones-Dias et al. 2016)
Undisturbed area	Isolation of the bacteria resistant to extended-spectrum β -lactams without selective pressure	(Upadhyay et al. 2016)
Manure		
Cattle manure	A higher frequency of resistant bacteria in manure-amended soil	(Udikovic-Kolic et al. 2014)
Dairy cow manure	Identification of the multiple resistance genes including a novel clade of resistant gene	(Wichmann et al. 2014)
Cattle, swine, and chicken manure	Higher concentration of the veterinary antibiotic residues in swine and chicken than cattle manure	(Hou et al. 2015)
Water		
Water supply in farm	Isolation of the ESBL-producing <i>E. coli</i> carrying TEM and CMY-2 genes (6/116, 5%)	(Hinthong et al. 2017)
Drinking water in a cattle pen	ESBLs, carbapenemase, and unique ARGs in the water trough	(Noyes et al. 2016)
Surface/wastewater	A higher prevalence of ESBLs in wastewater than surface water (27% (9/33) and 6.2% (7/113))	(Blaak et al. 2015)
Surface/wastewater	Higher ESBLs in wastewater than surface water (42.1% (24/57) and 1.7% (1/57))	(Said et al. 2016)
Surface water	High prevalence of ESBLs in surface water	(Zurfluh et al. 2013; Haque et al. 2014)
Air		
Cattle farms	Isolation of a multidrug-resistant strain in both inside and outside air	(Navajas-Benito et al. 2017)
Swine farms	Occurrence of ESBL-producing <i>E. coli</i> from inside and outside air of the swine farms	(Gao et al. 2015)
Broiler farms	Fecal and airborne transfer of ESBL-producing bacteria	(Laube et al. 2014)
Wild animals		
Songbirds on dairies	5.1% prevalence of CTX-M gene in wild songbirds on Ohio dairies	(Mathys et al. 2017)
Coastline birds	14% of prevalence of ESBLs in wild birds from Miami Beach, Florida	(Poirel et al. 2012)
Wild birds	A higher prevalence of ESBLs in cattle egret than other wild birds	(Hasan et al. 2016)
Flies	ESBL-producers from 9.1% of flies (123/1346) in urban and rural areas	(Schaumburg et al. 2016)
Flies	Isolation of ESBL-producing <i>E. coli</i> in flies at poultry farms (10.5%, 2/19) and cattle farms (12%, 20/159)	(Blaak et al. 2014; Usui et al. 2013)
Others	Investigation of diverse wild animals as important carriers of ESBLs	(Nhung et al. 2015; Cristóvão et al. 2017; Garcês et al. 2019; Schaufler et al. 2018; Wasyl et al. 2018)
Human		
Human in a livestock-dense area	Identification of risk factors for ESBL/AmpC transmission	(Wielders et al. 2017)
Farmers	Identical MLST and CTX-M gene between human and cattle isolates from the same farm	(Dahms et al. 2015)
Farm workers	Isolation of ESBL-producing <i>E. coli</i> from cattle and farm workers	(Tamang et al. 2013)
Farm workers	Similar ESBL gene types and identical MLST and plasmid types between human and pig isolates within the same farm	(Dohmen et al. 2015)
Slaughterhouse workers	Association between the job title in the slaughterhouse and the prevalence of ESBL- <i>E. coli</i> in human	(Dohmen W et al. 2017b)
Others		
Dust from a cattle farm	ESBL-producing <i>E. coli</i> from 15.4% (18/117) of dust from mixed and beef cattle farms	(Schmid et al. 2013)
Feed mixer, animal feed, bedding	ESBL-producing <i>E. coli</i> from water trough, feed mixer, feed, and bedding in dairy farms contained	(Braun et al. 2016)

antimicrobial selective pressure to bacteria and develop antibiotic resistance (Riesenfeld et al. 2004; Torres-Cortés et al. 2011; Udikovic-Kolic et al. 2014; Jones-Dias et al. 2016; Tripathi and Cytryn 2017), such as CTX-M type ESBLs from *Kluyvera* spp. (Bevan et al. 2017). The prevalence of ESBL-producing bacteria as measured by screening for *bla*_{CTX-M} genes using a real-time PCR method, was 18.3% (22/120) in soil samples obtained from Burgundy region in France, where beef cattle farms are densely located (Hartmann et al. 2012). In another study, soils in intensive agricultural practices (large inputs of pesticides) had the highest prevalence of ESBL-producing *E. coli* compared to soils in extensive (small inputs of pesticides) and organic (no inputs of pesticides) practices, showing that soil types can affect the prevalence of ESBL-producing bacteria (Jones-Dias et al. 2016). Although the anthropogenic impacts are critical to accelerate the occurrence of ARMs in soil, soil samples collected from undisturbed areas with no human activity and no antimicrobial selective pressure still contained ARMs, including AmpC β -lactamases (encoded on chromosome)- and ESBL-producing isolates (Upadhyay et al. 2016). In a similar study, novel and ancient β -lactam resistance determinants were found in the absence of selective pressure in areas of no anthropogenic activity in Alaska, suggesting that soil microbiota can contribute to the development of AR naturally (Allen et al. 2009). However, the occurrence of AR in remote areas and animal farm soils might be different, because AR in pristine areas is caused by naturally existed microorganisms without anthropogenic impacts, while most of the soil in farm environment is easily influenced by human activities. Furthermore, CRB prevalence in the gastrointestinal tract of cattle which were pasture-grazed was positively associated with the relative abundance of gamma-proteobacteria, a major antibiotic producer, in soil samples (Markland et al. 2019), suggesting that CRB may transmit at the interface of cattle and soil, and further studies will be necessary to understand the directionality of AR transmission between soil and cattle.

Water

ESBL-producing bacteria has been also found in water resources proximal to farm environment. A total of six *E. coli* isolates carrying *bla*_{TEM} and *bla*_{CMY-2} genes (6/116, 5%) were obtained from 35 water samples used for drinking and washing dairy cattle in Thailand (Hinthong et al. 2017). In a similar study, water in beef cattle pens contained the ESBL and carbapenemase genes, and unique antimicrobial resistance genes (ARGs),

suggesting that water in cattle farms could be another source of ESBL-producing bacteria (Noyes et al. 2016). Wastewater from sewage treatment plants and from hospitals have a higher predominance of ESBL-producing bacteria compared to surface water (rivers, canals, rivulets, lakes and the North Sea) in the Netherlands (Blaak et al. 2015) and similar results were obtained in another study in Tunisia, where wastewater had more ESBL-producing bacteria than surface water, 42.1% (24/57) vs. 1.7% (1/57) (Said et al. 2016). On the other hand, surface water in Switzerland (rivers and lakes) and in Bangladesh (lake) showed higher prevalence, 36.2% (21/58) and 75% (3/4), respectively (Zurfluh et al. 2013; Haque et al. 2014). There is also evidence showing the high prevalence of ESBL-producing *K. pneumoniae* at all stages of hospital sewage treatments (Prado et al. 2008). Substantial studies showed the presence of β -lactam resistance genes including *bla*_{TEM}, *bla*_{IMP}, and *bla*_{OXA-2} derivatives in sewage sludge in Europe (Tennstedt et al. 2005; Henriques et al. 2006; Mesa et al. 2006). Sewage sludge can provide ideal conditions for HGT because of high concentrations of bacteria (Gaze et al. 2011). Since the wastewater contributes to the presence of ARMs in surface water (Blaak et al. 2015) and soil through irrigation (Negreanu et al. 2012) and flooding (Devarajan et al. 2016), cattle grazing on pasture might be exposed to ESBL-producing bacteria by wastewater directly or indirectly.

Air

The aerosols in animal farms can harbour diverse microbes and microbes in farm animals can be associated with them (Yuan et al. 2010). The air collected from different points inside cattle farms and outside surroundings has been shown to contain TEM-1 producing *E. coli* isolates and the isolates harboured other resistance genes like *sul1*, *sul2*, *tet(A)*, and *tet(B)* (Navajas-Benito et al. 2017). Airborne ESBL-producing isolates were reported from swine and broiler chicken farms. Gao et al. (2015) reported that three out of four swine farms contained ESBL-producing bacteria in the air. ESBL-producing *Enterobacteriaceae* was detected in stable air samples from the pig farms (6/35) at the German-Dutch border region (Schmithausen et al. 2015). Similarly, 6% (2/36) ambient air samples in the vicinity of the pig barns and 9.5% (6/63) air samples inside the barn contained ESBL/AmpC-producing *E. coli* (von Salviati et al. 2015). In broiler chicken farms, air from inside and outside of the farms had a prevalence of ESBL-producing *E. coli* of 16% (10/63) and 7.5% (3/40), respectively (Laube et al. 2014). Huijbers et al.

(Huijbers et al. 2016) isolated ESBL/AmpC-producing *E. coli* in air samples on an organic broiler farm as well. The presence of ESBL-producing bacteria in the air suggests that inhalation of contaminated air might provide another transmission route, contributing to the prevalence of ESBL-producing bacteria in farm animals (Dohmen et al. 2017a).

Manure, farm environment and waste

In the US, about 14 million kilograms of antibiotics, approved for use in food-producing animals, were sold in 2016 (FDA 2017) and approximately 6.8 million tons of animal manure (FAO 2018) were spread onto pasture for forage and silage production as well as agricultural fields as a fertiliser to provide nutrients to crops and to improve soil quality. Therefore, continuous selective pressure by antibiotic residues in the treated soil may facilitate the acquisition of novel ARGs by the microorganisms. Soil treated with cattle manure has a higher abundance of β -lactam resistant bacteria than untreated soil, showing manure-amended soil could include more ARMs (Udikovic-Kolic et al. 2014). The resistome of cow manure including β -lactam, phenicol, aminoglycoside, and tetracycline resistance genes, showed a low identity of protein sequences against known reference genes, suggesting manure may carry various novel ARGs (Wichmann et al. 2014). Because of the residues of antimicrobials in cattle manure, animal manures may have a relatively higher prevalence of ARMs compared to other reported reservoirs in farm environments (Hou et al. 2015). In addition to manure, barn dust collected from cattle farms carried ESBL-producing *E. coli* (15.4% prevalence) (Schmid et al. 2013). Also, feed mixer, animal feed, and bedding in dairy farms were also shown to contain ESBL-producing *E. coli* (Braun et al. 2016), suggesting these bacteria are ubiquitous. A total of 56 environmental samples including water trough, feed, and bedding showed a prevalence of ESBL-producing *E. coli* as high as 28.6% (Braun et al. 2016). Isolates from the feed mixer and animal feed carried *bla*_{CTX-M-15} and *bla*_{TEM} genes, and isolates from bedding had *bla*_{CTX-M-15}, *bla*_{TEM}, and *bla*_{OXA-1} genes (Braun et al. 2016).

Wildlife as potential reservoirs of ESBL-producing bacteria

Wildlife carry ARMs in a wide range of habitats, and they can affect the transmission dynamics of ARMs at the livestock-wildlife interface (Greig et al. 2015; Vittecoq et al. 2016). Although wildlife is not treated

with antibiotics intentionally, they can acquire ARMs from a contaminated environment or natural resistome (Carroll et al. 2015; Swift et al. 2019), transferring the ARMs to livestock or vice versa via direct and indirect contacts through the use of shared resources such as pasture, water, or soil (Wiethoelter et al. 2015). Previous studies have highlighted the importance of wildlife, especially migratory birds as important agents of the ARM prevalence and spread (Greig et al. 2015). Birds can cover long distance during the migration season and they could potentially spread ARMs globally (Alcalá et al. 2016). One study reported 3% and 5.1% prevalence of bacteria encoding the *bla*_{CMY} or *bla*_{CTX-M} genes in wild songbirds on Ohio dairies, respectively (Mathys et al. 2017). Wild coastline birds (seagulls and pelicans) in Miami Beach, Florida had 14% prevalence of ESBL-producing bacteria (Poirel et al. 2012). Hasan et al. (2016) reported that the prevalence of ESBL-producing *E. coli* and *K. pneumoniae* was 8% in wild birds. The isolates from different sources were closely related to each other according to the ERIC-PCR data (Hasan et al. 2016). Interestingly, Hasan et al. (2016) reported that among five different bird species evaluated, cattle egrets, which forage at the feet of grazing cattle, showed the highest prevalence of ESBL-producing bacteria, suggesting a high probability of transmission of ARMs between birds and cattle in the environment where they co-inhabit (Hasan et al. 2016). Other wildlife including wolves, seabreams, lynxes, wild boars, foxes, deers, bats, and rodents can also be potential reservoirs of ESBL-producing bacteria (Nhung et al. 2015; Cristóvão et al. 2017; Schaufler et al. 2018; Wasyl et al. 2018; Garcês et al. 2019). In addition, flies near livestock have been shown to carry ESBL-producing bacteria (dos Santos Alves et al. 2018). Out of 1346 single flies obtained from an urban and rural area in Germany, 123 flies had ESBL producers (9.1% prevalence) (Schaumburg et al. 2016). Flies at poultry farms had a 10.5% prevalence of ESBL-producing *E. coli* (2/19) and houseflies and barn flies obtained from a cattle barn showed 10% prevalence (Usui et al. 2013; Blaak et al. 2014).

ESBL-producing bacteria in livestock farm workers

In the Netherlands, 2432 adults, who have lived in a livestock-dense area, were investigated to understand the risk of neighbouring residents regarding the carriage of ESBL-producing bacteria (Wielders et al. 2017). 4.5% (109/2432) of the adults carried ESBL- or AmpC-producing bacteria. Interestingly, keeping cows

recreationally was one of the identified risk factors for colonisation with ESBL-producing bacteria (Wielders et al. 2017). Among the general population, farmers closely exposed to livestock and contacted animals directly had increased chances of transmission of ARMs (Klous et al. 2016). In Germany, faeces from farmers (5/73) and pig (15/17), cattle (6/11), and poultry (3/6) carried ESBL-producing *E. coli*. Five farmers (3 from cattle farms and 2 from pig farms) harboured ESBL-producing *E. coli*, showing 6.8% prevalence and one human isolate had the same multi-locus sequencing typing (MLST) (ST3891) and *bla*_{CTX-M} allele as did cattle isolates from the same farm (Dahms et al. 2015). ESBL-producing *E. coli* have also been isolated from farm workers in Korea (Tamang et al. 2013) and Netherland (Dohmen et al. 2015; Dohmen et al. 2017a). The prevalence of ESBL-producing *E. coli* in human was significantly associated with job title (e.g., stable work, stabbing, dehairing, removal of organs, refrigeration, packaging, and expedition) in the abattoir, indicating the frequency of exposure to livestock enhance the transmission of ESBL-producing bacteria between human and livestock (Dohmen et al. 2017b). Therefore, understanding the role of animal carriage might be one of the key factors in understanding the prevalence of ESBL-producing bacteria in humans.

The movement of resistant bacteria and ARGs

Resistance genes can be transferred to other bacteria, even within a distantly related genus, through HGT with mobile elements such as bacteriophages, plasmids, and transposons (Andersson and Hughes 2010). However, due to the magnitude and complexity of the transmission and natural occurrence of ARMs at the interfaces, the process by which resistance is transferred between cattle and the environment within the food-animal production systems is poorly understood (Horigan et al. 2016). In this section, we summarise several studies which reported HGT and clonal transmission of ARMs between livestock and the environment to build a basic understanding of the transmission dynamics of ESBL-producing bacteria to postulate possible routes for colonisation of these bacteria in the gastrointestinal tract of cattle raised without antibiotic use.

Horizontal gene transfer among bacteria at the environmental interface

The presence of antimicrobial residues or high-density and high-complexity environments accelerates HGT among bacteria resulting in the spread and sharing ARGs

at the interfaces of livestock, human, and the environment (Andersson and Hughes 2014; Fletcher 2015; von Wintersdorff et al. 2016; Sommer et al. 2017). Among HGT mechanisms, conjugation is the most common mechanism to spread ARGs among bacteria. Most ARGs are located on mobile genetic elements (MGEs), which help ARGs transfer among bacteria (Karkman et al. 2018). HGT has been reported in a diverse environment (von Wintersdorff et al. 2016), including soil bacteria and human pathogens that share ARGs and flanking regions of the ARGs (Forsberg et al. 2012). The identified ARGs in soil were relevant to β -lactams, aminoglycosides, amphenicols, sulphonamides, and tetracyclines, and those ARGs had a high identity with those found in clinical pathogens (Forsberg et al. 2012). Moreover, Nesme et al. (2014) found ARGs from different environments (soil, ocean, and human faeces), and showed soil and human faeces shared ARGs (24/94), suggesting that genes flow between these environments (Nesme et al. 2014). Also, several MGEs such as conjugative plasmids including incompatibility groups (Inc) F, A/C, N, HI2, I1, and K with specific insertion sequences (IS) such as *ISEcp1* and *ISCR1* elements are frequently reported with ESBLs (Ali et al. 2016; Irrgang et al. 2017, 2018), indicating these IS elements are strongly associated with independent acquisition of the ESBL genes. IncN plasmids encoding CTX-M-1 have been found in bacteria isolated from pigs, farmers, and farm environments, such as manure and air, indicating the spread of conjugative IncN plasmids with *bla*_{CTX-M} genes among pigs, farmers, and surroundings (Moodley and Guardabassi 2009). Similarly, distinct plasmids with the ESBL genes were shared between farm animals (pig and poultry) and humans (de Been et al. 2014). Lifshitz et al. (Lifshitz et al. 2018) reported that cattle and community derived isolates were related to each other in sharing CTX-M-15 and its surrounding MGEs (*Tn3* or *IS1380* families) (Lifshitz et al. 2018). Another study showed that ESBL-producing *E. coli* isolates from cows were carrying CTX-M-15 flanked with *ISCR1* elements (Ali et al. 2016). *ISEcp1*-CTX-M-1- Δ *orf477*, was identified regardless of plasmid origins such as human, cattle, and swine, demonstrating MGEs are critical units to spread ARGs among different environments (Jakobsen et al. 2015). *ISEcp1* elements are also known to increase expression levels of ESBLs by providing a promoter at the upstream of the ESBL genes (Vandecraen et al. 2017).

Clonal transmission of ESBL-producing bacteria at the interfaces

The intersected sequencing types (STs) across human and animal populations and the environment were

identified in Tanzania. ESBL-producing *E. coli* ST38, ST131, and ST2852 were isolated across these three interfaces, showing dissemination of clonal isolates regardless of the original sources (Seni et al. 2018). In another study, molecular relatedness between ESBL-producing isolates from human and animal populations was substantially close (Dorado-García et al. 2018). Dorado-García et al. (2018) conducted a meta-analysis of ESBL-producing isolates from 35 studies in the Netherlands to understand major ESBL gene types, plasmid replicons, and *E. coli* STs using proportional similarity index (PSIs) and principal component analysis (PCA). Isolates from humans who live near farms showed higher similarity to the isolates from their animals including broilers and pigs, whereas isolates from humans in the general population were similar with human clinical samples, surface, and sewage water, and wild birds (Dorado-García et al. 2018). Dahms et al. (2015) reported that farm workers, who contacted livestock frequently, carried identical ST with cattle isolates, indicative of zoonotic transfer of ESBL-producing bacteria between humans and their animals. Similarly, uropathogenic ESBL-producing *E. coli* from diverse sources (livestock, human, surface water, and food) shared ST10 carrying CTX-M-1 (Müller et al. 2016). In poultry farms, the ESBL-producing *E. coli* isolates from all parasitic bird flies, and excreted manure carried identical ST with the *bla*_{TEM-52} gene, suggesting a clonal transfer between flies and birds happening at the poultry farms (Blaak et al. 2014). Bui et al. (Bui et al. 2018) found identical strains, based on genotyping using pulsed-field gel electrophoresis (PFGE), among chickens in the same farms. The isolates carried *bla*_{CTX-M-55} and *bla*_{CTX-M-65} in common, suggesting bird-to-bird transmission (Bui et al. 2018). Furthermore, ESBL-producing *E. coli* isolates from faeces, and farm air in broiler chicken farms were clonal variants, suggesting the ESBL-producing *E. coli* from broiler farms can spread to the surrounding environments and beyond (Laube et al. 2014). The indistinguishable ESBL genes, plasmids, and ST of ESBL-producing *E. coli* isolates were identified from retail chicken meat and humans, suggesting the potential transmission of ARMs in food production systems as well as in wildlife areas (Leverstein-van Hall et al. 2011).

Needs for high-resolution analysis of ESBL transmission

Many studies have shown transmission of ARMs between livestock and surroundings, but most studies used low-resolution techniques, such as PFGE, PCR-based genotyping technologies, and MLST, to evaluate

genetic similarity to conclude gene or bacterial transmission at the interfaces. However, pan-genome based single nucleotide polymorphism (SNP) analysis has provided high-resolution tools to verify whether isolated strains at the interfaces are truly clonal variants or not (Bekal et al. 2016). Not surprisingly, isolates defined as the same strains by low-resolution techniques were found to be non-clonal variants (Knudsen et al. 2017; Guo et al. 2018). In our recent study (Teng et al. 2019), strains belonging to the same ST with an identical profile of virulence genes did not cluster together in a phylogenetic tree. To overcome the issues raised by low-resolution techniques, the GenomeTrakr network has been created by the Food and Drug Administration (FDA) to track pathogens that caused foodborne outbreaks, by comparing variant SNPs in the whole genomes of the isolated strains (Wang et al. 2016). However, there are still limited studies showing ESBL transmission by applying whole genome sequencing (WGS). Schaufler et al. showed the interspecies transmission of ESBL-producing *E. coli* ST410 through SNP analysis (Schaufler et al. 2016), showing a small number of SNPs (45 total SNPs, 8.6 SNPs/Mbp) between isolates from wild mute swan and humans. Furthermore, human isolates were closely related with avian and dog isolates with 24 and 29 SNPs, respectively (Schaufler et al. 2016). Similarly, Ma et al. identified identical plasmid groups, IncFIB and FII, and similar virulence factors in intrauterine pathogenic *E. coli* (IUPEC) strains from different dairy cows using WGS (Ma et al. 2018). However, the IUPEC strains were not clonal variants by phylogenetic tree analysis of whole genomes, revealing no animal to animal transmission of IUPEC (Ma et al. 2018). Therefore, we propose that accurate and correct understanding of gene and ARM transmission using high-resolution tools such as WGS is pivotal to identify transmission origin and route of ESBL-producing bacteria at the interfaces of livestock and the environment.

Mitigation for antibiotic resistance

Total elimination of AR is an impossible task, but effective strategies would slow down the development of new types of AR and its spread (Livermore et al. 2006). Antimicrobial stewardship for the selection, dosage, and duration of antimicrobial treatment is critical to reduce AR occurrence in the livestock industry (Ma et al. 2019). Efforts to control ARM transmission at the interfaces of livestock and environment would be extremely challenging due to the range of factors involved in the transmission of ARMs. To reduce the occurrence and acquisition of ARMs via multiple

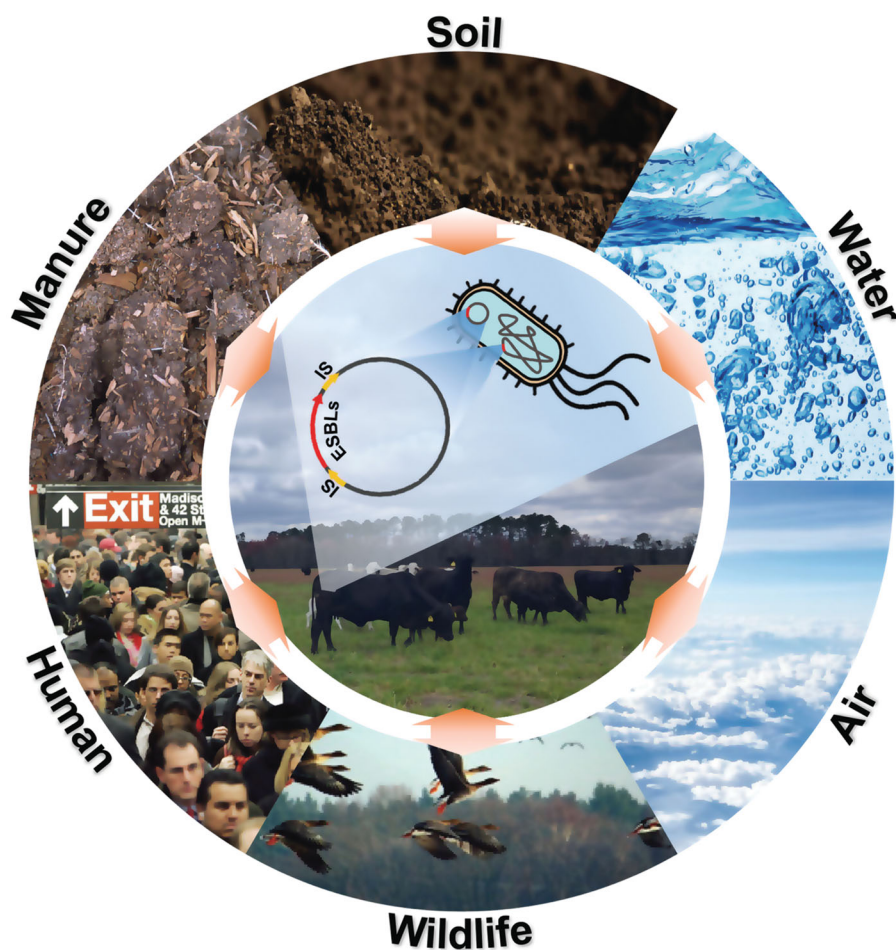


Figure 1. Potential transmission routes of the ESBL genes and ESBL-producing bacteria at the interfaces of livestock and the environment. ESBL-producing bacteria in livestock can naturally occur and transmit through the environmental sources, such as manure, soil, water, air, wildlife, and human (especially farm workers) by horizontal gene transfer of the ESBL genes in chromosomal DNA and on plasmids mediated by IS elements or bacterial transmission.

sources as has been discussed here, critical control points, where transmission of ARMs between livestock and environment is expected or occurring, should be identified and managed effectively (Berendonk et al. 2015). Good farming management such as improved farm hygiene and biosecurity can become one way to decrease the prevalence and concentration of ARMs in livestock (Markland et al. 2019). For example, the frequency of cleaning drinking water troughs was negatively associated with the prevalence of ARMs and the presence of quarantine programmes in farms, and burial/burning of deceased animals were related to the reduction of ARMs detection in cattle (Markland et al. 2019). A better understanding of interactions among microbiological, animal and environmental factors would provide insights into predicting the occurrence of ARMs and the creation of novel management strategies. In addition, the transmission rates of ARMs via different vehicles or sources need to be quantified, and modelling of transmission should be developed with

such results to evaluate the risks of transmission at the interfaces and colonisation of ARMs in hosts. There are still data gaps to quantify the relative contribution of each factor responsible for ARMs transmission in the beef cattle industry (Horigan et al. 2016), indicating the urgency of collecting ecological and epidemiological data for mitigation of AR. Currently, there are available alternatives to antibiotics, such as prebiotics and probiotics, phage therapy, vaccines, antimicrobial peptides, antimicrobial polymers, and combination of synergistic antibiotics (Ma et al. 2019), although the effectiveness of these methods are not fully evaluated. Development and application of better AR mitigation strategies will be needed to reduce the risks of AR.

Conclusions

Multi-drug resistant pathogens are a major threat to global public health due to the increasing frequency of antimicrobial resistance and reducing efficacy of

antibiotics. The lack of fully understanding of how ESBLs-producing *Enterobacteriaceae* are arising at the interfaces of livestock, wildlife, and the environment (Figure 1), inhibits our ability to develop mitigation strategies. Quantitative mathematical modelling of risks of ARG/ARM transmission may help identify control points at the interfaces. High-resolution technologies may be required to accurately identify ARM transmission pathways, in order to facilitate tracking of the causative pathogens in outbreak settings. There is limited information available to determine the critical natural carrier/reservoir of ESBL-producing bacteria. Effective mitigation strategies such as farm management, biosecurity, and hygiene might facilitate the reduction of ESBL-producing bacteria in livestock. New strategies are needed to combine knowledge of the environmental, animal, and bacterial aspects to tackle this global issue.

Disclosure statement

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