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# Antimicrobial Resistance in *Escherichia coli*

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**ABSTRACT** Multidrug resistance in *Escherichia coli* has become a worrying issue that is increasingly observed in human but also in veterinary medicine worldwide. *E. coli* is intrinsically susceptible to almost all clinically relevant antimicrobial agents, but this bacterial species has a great capacity to accumulate resistance genes, mostly through horizontal gene transfer. The most problematic mechanisms in *E. coli* correspond to the acquisition of genes coding for extended-spectrum  $\beta$ -lactamases (conferring resistance to broad-spectrum cephalosporins), carbapenemases (conferring resistance to carbapenems), 16S rRNA methylases (conferring pan-resistance to aminoglycosides), plasmid-mediated quinolone resistance (PMQR) genes (conferring resistance to [fluoro]quinolones), and *mcr* genes (conferring resistance to polymyxins). Although the spread of carbapenemase genes has been mainly recognized in the human sector but poorly recognized in animals, colistin resistance in *E. coli* seems rather to be related to the use of colistin in veterinary medicine on a global scale. For the other resistance traits, their cross-transfer between the human and animal sectors still remains controversial even though genomic investigations indicate that extended-spectrum  $\beta$ -lactamase producers encountered in animals are distinct from those affecting humans. In addition, *E. coli* of animal origin often also show resistances to other—mostly older—antimicrobial agents, including tetracyclines, phenicols, sulfonamides, trimethoprim, and fosfomycin. Plasmids, especially multiresistance plasmids, but also other mobile genetic elements, such as transposons and gene cassettes in class 1 and class 2 integrons, seem to play a major role in the dissemination of resistance genes. Of note, coselection and persistence of resistances to critically important antimicrobial

agents in human medicine also occurs through the massive use of antimicrobial agents in veterinary medicine, such as tetracyclines or sulfonamides, as long as all those determinants are located on the same genetic elements.

## INTRODUCTION

*Escherichia coli* is a bacterium with a special place in the microbiological world since it can cause severe infections in humans and animals but also represents a significant part of the autochthonous microbiota of the different hosts. Of major concern is a possible transmission of virulent and/or resistant *E. coli* between animals and humans through numerous pathways, such as direct contact, contact with animal excretions, or via the food chain. *E. coli* also represents a major reservoir of resistance genes that may be responsible for treatment

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failures in both human and veterinary medicine. An increasing number of resistance genes has been identified in *E. coli* isolates during the last decades, and many of these resistance genes were acquired by horizontal gene transfer. In the enterobacterial gene pool, *E. coli* acts as a donor and as a recipient of resistance genes and thereby can acquire resistance genes from other bacteria but can also pass on its resistance genes to other bacteria. In general, antimicrobial resistance in *E. coli* is considered one of the major challenges in both humans and animals at a worldwide scale and needs to be considered as a real public health concern.

This chapter gives an update of antimicrobial resistance in *E. coli* of animal origin by focusing on resistance to those classes of antimicrobial agents mainly used in veterinary medicine and to which *E. coli* isolates of animal origin are known to exhibit resistance.

## **E. COLI IN ANIMALS: A PATHOGENIC AND A COMMENSAL BACTERIUM**

“Colibacillosis” is a general term for a disease caused by the bacterium *E. coli*, which normally resides in the lower intestines of most warm-blooded mammals. Hence, *E. coli* is a versatile microorganism with a number of pathogenic isolates prone to cause intestinal and extra-intestinal infections, while most others are harmless for their host and refer to commensalism. The pathogenic *E. coli* isolates can be classified into different pathotypes, or pathovars, where each pathotype causes a different disease (1). The intestinal pathogenic *E. coli* pathovars are responsible for disorders in the gut ranging from mild diarrhea to severe colitis, while the extra-intestinal pathogenic *E. coli* pathovars are mostly asymptomatic inhabitants of the intestinal tract that cause extra-intestinal diseases after migrating to other parts of the body, such as the urinary tract or the blood stream (2). Animal diseases due to *E. coli* can also be caused by *E. coli* isolates originating from the environmental reservoir or other infected individuals. Pathogenic and nonpathogenic *E. coli* differ by the acquisition or loss of virulence-associated traits associated with *E. coli* pathogenicity. The number of genes present in the *E. coli* genome varies from 4,000 to 5,000 genes, with approximately 3,000 genes shared by the different isolates, whereas the others mostly correspond to colonization or virulence determinants. Advanced insights in the genomic plasticity of *E. coli* have been possible by the use of whole-genome sequencing, providing a better understanding of the core and accessory genomes of pathogenic and commensal *E. coli* isolates (3).

In animals, *E. coli* is one of the leading causes of diarrhea, together with other pathogens such as rotavirus, coronavirus, *Cryptosporidium parvum*, or a combination of these (4). These enterotoxigenic *E. coli* (ETEC) strains bind and colonize the intestinal epithelium through adhesins expressed in the context of fimbriae, such as the F4 (formerly designated K88), F5 (K99), F6 (987P), F17, and F18 fimbriae (5). ETEC also produces various enterotoxins, of which heat-labile and heat-stable toxins and/or enteroaggregative heat-stable toxin 1 (EAST1) lead to diarrhea. ETEC affects various animal species, mostly young animals, particularly food-producing animals (piglets, newborn calves, chickens) but also companion animals such as dogs. In livestock, diarrhea is considered one of the major diseases, which can propagate among animals with possibly significant consequences at the herd/flock level. Diarrhea is observed in pigs and calves during the first 3 to 5 days of life and in pigs 3 to 10 days after weaning. The trend toward early weaning in several countries and continents may have played a significant role in the rising occurrence of postweaning diarrhea in the pig sector. As a consequence, lethal ETEC infections in animals can also occur as a result of severe dehydration and electrolyte imbalance.

*E. coli* infections in animals are not restricted to young individuals but occur in adults as well. As mentioned above, extra-intestinal pathogenic *E. coli* is responsible for infections of the lower and upper urinary tract, particularly in companion animals (6, 7). In poultry, avian-pathogenic *E. coli* causes colibacillosis initiated in the respiratory tract by inhalation of fecal dust before spreading further in the whole body, causing septicemia, pericarditis, and mortality (8). In dairy cattle, mastitis is a common inflammatory response of the mammary gland, significantly decreasing milk production and causing dramatic economic losses, with *E. coli* being one of the major causes—together with *Staphylococcus aureus*, *Streptococcus uberis*, *Streptococcus agalactiae*, and *Streptococcus dysgalactiae* (9, 10). In particular, *E. coli* is responsible for more than 80% of cases of acute mastitis where the severe clinical signs are induced by the lipopolysaccharide (LPS) as a primary virulence factor followed by the subsequent release of inflammatory mediators (11). Nonetheless, it is broadly considered that mastitis in dairy cattle due to *E. coli* is neither associated with specific *E. coli* serovars nor involves a common set of virulence factors shared among *E. coli* isolates.

*E. coli* infections in animals are subjected to various pharmaceutical treatments including antimicrobials. For instance, ampicillin, streptomycin, sulfonamides,

or oxytetracyclines are commonly used to treat bovine mastitis, but broad-spectrum cephalosporins and fluoroquinolones also have indications through systemic or local administration depending on the severity of the clinical symptoms (12) and the resistance properties of the causative *E. coli* isolates. Nonetheless, the role of antimicrobials in the treatment of coliform mastitis is becoming more and more open to debate. Recommendations provided for veterinarians refer to the preferable use of first-line antimicrobial agents and avoidance of antimicrobial therapy during the dry-off period of dairy cattle. Global data and trends on the antimicrobial resistance of *E. coli* in mastitis have been highlighted in several national reports and vary among countries even though relevant comparisons are difficult. To date, the global picture indicates that antimicrobial susceptibility of *E. coli* in mastitis remains high. In particular, extended-spectrum  $\beta$ -lactamases (ESBLs) or overexpressed cephalosporinases (AmpCs) produced by *E. coli* and conferring resistance to broad-spectrum cephalosporins have been sporadically isolated from milk samples (13–16). Those families of antimicrobial agents may also be prescribed in newborns affected by diarrhea. Again, action plans against antimicrobial resistance in the animal sector constantly advise veterinarians to use antimicrobials prudently and emphasize the need to consider all other preventive and therapeutic options and restrict the use of antimicrobial agents to those situations where it is indispensable (17). For instance, strategies to prevent and treat neonatal diarrhea should include not only the prescription of antimicrobials but also good colostrum management practices to ensure adequate passive immunity and appropriate oral or intravenous fluid therapy to compensate for dehydration, acidosis, and electrolyte imbalance (18). Global hygiene procedures at the farm level and vaccinations are also essential measures for improvement in antimicrobial stewardship. In contrast to mastitis, ESBL/AmpC genes have been abundantly reported in *E. coli* originating from the digestive tract in animals. This includes pathogenic *E. coli* recovered from diarrheic samples of young animals, yet it remains highly difficult to confirm that a specific *E. coli* isolate is responsible for the intestinal disease. More importantly, ESBL/AmpC genes have been widely recognized in commensal *E. coli* isolated from fecal samples of various food-producing and companion animals through selective screenings using cephalosporin-containing media (19–21). High prevalence rates of ESBL/AmpC-producing *E. coli* were found in certain settings and countries, such as in the veal calves sector in Europe and in broiler production worldwide. In those

cases, it more likely reflects the selective impact of the use of antimicrobials—and particularly of broad-spectrum cephalosporins such as ceftiofur—on the commensal *E. coli* microbiota. In broilers, such a situation has become a point of major concern on a global scale since broad-spectrum cephalosporins are both of critical importance in human medicine and not authorized for use in poultry. In addition to national actions taken, mostly in Europe, to restrict the use of critically important antimicrobial agents in animals, the use of antimicrobial agents as growth promoters has been banned in animals in Europe since 2006, but it is still common practice in most countries. Altogether, since antimicrobial agents have a major impact on the gut microbiota where *E. coli* resides, multidrug-resistant *E. coli*, such as ESBL/AmpC-producing *E. coli*, has become one of the main indicators to estimate the burden of antimicrobial resistance in animals and other sectors in a One Health perspective.

## RESISTANCE TO $\beta$ -LACTAMS

There are numerous genes in *E. coli* of human and animal origin that confer resistance to  $\beta$ -lactams. Some of them, such as *bla*<sub>TEM-1</sub>, are widespread in *E. coli* from animals but code only for narrow-spectrum  $\beta$ -lactamases that can inactivate penicillins and aminopenicillins. However, in recent years, genes that code for ESBLs/AmpCs have emerged in *E. coli* from humans and animals. Most recently, genes coding for carbapenemases have also been detected occasionally in *E. coli* of animal origin. Because of the relevance of these latter two groups of  $\beta$ -lactamases, the following subsections provide more detailed information on ESBLs, AmpCs, and carbapenemases.

### Clavulanic-Acid Inhibited Class A ESBLs

ESBLs belong mostly to class A of the Ambler classification (22) and group 2be according to the updated functional classification of  $\beta$ -lactamases by Bush and Jacoby (23). ESBL-producing strains of *E. coli* are clinically relevant in veterinary medicine since they confer resistance to penicillins, aminopenicillins, and cephalosporins, including the third-generation cephalosporins ceftiofur and cefovecin and the fourth-generation cephalosporin cefquinome, which are approved veterinary drugs. Thus, ESBLs may be the cause of treatment failures and limit the therapeutic options of veterinarians, because they have been identified in increasing numbers in *E. coli* of food-producing and companion animals worldwide (24, 25). ESBL-producing *E. coli* from animals has been isolated not only from infection sites, but

also from the feces of healthy individuals (26–29). Moreover, ESBL-producing *E. coli* has also been detected in wild animals, emphasizing the wide distribution of these resistance determinants (30).

TEM- and SHV-ESBLs were among the first described ESBLs in the 1980s, and they were predominant until 2000. Since then, CTX-M-ESBLs emerged and have been predominantly identified in commensal and pathogenic ESBL-producing *E. coli* isolates of human and animal origin around the world (31, 32). The reason for this shift remains unknown, despite many investigations and surveillance studies. It is difficult to compare prevalence data of ESBL-producing *E. coli* isolates because several resistance-monitoring programs register the resistance rates for cephalosporins in *E. coli* isolates of animal origin but do not necessarily confirm whether

this resistance is based on ESBL production or another  $\beta$ -lactamase. Moreover, the molecular identification of ESBL genes in monitoring programs is not systematic. The nonharmonized methodology is also reflected in sampling plans and therefore in the origin of the *E. coli* isolates, e.g., healthy or diseased animals (33). Nevertheless, the European Food Safety Authority compiled a scientific opinion which states that the prevalence of resistance to cefotaxime in food-producing animals varies by country and animal species. In addition, the ESBL genes *bla*<sub>CTX-M-1</sub>, *bla*<sub>CTX-M-14</sub>, *bla*<sub>TEM-52</sub>, and *bla*<sub>SHV-12</sub> were identified as the most common ones along with a wide range of other *bla*<sub>CTX-M</sub>, *bla*<sub>TEM</sub>, and *bla*<sub>SHV</sub> variant genes (34) (Table 1).

A large study conducted in Germany analyzed ESBL-producing *E. coli* isolates collected from diseased

**TABLE 1** Examples of acquired ESBL genes in *E. coli* of animal origin from Europe, the U.S., Latin America, Africa, and Asia

ESBL gene	Geographical origin	Source	Sequence type(s)	Reference
<i>bla</i> <sub>CTX-M-1</sub>	Denmark	Pig	10, 189, 206, 453, 542, 744, 910, 1406, 1684, 2739, 4048, 4052, 4053, 4056,	<a href="#">257</a>
	Sweden	Poultry	57, 135, 155, 219, 602, 752, 1594, 1640	<a href="#">258</a>
	Great Britain	Poultry	4, 10, 57, 88, 155, 371, 1515, 1517, 1518, 1549, 1550	<a href="#">259</a>
	Switzerland	Poultry, cattle, pig	48, 83, 305, 525, 528, 529, 533, 534, 536, 540	<a href="#">260</a>
	The Netherlands	Veal calves	10, 58, 88, 117, 162, 224, 354, 448, 617, 648, 744, 973	<a href="#">21</a>
	France	Dairy cattle	23, 58	<a href="#">13</a>
	Germany	Dairy cattle	10, 117, 540, 1431, 5447	<a href="#">14</a>
	Germany	Swine, cattle, poultry, horse	10, 23, 83, 100, 131, 167, 362, 453, 648, 925, 973, 1684, 2699	<a href="#">43</a>
	Germany	Dog	10, 23, 69, 160, 224	<a href="#">28</a>
	U.S.	Dog, cat	23, 38, 44, 68, 69, 131, 167, 405, 410, 443, 648, 1011, 1088, 5174, 5206, 5220	<a href="#">261</a>
<i>bla</i> <sub>CTX-M-14</sub>	The Netherlands	Veal calves	10, 57, 952	<a href="#">21</a>
	France	Dairy cattle	10, 23, 45, 58	<a href="#">13</a>
	China	Pig, poultry	10, 155, 206, 224, 359, 405, 602, 648, 2929, 2930, 2962	<a href="#">262</a>
	China	Dog	10, 38, 104, 131, 167, 405, 648, 146, 3630	<a href="#">97</a>
<i>bla</i> <sub>CTX-M-15</sub>	UK	Poultry	57, 156	<a href="#">259</a>
	UK	Dog	131, 410, 1284, 2348, 4184	<a href="#">99</a>
	The Netherlands	Veal calves	58, 59, 88, 361, 410, 648	<a href="#">21</a>
	Germany	Livestock	10, 88, 90, 167, 410, 617, 648	<a href="#">263</a>
	Germany	Dairy cattle	10, 361, 1508	<a href="#">14</a>
	Germany, Denmark, Spain, France, the Netherlands	Dog, horse	131	<a href="#">264</a>
	Germany, Italy	Dog, cat, cattle, horse	648	<a href="#">96</a>
	Germany	Dog	410, 3018	<a href="#">28</a>
	U.S.	Dog, cat	23, 38, 44, 68, 69, 131, 167, 405, 410, 443, 617, 648, 1011, 1088, 5174, 5206, 5220	<a href="#">261</a>
	Mexico	Dog	410, 617	<a href="#">138</a>
<i>bla</i> <sub>SHV-12</sub>	Spain, Germany	Wild bird, dog, poultry	23, 57, 117, 155, 362, 371, 453, 616, 1564, 2001	<a href="#">39</a>
	China	Dog	10, 75, 131, 167, 405, 648, 2375, 3058	<a href="#">97</a>
	China	Dog	10, 38, 44, 69, 73, 75, 131, 302, 405, 648, 1700, 2375	<a href="#">97</a>
	Nigeria	Poultry	10, 405	<a href="#">221</a>
	Spain, Germany	Wild bird, dog, poultry	23, 57, 117, 155, 362, 371, 453, 616, 1564, 2001	<a href="#">39</a>
	China	Dog	10, 75, 131, 167, 405, 648, 2375, 3058	<a href="#">97</a>
	China	Dog	10, 75, 131, 167, 405, 648, 2375, 3058	<a href="#">97</a>

food-producing animals in the GERM-Vet monitoring program from 2008 to 2014 (35). This study detected the gene *bla*<sub>CTX-M-1</sub> in 69.9% of the ESBL producers, followed by *bla*<sub>CTX-M-15</sub> in 13.6%, *bla*<sub>CTX-M-14</sub> in 11.7%, *bla*<sub>TEM-52</sub> in 1.9%, and *bla*<sub>SHV-12</sub> in 1.4%. The genes *bla*<sub>CTX-M-3</sub> and *bla*<sub>CTX-M-2</sub> were identified in 1.0% and 0.5%, respectively. The distribution of ESBL genes varies with regard to the different animal hosts and the isolation sites; for example, ESBL-producing *E. coli* were isolated more frequently from cases of enteritis in calves than from cases of bovine mastitis (35). Moreover, the geographical location also plays a role. For instance, the study by Day and co-workers identified the gene *bla*<sub>CTX-M-1</sub> as the most common among bovine ESBL-producing *E. coli* from Germany, while the gene *bla*<sub>CTX-M-15</sub> was most frequent in *E. coli* isolates of bovine origin from the United Kingdom (36). In ESBL-producing *E. coli* isolates from European companion animals, the gene *bla*<sub>CTX-M-1</sub> was most common, but the gene *bla*<sub>CTX-M-15</sub> was also frequently identified (24, 37). In the United States, the gene *bla*<sub>CTX-M-15</sub> was predominant among ESBL-producing *E. coli* from urinary tract infections of companion animals (38). The gene *bla*<sub>CTX-M-14</sub> was less frequent in Europe, but in Asia among the most common ESBL genes in poultry, companion animals, and humans (24). The ESBL gene *bla*<sub>SHV-12</sub> was not frequently reported but was identified in ESBL-producing *E. coli* from poultry, dogs, and wild birds in Spain and Germany (39).

Worldwide, the most common ESBL gene in *E. coli* isolates of human origin is *bla*<sub>CTX-M-15</sub>, which is mainly associated with the pandemic *E. coli* clone O25:H4-ST131 (40). This clone has been rarely identified in animals and if so, mostly in companion animals (24, 25, 41, 42). The production of various ESBLs has been demonstrated in animal *E. coli* isolates of a wide variety of multilocus sequence types (24, 35, 36, 43) (Table 1). According to Ewers and colleagues, an exclusive linkage of a specific *bla* gene or a distinct host with a certain sequence type (ST) is not evident (24). Nevertheless, ESBL-producing *E. coli* belonging to certain STs have been more frequently detected among animals and humans than others, namely ST10, ST23, ST38, ST88, ST131, ST167, ST410, and ST648, which are supposed to facilitate the spread of ESBL genes (25, 36, 43, 44).

The dissemination of ESBL genes among *E. coli* from animals is mainly driven by horizontal gene transfer. ESBL genes are associated with several insertion sequences (ISs), such as *ISEcp1*, *ISCR1*, *IS26*, and *IS10*, transposons such as *Tn2*, and integrons (43, 45, 46). The

majority of ESBL genes are plasmid-located, whereas the integration of ESBL genes in the chromosomal DNA of *E. coli* of animal origin has been rarely described (47–49). The most prevalent replicon types identified among ESBL-carrying plasmids from *E. coli* are IncF, IncI1, IncN, IncHI1, and IncHI2, but plasmids of other replicon types also play a role in the dissemination of ESBL genes (47). The study by Day and co-workers identified 16 ESBL genes on 341 transferable plasmids, belonging to 19 replicon types (36). Despite this complexity, some plasmids that carry ESBL genes seem to be more successful than others. Plasmids carrying *bla*<sub>CTX-M-15</sub> and belonging to the IncF family had been detected in the pandemic *E. coli* clone O25:H4-ST131 (47). The ESBL gene *bla*<sub>CTX-M-1</sub> was frequently identified on plasmids belonging to the IncN or IncI1 families, while *bla*<sub>CTX-M-14</sub> was detected on IncK plasmids, and *bla*<sub>CTX-M-3</sub> on IncL/M plasmids (47). IncI1, IncK, and IncX plasmids carried the ESBL gene *bla*<sub>SHV-12</sub> (39). A plasmid multilocus sequence typing scheme assigns members of the most common plasmid families to pSTs to trace epidemic plasmids (47). Some plasmids harbor additional resistance genes besides the ESBL gene, which may facilitate the coselection and persistence of ESBL gene-carrying plasmids even without the selective pressure of  $\beta$ -lactams, when the respective antimicrobial agents are used (14, 43).

Many studies have tried to figure out whether ESBL-producing *E. coli* identified in humans might originate from animal reservoirs. Most of those studies could not find an obvious link, and most often, it was clearly shown that there was no link at all, animals and humans representing reservoirs of different clonal lineages that possessed various ESBL determinants (50, 51). Nevertheless, a Dutch study showed that a significant number of either human- or poultry-associated ESBL-producing *E. coli* isolates harbored genetically indistinguishable ESBL-encoding plasmids, suggesting that plasmids might be common vehicles that are likely transmitted through the food chain (52). Indeed, numerous studies have pointed out that chickens may represent a significant reservoir of ESBLs, which has become a considerable concern worldwide, although broad-spectrum cephalosporins are not approved for use in the poultry sector. ESBL-producing *E. coli* has been reported as a cause of infections in broilers and laying hens but also as a colonizer of living chickens and a contaminant of chicken meat at retail in several European and non-European countries, including countries in which the use of antimicrobial agents has been reduced following national action plans in veterinary medicine (53).

## Acquired AmpC Cephalosporinases

Although class A ESBL enzymes are the most common sources of acquired resistance to broad-spectrum cephalosporins in *E. coli*, class C  $\beta$ -lactamases, also known as AmpC-type enzymes, confer high-level resistance to those antimicrobial agents (54). The main plasmid-encoded AmpC enzymes are CMY-, DHA-, and ACC-type  $\beta$ -lactamases, with a higher prevalence of CMY-type enzymes worldwide (55). In animals, the majority of identified AmpC enzymes have been of the CMY type (Table 2) (25, 56). A recent study performed in Denmark identified CMY-2-producing *E. coli* isolates from poultry meat, poultry, and dogs (57). The study showed that the dissemination of *bla*<sub>CMY-2</sub> was mainly due to the spread of IncI1- $\gamma$  and IncK plasmids. In Sweden, though there are, in general, low rates of resistance to broad-spectrum cephalosporins, the occurrence of CMY-2-producing *E. coli* was demonstrated when Swedish chicken meat, Swedish poultry, and imported chicken meat were examined (58). The occurrence of CMY-2-producing *E. coli* in the Swedish broiler sector has been attributed to importation of 1-day old chicks from the United Kingdom, where broad-spectrum cephalosporins had been administered prophylactically to the young birds before exportation (59). It has also been shown that migratory birds may be colonized with CMY-2-positive *E. coli* (60). In a study conducted in Florida, a series of clonally unrelated CMY-2-producing *E. coli* isolates were recovered from feces of seagulls (61). They belong mainly to phylogroup D, corresponding to human commensal isolates, but some STs had

previously been identified from human bacteremia. The *bla*<sub>CMY-2</sub> gene was mainly found on IncI1 plasmids, as reported with human isolates. Therefore, there was a significant correlation between the genetic features of those isolates and those known for human isolates in the United States, showing that seagulls were likely colonized by human isolates. This is an example showing that migratory birds crossing long distances, such as along the eastern United States coastline, may be reservoirs and therefore sources of such multidrug-resistant isolates, as is also exemplified in South America and Europe (62, 63).

## Acquired Carbapenemases

Carbapenemases have been rarely identified in animal *E. coli*. This is likely the consequence of a very weak selective pressure (if any) by carbapenems, since those antimicrobial agents are not (or only in rare cases for individual non-food-producing animals) prescribed in veterinary medicine. Nevertheless, there has been some concern in recent years since carbapenemase-producing bacteria, including *E. coli*, have been isolated from animals worldwide (64–66).

The first carbapenemase determinant identified in an animal *E. coli* isolate was VIM-1, which was recovered from a pig in Germany (67) (Table 3). Since then, other VIM-1-producing *E. coli* isolates have been identified in different pig farms in the same country (68, 69). This carbapenemase has so far never been found elsewhere in animal isolates. Other identified carbapenemases in *E. coli* are NDM-1 and NDM-5. NDM-1 has been iden-

**TABLE 2** Examples of acquired *bla*<sub>CMY-2</sub> genes in *E. coli* of animal origin from Europe, the North and South America, Asia, and Africa

Geographical origin	Source	Sequence type(s)	Reference
Germany	Pig	625	265
Spain	Wild bird (yellow-legged gull)	10	266
Denmark, Germany, France	Poultry and poultry meat, dog	10, 23, 38, 48, 68, 69, 88, 93, 115, 117, 131, 206, 212, 219, 297, 350, 361, 372, 405, 410, 428, 448, 457, 546, 616, 746, 754, 919, 963, 1196, 1056, 1303, 1518, 1585, 1594, 1640, 1775, 2040, 2144, 2168, 2196, 2558, 3272, 3574, 4048, 4124, 4125, 4240, 4243	57
Portugal	Poultry	57, 117, 429, 2451	267
Switzerland	Poultry meat	38, 1564	268
Switzerland	Poultry	3, 9, 61, 527, 530, 535, 539	
Austria	Wild bird (rook)	224	60
U.S.	Poultry meat	131	269
Brazil	Poultry	453, 457, 1706	270
China	Pig, poultry	10, 48, 69, 101, 155, 156, 354, 359, 362, 457, 648, 1114, 1431, 2294, 2690, 3014, 3244, 3245, 3269, 3376, 3402, 3403, 3404	271
Japan	Cattle	1284, 2438	272
Japan	Dog	10, 354, 493, 648, 3557	273
Tunisia	Poultry	117, 155, 2197	274

**TABLE 3** Examples of acquired carbapenemase genes in *E. coli* of animal origin from Europe, North and South America, Africa, Australia, and Asia

Carbapenemase gene	Geographical origin	Source	Sequence types	Reference
<i>bla</i> <sub>NDM-1</sub>	China, U.S.	Dog, cat, pig	167, 1695, 1585, 1721, 359	<a href="#">70</a> , <a href="#">275</a> , <a href="#">276</a>
<i>bla</i> <sub>NDM-5</sub>	China, Algeria, India	Dog, pig, cow, duck	48, 54, 90, 156, 165, 167, 410, 648, 1114, 1178, 1234, 1437, 2439, 3331, 4429, 4463, 4656	<a href="#">74</a> , <a href="#">75</a> , <a href="#">277–279</a>
<i>bla</i> <sub>VIM-1</sub>	Germany	Seafood, pig	10, 88	<a href="#">67</a> , <a href="#">68</a> , <a href="#">280</a> , <a href="#">281</a>
<i>bla</i> <sub>IMP-4</sub>	Australia	Silver gull	48, 58, 167, 189, 216, 224, 345, 354, 541, 542, 744, 746, 1114, 1139, 1178, 1421, 2178, 4657, 4658,	<a href="#">76</a>
<i>bla</i> <sub>OXA-48</sub>	Germany, U.S., France, Lebanon, Algeria	Dog, cat, chicken	38, 372, 648, 1196, 1431	<a href="#">77–79</a> , <a href="#">261</a>
<i>bla</i> <sub>OXA-181</sub>	Italy	Pig	359, 641	<a href="#">80</a>
<i>bla</i> <sub>KPC-2</sub>	Brazil	Dog	648	<a href="#">287</a>

tified in the United States and in China, in isolates recovered from dogs, cats, and pigs ([70](#), [71](#)). NDM-5 has been detected in China, India, and Algeria, from cattle, poultry, dogs, cats, and fish ([72–75](#)). The gene encoding IMP-4 has been identified in *E. coli* isolates recovered from silver gulls in Australia ([76](#)). Interestingly, the OXA-48 carbapenemase, which is the most prevalent carbapenemase in human enterobacterial isolates in Europe, has been found in *E. coli* isolates recovered from dogs, cats, and chickens in Germany, France, Lebanon, Algeria, and the United States ([37](#), [77–79](#)). Finally, the OXA-181 enzyme, which is a variant of OXA-48 increasingly reported in humans, has recently been identified in animals as well, being found in clonally unrelated *E. coli* isolates recovered from pigs in Italy ([80](#)). Even though the class A  $\beta$ -lactamase KPC is one of the most commonly identified carbapenemases in human isolates in some parts of the world, including in North America, China, and some European countries (Italy, Greece, Poland), it has not yet been identified in animal *E. coli* isolates so far ([81](#), [82](#)), except for a single *bla*<sub>KPC-2</sub>-carrying isolate from a dog in Brazil that suffered from a urinary tract infection ([287](#)).

Overall, and notably, the different carbapenemase genes that have been identified among animals in different countries reflect the types of carbapenemases known to be the most prevalent in human isolates in those countries. Considering that carbapenems are not used in veterinary medicine, it remains to be determined which antimicrobial selective pressure is responsible for the selection of such carbapenemase producers in animals. Penicillins, however, are excellent substrates for any kind of  $\beta$ -lactamases, including carbapenemases, and therefore their use might correspond to a selective pressure anyhow. In addition, it remains to be evaluated whether animals may act as potential sources of transmission of those resistance traits toward humans or if,

conversely, this epidemiology just reflects the consequence of a higher prevalence in humans that may eventually target animals through an environmental dissemination. Since the occurrence of carbapenemase-producing *Enterobacteriaceae* in animals is marginal, it therefore does not correspond to a significant threat to human medicine ([65](#)).

## RESISTANCE TO QUINOLONES AND FLUOROQUINOLONES

Quinolones and fluoroquinolones are important antimicrobial agents for treating various types of infections in both humans and animals. They are known to be bactericidal against virtually all bacteria. Resistance to these antimicrobial agents is usually due to mutations in the drug targets, namely, the genes for DNA gyrase and topoisomerase IV, but other mechanisms such as reduced permeability of the outer membrane, protection of the target structures, or upregulated efflux pumps may also play a role ([83](#)).

### Resistance to (Fluoro)Quinolones by Chromosomal Target Site Mutations

The primary target of (fluoro)quinolones in *E. coli* is the gyrase, which consists of two GyrA subunits and two GyrB subunits. Topoisomerase IV constitutes a secondary target in Gram-negative bacteria. This enzyme consists of two ParC and two ParE subunits. Most mutations were found within the quinolone resistance-determining region, which is between Ala67 and Gln107 in GyrA, and most frequently mutations occur at codons 83 and 87 ([83](#)). Single mutations in the gene *gyrA* may confer resistance to quinolones, but for resistance to fluoroquinolones, further mutations within *gyrA* and/or *parC* are needed. Most *parC* mutations occur at codons 80 and 84 ([83](#)). In clinical *E. coli* isolates from com-



panion animals, different combinations of mutations were detected at codons 83 and 87 in *gyrA* and at codons 80 and 84 in *parC* (84, 85). Mutations within *gyrA* and *parC* were also described in *E. coli* isolates originating from diseased food-producing animals (86, 87).

### Resistance to (Fluoro)Quinolones by Plasmid-Borne Resistance Mechanisms

Since the identification of the first plasmid-mediated quinolone resistance (PMQR) determinant, *qnrA1*, in 1997, there is serious concern about the global dissemination of PMQR genes (88, 89). Several plasmid-encoded resistance mechanisms have been identified, including (i) Qnr-like proteins (QnrA, QnrB, QnrC, QnrD, and QnrS) which protect DNA from quinolone binding, (ii) the AAC(6')-Ib-cr acetyltransferase that modifies certain fluoroquinolones such as ciprofloxacin and enrofloxacin, and (iii) active efflux pumps (QepA and OqxAB). Overall, these resistance determinants do not confer a high level of resistance to quinolones (or fluoroquinolones), but rather, confer reduced susceptibility to those antimicrobial agents. However, they might contribute to the selection of isolates exhibiting higher levels of resistance through additional chromosomally encoded mechanisms (89).

PMQRs have been identified widely among human isolates but also among animal isolates. Especially in China, numerous studies have shown high prevalences of Qnr, AAC(6')-Ib-cr, and QepA determinants among food-producing animals (86, 90), and some studies highlighted an increased prevalence through the years (91). A Europe-wide retrospective study identified the genes *qnrS1* and *qnrB19* in *E. coli* isolates from food-producing animals, namely, poultry, cattle, and pigs (92). PMQRs were detected not only in food-producing animals, but also in companion animals. In *E. coli* isolates from diseased companion animals, the genes *qnrS1*, *qnrB1*, *qnrB4*, and *qnrB10* were identified (84). The gene *qnrB19* was described in equine *E. coli* isolates (93, 94). The replicon types often associated with plasmids that carried the PMQR genes *qnrS1* and *qnrB19* are IncN and IncX but also include several others (47, 94, 95).

In *E. coli* belonging to several STs of companion animal origin, the gene *aac(6')Ib-cr* was identified (96–99). This gene was located on plasmids of the IncF family, and a *bla*<sub>CTX-M</sub> ESBL gene, usually *bla*<sub>CTX-M-15</sub>, was often collocated (96, 98). Furthermore, *aac(6')Ib-cr* was described in *E. coli* isolates from the feces of French cattle, where it was also collocated with *bla*<sub>CTX-M-15</sub> on

plasmids belonging to the IncF family (100). The gene *qepA* was identified in *E. coli* of companion animal origin belonging to different STs (97). Plasmids of the IncF family harbored *qepA* in *E. coli* from food-producing and companion animals (101). The PMQR gene *oqxAB* was identified in unrelated *E. coli* isolates from food-producing animals and located on different plasmids belonging to the IncF and IncHI2 families (102). The case of OqxAB is peculiar since this resistance determinant confers reduced susceptibility not only to quinolones (such as flumequine), but also to other drugs such as trimethoprim and chloramphenicol that are also used in veterinary medicine. Therefore, this resistance determinant encompasses different families of antimicrobial agents to which resistance (or reduced susceptibility) can be coselected (103).

### RESISTANCE TO AMINOGLYCOSIDES

Aminoglycosides are drugs of natural origins whose producers can be found in the genus *Streptomyces* (104, 105) and *Micromonospora*, and they are often used in combination with another antimicrobial (mostly a  $\beta$ -lactam) to exploit their rapid bactericidal action for treating complicated infections such as sepsis, pneumonia, meningitis, and urinary tract/abdominal infections, both in humans and animals, including food-producing animals and companion animals (106). The most frequently used molecules in veterinary medicine are neomycin and derivatives of streptomycin. Gentamicin, kanamycin, and paromomycin are used as well. Amikacin is reserved for the treatment of infections in pets and horses (106).

Aminoglycosides affect a broad spectrum of pathogens among Gram-negative and -positive bacterial species, interfering with translation (107). Two major issues could limit the therapeutic power of these important molecules: the first is linked to their toxicity. Nevertheless, this issue is managed by opportune therapeutic regimens based on recent advances in the understanding of aminoglycoside pharmacodynamics (108). The second issue is the emergence of bacterial resistance linked to the usage of aminoglycosides, which has disseminated globally. The following subsections provide an overview of mechanisms of resistance toward aminoglycosides and their epidemiology in *E. coli* of animal origin.

### Resistance to Aminoglycosides by Target Modifications

Resistance to aminoglycosides can develop by target mutations involving the 16S RNA and/or the S5 and

S12 ribosomal proteins (107, 109, 110). However, this strategy is successful in conferring high-level resistance only in bacterial species with a limited number of copies of 16S RNA encoding operons. *E. coli* harbors seven copies of such operons, making the establishment of aminoglycoside resistance by point mutations rather improbable.

Modification of the target site of aminoglycosides can be achieved also by methylation of residues G1405 and A1408 of site A of the 16S RNA, resulting in high-level resistance to amikacin, tobramycin, gentamicin, and netilmicin (109). The 16S RNA methylases, including ArmA, RmtA/B/C/D/E/F/G/H, and NmpA, originated from natural aminoglycoside producers as self-defense against antimicrobial production (104). The first detection of ArmA dates back to 2003, when Galimand and colleagues reported the enzyme in a *Klebsiella pneumoniae* isolate from a human and the respective gene on a conjugative plasmid (111). Since then, the *armA* gene has been reported in several enterobacteria, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* isolates (112–116). The dissemination of the *armA* gene is favored by its location on the composite transposon Tn1548, which also carries genes coding for sulfonamide resistance, which in turn is located on self-transmissible plasmids belonging to several incompatibility groups (117). Emergence of ArmA in *E. coli* from animals was reported in 2005 in Spain in one pig (118), whereas the first report of *E. coli* producing RmtB was in 2007 in China by Chen and co-workers who reported a prevalence of 32% ( $n = 49/152$ ) among healthy pigs in farms (119). In an investigation conducted in China in 2008, Du et al. reported the presence of ArmA and RmtB in *E. coli* from diseased poultry, with an occurrence of 10% ( $n = 12/120$ ) (120). Later, Liu et al. reported the presence of *E. coli* ArmA and RmtB producers among various food-producing animals in 2009 to 2010, with an occurrence of 1.27% and 11.5% for ArmA and RmtB, respectively ( $n = 2$  and  $18/157$ ) (121). RmtB was found in *E. coli* isolates associated with bovine mastitis in China in 2013 to 2014, with an occurrence of 5.3% ( $n = 13/245$ ) (122). Yang and colleagues reported the presence of *E. coli* producing RmtD in diseased chickens in 2012 to 2014 in China. The enzyme co-occurred with RmtB with a prevalence of 8.3% ( $n = 3/36$ ). In the same study, other methylases were found, namely, RmtB together with ArmA in 8.3% of isolates ( $n = 3/36$ ), RmtB alone in 72.2% of isolates ( $n = 26/36$ ), and ArmA in 11.1% of isolates ( $n = 4/36$ ) (123).

More recently, a scattered porcine *E. coli* isolate harboring the *armA* gene was detected in Italy. The

isolate was multidrug-resistant, notably harboring the *bla*<sub>CMY-2</sub>, *bla*<sub>OXA-181</sub>, and *mcr-1* genes (80). Recently, two *E. coli* isolates producing RmtB were reported from diseased bovines in France. The gene colocalized on an IncF33:A1:B1 plasmid with *bla*<sub>CTX-M-55</sub> and in one isolate also with the *fosA3* gene (124). The RmtD variant has been found less frequently. Other than the report from Yang et al. (123), another recent report has been published from Brazil, on one *E. coli* isolate from a diseased horse producing RmtD and harboring the *bla*<sub>CTX-M-15</sub> and *aac(6)-Ib-cr* genes (125). The RmtE methylase was reported for the first time from commensal *E. coli* isolates from healthy calves in the United States (126). Later, two *E. coli* isolates were identified as RmtE producers in diseased food-producing animals in China, from 2002 to 2012 (127). Reports on RmtA are also quite infrequent, with a recent one from Zou et al., who found a frequency of 10% of *rmtA* gene occurrence among 89 *E. coli* isolates from giant pandas in China (128). To the best of our knowledge, RmtF/G/H enzymes have not yet emerged in *E. coli*, and NmpA has never been reported from animals. Overall, it can be stated that methylases have not widely disseminated since their discovery, probably for reasons related to fitness (129, 130). An exception is in China, where probably the antimicrobial usage, not only relative to aminoglycosides, may play a role in the emergence and dissemination of these enzymes. On the contrary, aminoglycoside-modifying enzymes have disseminated globally, and an overview of those most frequently encountered in animals is provided in the next subsection.

### Resistance to Aminoglycosides by Enzymatic Inactivation

The inactivation of aminoglycosides is conducted by enzymes which modify the molecules so that they become unable to reach or bind to the target site. Currently, three types of aminoglycoside-modifying enzymes are known, and according to the modifying group that is linked to the aminoglycosides, they are classified as acetyltransferases, nucleotidyltransferases, and phosphotransferases.

The aminoglycoside acetyltransferases catalyze the addition of an acetyl group (CH<sub>3</sub>CO) to an amine group (–NH<sub>2</sub>) at positions 1, 2, 3, or 6 of the aminoglycoside structure, which determines the subgroup of the enzyme (131). For each enzyme, several variants have been reported, and they are usually defined by a roman number. AAC(3)-II/IV and AAC(6)-Ib are the most frequently encountered acetyltransferases among *E. coli* of human and animal origins. They have been globally reported from several hosts (128, 132–140).

Among aminoglycosides, the nucleotidyltransferases ANT(2<sup>''</sup>) and ANT(3<sup>''</sup>) are most commonly found in Gram-negative bacteria. ANT(2<sup>''</sup>) and ANT(3<sup>''</sup>) are encoded by the genes *aadB* and *aadA*, respectively (131), which are both frequently located on gene cassettes in class 1 integrons. These genes have also spread globally, and they have been found in *E. coli* from animals including pets, wild animals, and food-producing animals (134, 141–148).

Among the aminoglycoside phosphotransferases, APH(6)-Ia and APH(6)-Id encoded by the *strA* and *strB* genes, respectively, are most commonly encountered in *E. coli* worldwide. They mediate resistance to streptomycin and are frequently associated with a unique mobile element, sometimes together with the *aph(3'')-III* genes mediating kanamycin resistance. These resistance mechanisms have been found in several hosts including wild rabbits (145), cattle (149–152), poultry (153, 154), and swine (155–157).

## RESISTANCE TO FOSFOMYCIN

Fosfomycin inhibits the MurA enzyme, which is involved in peptidoglycan synthesis. The use of fosfomycin in veterinary medicine is limited to the treatment of infections caused by a number of Gram-positive and Gram-negative pathogens, including *E. coli*, mainly in piglets and broiler chickens (158, 159). Two major fosfomycin resistance mechanisms have been described: (i) mutations in the *glpT* and *uhpA/T* genes encoding proteins involved in the fosfomycin uptake system and (ii) the acquisition of fosfomycin-modifying enzymes such as the metalloenzymes FosA, FosB, and FosX or the kinases FomA and FomB (160). Most of the *fos*-like genes are plasmid-borne, and plasmids carrying the *fos* genes commonly carry additional resistance genes (124, 161, 162) that increase the risk of coselection of fosfomycin resistance under the selective pressure by other antimicrobial agents.

A considerable number of studies report acquired fosfomycin resistance among *E. coli* of animal origin. Isolates carrying the plasmid-mediated *fosA* gene have been reported from companion animals. The first cases were reported in China in 2012 and 2013 from dogs and cats (163). Another study described a high prevalence of FosA3-producing *E. coli* in pets and their owners, highlighting the transmission of fosfomycin-resistant *E. coli* isolates between humans and animals (164). Another Chinese study described the *fosA3* gene in *E. coli* from fresh pork and chicken meat (165). In that study, the *fosA3* gene was often found together with

ESBL genes (*bla*<sub>CTX-M-55</sub>, *bla*<sub>CTX-M-15</sub>, or *bla*<sub>CTX-M-123</sub>) on plasmids of 78 to 138 kb in size. In a recent French study, the emergence of plasmids carrying multiple resistance determinants including *fosA3*, *bla*<sub>CTX-M-55</sub>, *rmtB*, and *mcr-1* was reported in various animal species (124). In that study, it was speculated that this plasmid could have an Asian origin since *bla*<sub>CTX-M-55</sub> is the second most prevalent ESBL gene in that part of the world. In 2013, the complete sequence of the 76,878-bp plasmid pHN7A8 from a dog in China was determined. This plasmid represents a F33:A<sup>-</sup>:B<sup>-</sup>-type epidemic plasmid that carried the resistance genes *bla*<sub>CTX-M-65</sub>, *fosA3*, and *rmtB* (166). Plasmids with similar *fosA3* regions were reported from *E. coli* isolates of pig (167), duck (168), and chicken origin (169). The widespread occurrence of the *fosA3* gene in China was demonstrated in a study that identified 12/892 *E. coli* isolates as *fosA3*-positive. These isolates originated from pigs, chickens, ducks, a goose, and a pigeon (170). Furthermore, the analysis of 1,693 *E. coli* isolates from various animal species identified 97 *fosA3*-positive isolates from beef cattle, pigs, broiler chickens, stray cats, stray dogs, and wild rodents in China (171). Recently, several epidemic *fosA3*-carrying multiresistance plasmids of diverse incompatibility groups have been identified to be disseminated among *E. coli* from pigs, dairy cattle, and chickens in northeast China (162). Some of these plasmids have been sequenced completely, including the plasmids pECM13 from cattle (113,006 bp, IncI1, and cohabiting *bla*<sub>CTX-M-14</sub>, *rmtB*, *aadA2*, and *bla*<sub>TEM-1</sub>), pECB11 from chicken [92,545 bp, F33:A<sup>-</sup>:B<sup>-</sup>, and cohabiting *bla*<sub>CTX-M-55</sub>, *floR*, *cfr*, *bla*<sub>TEM-1</sub>, *tet(A)*, *strA*, and *strB*], and pECF12 from chicken [77,822 bp, F33:A<sup>-</sup>:B<sup>-</sup>, and cohabiting *bla*<sub>CTX-M-3</sub>, *rmtB*, *tet(A)*, *strA*, and *strB*]. *E. coli* isolates from pigs harboring the *fosA3* gene were also detected in Taiwan (172).

## RESISTANCE TO TETRACYCLINES

Tetracyclines are widely used in veterinary medicine. A summary of sales data in the 25 European Union and European Economic Area countries revealed that tetracyclines accounted for 37% of the total sales of veterinary antimicrobial agents, followed by penicillins (23%) (173). As a consequence of the selective pressure imposed by the widespread use of tetracyclines, many bacteria—including *E. coli*—have developed tetracycline resistance. According to the tetracycline resistance gene nomenclature center (<https://faculty.washington.edu/marilynr/>), nine tetracycline efflux genes [*tet(A)*, *tet(B)*, *tet(C)*, *tet(D)*, *tet(E)*, *tet(G)*, *tet(J)*, *tet(L)*, and

*tet(Y)*], two tetracycline resistance genes encoding ribosome protective proteins [*tet(M)* and *tet(W)*], and one gene coding for an oxidoreductase that inactivates tetracyclines [*tet(X)*] have been identified in *E. coli*. The major mechanisms of tetracycline resistance encountered in *E. coli* of animal origin include (i) the active efflux by proteins of the major facilitator superfamily and (ii) ribosome protection. A PubMed search for tetracycline resistance genes in *E. coli* of animal origin revealed that not all of these 12 *tet* genes occur in *E. coli* from animal sources. The following examples provide an overview of the distribution of *tet* genes among *E. coli* from various animal sources.

Among 155 *E. coli* isolates from fecal samples of cattle in Korea, the genes *tet(A)*, *tet(B)*, and *tet(C)* were detected in 72, 70, and nine isolates, respectively. Two isolates each carried *tet(A) + tet(B)* or *tet(B) + tet(C)* (174). In 99 *E. coli* isolates from bovine mastitis in the United States collected from 1985 to 1987 and in 2009, the genes *tet(A)*, *tet(B)*, and *tet(C)* were detected, with *tet(C)* being present in more than half of the investigated isolates in each of the two time periods (175). Of 129 *E. coli* isolates from cases of bovine mastitis in the United States, 68 carried the gene *tet(C)*, while another 14 isolates harbored *tet(C) + tet(A)* (176). A study in Switzerland identified the genes *tet(A)*, *tet(B)*, and *tet(A) + tet(B)* in 24, 16, and two *E. coli* isolates from bovine mastitis (177). In the same study, the genes *tet(A)*, *tet(B)*, *tet(C)*, and *tet(A) + tet(B)* were detected in 60, five, one, and two *E. coli* isolates, respectively, from diarrhea and enterotoxemia in pigs (177). In 99 tetracycline-resistant *E. coli* isolates from pigs in Spain, the genes *tet(A)* ( $n = 46$ ), *tet(B)* ( $n = 12$ ), and *tet(A) + tet(B)* ( $n = 28$ ) but also *tet(A) + tet(M)* ( $n = 11$ ) and *tet(A) + tet(B) + tet(M)* ( $n = 2$ ) were detected (178). The *tet(M)* gene was shown by Southern blot hybridization to be located on plasmids. In a study in Germany, either the genes *tet(A)* ( $n = 71$ ), *tet(B)* ( $n = 46$ ), and *tet(C)* ( $n = 3$ ) alone or the combinations of the genes *tet(A) + tet(B)* ( $n = 2$ ), *tet(A) + tet(C)* ( $n = 2$ ), *tet(A) + tet(D)* ( $n = 3$ ), *tet(A) + tet(M)* ( $n = 1$ ), *tet(B) + tet(M)* ( $n = 2$ ), *tet(B) + tet(C)* ( $n = 2$ ), and *tet(B) + tet(D) + tet(M)* ( $n = 1$ ) were detected in *E. coli* from pigs (179). Among 283 tetracycline-resistant extra-intestinal pathogenic *E. coli* isolates from pigs in China, the genes *tet(A)* ( $n = 68$ ), *tet(B)* ( $n = 141$ ), *tet(C)* ( $n = 3$ ), *tet(D)* ( $n = 1$ ), and *tet(G)* ( $n = 108$ ) were identified (156). A wide variety of *tet* genes was also seen among 73 tetracycline-resistant *E. coli* isolates from broilers in Iran, including the gene *tet(E)* alone ( $n = 1$ ) or in the combinations *tet(E) + tet(C)* ( $n = 4$ ), *tet(E) + tet(D) + tet(M)* ( $n = 2$ ), *tet(E) + tet(D) + tet(A) + tet(G)* ( $n = 3$ ), and

*tet(E) + tet(M) + tet(A) + tet(B) + tet(C)* ( $n = 1$ ) (180). In 33 *E. coli* isolates from cases of septicemia among laying hens in Switzerland, the genes *tet(A)* and *tet(B)* were found in 21 and 10 isolates, respectively, while two isolates carried neither *tet(A)*, *tet(B)*, nor *tet(C)* (177). In the same study, the genes *tet(A)* and *tet(B)* were detected in eight and nine *E. coli* isolates from urinary tract infections in dogs and cats, respectively. The same two *tet* genes were also found in *E. coli* isolates from healthy dogs and cats in Spain (181). A large-scale study of *tet* genes in 325 nonclinical *E. coli* isolates from various animal sources in the United States identified the gene *tet(B)* in isolates from a goose, a duck, and a deer; the genes *tet(A)* and *tet(B)* in isolates from turkeys, cats, goats, and cows; *tet(A)*, *tet(B)*, and *tet(C)* in isolates from dogs, sheep, and horses; and *tet(A)*, *tet(B)*, *tet(C)*, and *tet(M)* in isolates from pigs and chickens (182). However, in that study neither *tet(E)* nor *tet(G)*, *tet(L)*, or *tet(X)* were detected in the 325 *E. coli* isolates. Among 58 tetracycline-resistant *E. coli* isolates from giant pandas, the genes *tet(A)*, *tet(E)*, and/or *tet(C)* were detected in 33, 24, and four isolates, respectively (128).

These examples show that different *tet* genes—alone or in combination with others—occur at different frequencies in *E. coli* isolates from different animal sources and/or geographic regions. In general, the genes *tet(A)* and *tet(B)* were the most prevalent tetracycline resistance genes in *E. coli* of animal origin. Both of these genes are part of small nonconjugative transposons, Tn1721 [*tet(A)*] (183) and Tn10 [*tet(B)*] (184), which are often integrated into conjugative and nonconjugative plasmids. Several of the aforementioned examples revealed the presence of more than a single *tet* gene in the same isolate. This might be explained by the observation that several *tet* genes are frequently found on plasmids or other mobile genetic elements which may have been acquired by the respective *E. coli* isolates at different times and under different conditions. When other resistance genes are collocated with a *tet* gene on the same plasmid, such a plasmid can be acquired under the selective pressure imposed by the use of antimicrobial agents other than tetracyclines. Multidrug resistance plasmids that also carry *tet* genes have been detected in *E. coli* from bovine mastitis in Germany. Here, the gene *tet(A)* was located on IncHI2/IncP plasmids of ca. 225 kb, which also harbored the resistance genes *bla*<sub>CTX-M-2</sub>, *bla*<sub>TEM-1</sub>, *sul1*, *sul2*, *dfrA1*, and *aadA1* (14). IncI1 plasmids that range in size from 90 to 120 kb and carry the resistance gene *tet(A)* along with the genes *bla*<sub>SHV-12</sub>, *aadA1*, *cmlA1*, and *aadA2* or the genes *bla*<sub>SHV-12</sub>, *qacG*, and *aadA6* were identified in *E. coli* isolates from wild

birds, dogs, and poultry in Spain or Germany (39). In canine *E. coli* isolates from Brazil, several multiresistance plasmids were identified. These included (i) a ca. 250-kb IncFIB/IncHI2 plasmid that carried the gene *tet(B)* together with the resistance genes *bla*<sub>CTX-M-2</sub>, *sul1*, *aadA29*, *strA*, and *strB*; (ii) a ca. 240-kb IncFIC plasmid that harbored the *tet(A)* gene together with the resistance genes *bla*<sub>CMY-2</sub>, *cmlA*, *floR*, *strA*, *strB*, *sul1*, *sul3*, and *aadA7*; (iii) a 240-kb IncHI2 plasmid with the resistance genes *bla*<sub>CTX-M-2</sub>, *sul1*, *aadA29*, *strA*, and *strB*; and (iv) a 40-kb IncFIB/IncN plasmid with the resistance genes *tet(A)*, *sul1*, *dfrA16*, and *dfrA29* (185). Lastly, an 81-kb plasmid that carried the resistance genes *qnrS1*, *bla*<sub>CTX-M-14</sub>, *bla*<sub>TEM-1</sub>, *floR*, and *tet(A)* was found in an *E. coli* isolate from a pig in China (186). These few examples illustrate that *tet* gene-carrying multiresistance plasmids occur in *E. coli* of different animal species in different parts of the world. Given the widespread use of tetracyclines in veterinary medicine, such plasmids not only facilitate the dissemination of certain *tet* genes, but also support the coselection and persistence of other resistance genes.

## RESISTANCE TO PHENICOLS

Phenicol antibiotics are broad-spectrum antimicrobial agents of which nonfluorinated (e.g., chloramphenicol) and fluorinated (e.g., florfenicol) derivatives are used in veterinary medicine. Due to its toxicity and important adverse effects in humans, such as dose-unrelated irreversible aplastic anemia, dose-related reversible bone marrow suppression, and Gray syndrome in neonates, chloramphenicol and its derivatives thiamphenicol and azidamphenicol were banned in 1994 in the European Union from use in food-producing animals (187). Currently, the use of nonfluorinated phenicols in animals is limited to the treatment of companion animals and pets. However, the fluorinated derivative florfenicol is licensed for the treatment of bacterial infections in food-producing animals (187).

Phenicol resistance in *E. coli* of animal origin is mediated by three major mechanisms: (i) enzymatic inactivation of nonfluorinated phenicols by chloramphenicol acetyltransferases encoded by *cat* genes, (ii) active efflux of nonfluorinated phenicols (*cmlA* genes) or fluorinated and nonfluorinated phenicols (*floR* genes) by major facilitator superfamily proteins, and (iii) target site methylation by an rRNA methylase encoded by the multiresistance gene *cfp*, which confers resistance to five classes of antimicrobial agents, including fluorinated and nonfluorinated phenicols (187).

Among 102 *E. coli* isolates from pigs in China, 91 (89%) were resistant to chloramphenicol. The genes *catA1* and *catA2* but also the cassette-borne gene *cmlA* were detected in 58%, 49%, and 65%, respectively, of the chloramphenicol-resistant isolates. In addition, the gene *floR* was detected in 57% of the florfenicol-resistant isolates and in 52% of chloramphenicol-resistant isolates (188). In a study of 318 ETEC, non-ETEC from cases of diarrhea, and commensal *E. coli* isolates from healthy pigs in Canada, the genes *catA1*, *cmlA*, and *floR* were detected among the chloramphenicol-resistant isolates. The gene *catA1* was significantly more frequent in ETEC than in non-ETEC and commensal *E. coli* (189). The genes *floR* and *cmlA* were detected among 48 *E. coli* isolates from calves with diarrhea. Of the 44 isolates for which florfenicol MICs were  $\geq 16$  mg/liter, 42 carried the *floR* gene. Twelve *E. coli* isolates were positive for *cmlA*, and their corresponding chloramphenicol MICs were  $\geq 32$  mg/liter. In addition, eight isolates were positive for *floR* and *cmlA*, and their florfenicol and chloramphenicol MICs were  $\geq 64$  mg/liter (190). In a study of antimicrobial resistance in German *E. coli* isolates from cattle, pigs, and poultry, not further specified *catA* genes were found in seven isolates from cattle and six isolates each from pigs and poultry. Moreover, *cmlA1*-like genes were detected in a single isolate from cattle, six isolates from pigs, and three isolates from poultry. The *floR* gene was not detected (191). Among 116 avian-pathogenic *E. coli* isolates from chickens in Egypt, 98 (84.5%) were resistant to chloramphenicol. The resistance genes *catA1*, *catA2*, and *cmlA* were found in 86, four, and eight isolates, respectively, while the genes *catA3* and *cmlB* were not detected (192). Among 102 chloramphenicol-resistant *E. coli* isolates from horses in the UK, 75 harbored the gene *catA1*. The remaining 27 isolates were PCR negative for the genes *catA2*, *catA3*, and *cmlA*, while the presence of the genes *floR* and *cfp* was not tested (193). The cassette-borne chloramphenicol resistance genes *catB3* and *cmlA6* were identified in four and two canine *E. coli* isolates, respectively, all from the United States. The gene *catB3* was located together with the resistance genes *aacA4* and *dfrA1*, and the gene *cmlA6* was located together with the genes *aadB* and *aadA1* in class 1 integrons of different sizes (194). In a study of 62 *E. coli* isolates from dogs in Iran, three isolates harbored the *cmlA* gene, whereas six isolates were positive for the *floR* gene (195). Among 36 chloramphenicol- and florfenicol-resistant *E. coli* isolates from dogs suffering from urinary tract infections in Taiwan, all isolates harbored the *cmlA* gene and 18 carried the *floR* gene (196). The *cmlA* gene was also

detected in two chloramphenicol-resistant *E. coli* isolates from fecal samples of free-range Iberian lynx (143). Of 89 *E. coli* isolates from giant pandas, 28 and 23 were resistant to chloramphenicol and florfenicol, respectively. The *floR* gene was detected in 23 isolates and the *cmlA* gene in nine isolates, with two isolates carrying both genes. The *cfr* gene was not detected in any of the isolates, and *cat* genes were not tested (128). The genes *catA1* and *cmlA* were also detected in two and one multiresistant *E. coli* isolates, respectively, from shellfish in Vietnam (197).

The genes *catA1*, *cmlA*, and *floR* are often found on plasmids. In bovine *E. coli* from the United States, the *floR* gene was located on large plasmids of 225 kb (190), which were larger than those found in *E. coli* from sick chickens (198). Southern blot analysis confirmed the presence of the *cmlA* gene on plasmids of >100 kb in *E. coli* from pigs (199). Conjugation assays identified two distinct class 1 integrons that linked *cmlA* to the streptomycin/spectinomycin resistance genes *aadA1* and *aadA2* and to the sulfonamide resistance genes *sul1* or *sul3* (199). Transformation experiments conducted with Canadian *E. coli* from pigs revealed that *aadA* and *sul1* were located together with *catA1* on a large ETEC plasmid (189). Plasmids that harbored the gene *cmlA* also carried the resistance genes *aadA* and *sul3*. Moreover, plasmids that harbored the genes *aadB* and *floR* also carried *sul2*, *tet(A)*, *bla<sub>CMY-2</sub>*, *strA*, and *strB* but occasionally also *aac(3)-IV* (189). Among Brazilian *E. coli* from dogs, a 35-kb IncF/IncFIB plasmid was identified that harbored the genes *strA* and *strB*, and an unusual class 1 integron with the genes *dfrA12*, *aadA2*, *cmlA1*, and *aadA1* linked to a *sul3* gene (185). The ca. 35-kb plasmid pMBSF1 from porcine *E. coli* in Germany carried the *floR* gene together with the genes *strA* and *strB* (200). The *floR* gene was also detected on conjugative plasmids ranging in size from 110 to 125 kb from bovine *E. coli* in France. All these plasmids mediated additional resistances to sulfonamides, streptomycin, ampicillin, and/or trimethoprim (201). These examples show that phenicol resistance genes can also be coselected under the selective pressure imposed by nonphenicol antimicrobial agents.

The multiresistance gene *cfr*—originally identified in staphylococci of animal origin—was also found to be functionally active in *E. coli* (202). The gene *cfr* was first reported in *E. coli* from a nasal swab of a pig in China (203). Later, it was identified on the 135,615-bp IncA/C multiresistance plasmid pSCEC2 from a pig in China. This plasmid also harbored the resistance genes *sul2*, *tet(A)*, *floR*, *strA*, and *strB* (157). In another study in

China, the *cfr* gene was detected on plasmids of ca. 30 kb in *E. coli* isolates from pigs (204). The complete sequence of the 37,672-bp plasmid pSD11, again from *E. coli* of porcine origin in China, was reported by Sun and colleagues (205). The colocation of *cfr* with the ESBL gene *bla<sub>CTX-M-14b</sub>* on the 41,646-bp plasmid pGXEC3 from a porcine *E. coli* isolate was reported in 2015 (206). In the same year, another *cfr*-carrying plasmid, the conjugative 33,885-bp plasmid pFSEC-01, was reported (207). Although this plasmid was found in a porcine *E. coli* isolate, it closely resembled in its structure the plasmid pEA3 from the plant pathogen *Erwinia amylovora*. Most recently, another six *cfr*-carrying *E. coli* isolates—five from pigs and one from a chicken—were identified. In all cases, the *cfr* gene was located as the only resistance gene on plasmids of either 37 or 67 kb. Two of these plasmids were completely sequenced: the 37,663-bp IncX4 plasmid pEC14cfr and the 67,077-bp F14: A<sup>-</sup>: B<sup>-</sup> plasmid pEC29cfr (161).

## RESISTANCE TO SULFONAMIDES AND TRIMETHOPRIM

Sulfonamides and trimethoprim are synthetic antimicrobial agents that inhibit different steps in the folic acid synthesis pathway. Each of these agents acts in a bacteriostatic manner, whereas the combination of a sulfonamide with trimethoprim results in synergistic bactericidal actions on susceptible organisms; as such, the combination is referred to as a “potentiated” sulfonamide. Sulfonamides and trimethoprim have been used for decades in animals and humans. Acquired resistance mechanisms have been frequently identified, mainly due to (i) mutational modifications in the genes encoding the target enzymes, namely, the dihydropteroate synthase or dihydrofolate reductase, respectively, or (ii) the acquisition of *sul* genes encoding dihydropteroate synthetases that are insensitive to sulfonamides or *dfr* genes encoding dihydrofolate reductases that are insensitive to trimethoprim (208).

### Resistance to Sulfonamides

In *E. coli* from food-producing and companion animals, sulfonamide resistance is mediated by any of the following three *sul* genes: *sul1*, *sul2*, or *sul3*. The *sul1* gene is particularly widespread because it is part of the 3'-conserved segment of class 1 integrons (209). As such, the *sul1* gene is often found together with other antimicrobial resistance genes that are located on gene cassettes in the variable part of class 1 integrons (209). Class 1 integrons are present in *E. coli* from healthy and

diseased food-producing animals, companion animals, and wildlife all over the world as illustrated in the following examples. In Germany, 58 of 417 *E. coli* isolates from diseased swine, horses, dogs, and cats, collected in the BfT-GermVet monitoring study, harbored class 1 integrons (210). Other studies identified class 1 integrons in *E. coli* from healthy and diseased dogs in Brazil (185), in clinical avian *E. coli* isolates in the United States (211), in *E. coli* from lizards in Indonesia (212), in Shiga toxin-producing *E. coli* from cattle in the United States (213), in *E. coli* from free-range reindeer in Norway (214), in calf-pathogenic *E. coli* in China (215), in *E. coli* from pigs in Denmark (216), and even in *E. coli* from giant pandas in China (128). Class 1 integrons including the *sul1* gene are often located on plasmids, including ESBL-gene-carrying multiresistance plasmids (14, 216–218).

The gene *sul2* is also widely disseminated among *E. coli* of various animal species in different parts of the world. It has been found in *E. coli* from pigs in Canada (219) and Denmark (216), in food-producing animals in Kenya (220), in poultry in Nigeria (221) and Germany (222), and in horses in the Czech Republic (93). The *sul2* gene is often linked to the streptomycin resistance genes *strA-strB*. Similarly to *sul1*, the *sul2* gene is commonly found on plasmids that also harbor other antimicrobial resistance genes (93, 157, 220, 221, 223).

The gene *sul3* was first described in 2003 in *E. coli* isolates from pigs in Switzerland (224). Since then, this gene has been identified mostly on plasmids in *E. coli* from pigs in the United States (199), Canada (219), and Denmark (216); from poultry in Germany (222); and from dogs in Spain (138) and Brazil (185). Several reports described the *sul3* gene to be linked to other resistance genes, such as the macrolide resistance gene *mef(B)* (225), and to unusual class 1 integrons (39, 185, 199, 226).

### Resistance to Trimethoprim

Numerous *dfr* genes that confer trimethoprim resistance have been detected in *Enterobacteriaceae* and other Gram-negative bacteria. Based on their sizes and structures, they have been divided into two major groups, *dfrA* and *dfrB* (227). The *dfrA* genes code for proteins of 152 to 189 amino acids, while the *dfrB*-encoded proteins are only 78 amino acids in size. Most of the *dfrA* and *dfrB* genes found in *E. coli* of animal origin are located on gene cassettes that are inserted into class 1 or class 2 integrons. Some examples are given for *dfrA* genes that have been identified in *E. coli* from dogs (*dfrA1*, *dfrA12*, *dfrA17*, *dfrA29*) (138, 185, 210), cats (*dfrA1*,

*dfrA12*) (210), horses (*dfrA1*, *dfrA9*, *dfrA12*, *dfrA17*) (193, 210), pigs (*dfrA1*, *dfrA5*, *dfrA8*, *dfrA12*, *dfrA13*, *dfrA14*, *dfrA16*, *dfrA17*) (144, 156, 210, 228, 229), cattle (*dfrA1*, *dfrA8*, *dfrA12*, *dfrA17*) (14, 215, 229), chickens (*dfrA1*, *dfrA5*, *dfrA12*, *dfrA14*, *dfrA16*) (144, 229), and giant pandas (*dfrA1*, *dfrA7*, *dfrA12*, *dfrA17*) (128). In contrast to *dfrA* genes, *dfrB* genes have rarely been detected in *E. coli* from animals. A *dfrB4* gene and a *dfrA17* gene were detected in class 1 integrons from sea lions (230). In the study by Seputienė et al. (229), the *dfrA8* gene was located in neither class 1 nor in class 2 integrons. Moreover, only seven of the 13 *dfrA14* genes in *E. coli* isolates of animal origin were integron-associated. In previous studies of *E. coli* from food-producing animals, a functionally active *dfrA14* gene was found outside an integron but inserted into a plasmid-borne *strA* gene (220, 231).

### RESISTANCE TO POLYMYXINS

Colistin (also known as polymyxin E) is a polypeptide antimicrobial agent that targets the LPS in the outer membrane of Gram-negative bacteria (232). Colistin is widely used in veterinary medicine, mainly for the treatment or prevention of intestinal infections, particularly neonatal and postweaning diarrhea in pigs and intestinal infections in poultry and cattle (233). Very recently, due to the considerable concerns that colistin resistance might be transferable from animals to humans, specific regulations on the use of colistin have been set up in Europe under the umbrella of the European Medicines Agency (234). In April 2017, a ban of colistin as a growth promoter also became effective in China (235). Colistin is active against various species of *Enterobacteriaceae*, including *E. coli*, whereas others such as *Proteus* spp. and *Serratia* spp. are intrinsically resistant (232). Resistance to colistin can be due to mutations in chromosomal genes or to acquired resistance genes.

### Chromosome-Encoded Polymyxin Resistance

Polymyxin resistance in *E. coli* isolates may be related to genes encoding LPS-modifying enzymes. The operon *pmrCAB* codes for three proteins, namely, a phosphoethanolamine phosphotransferase PmrC, a response regulator PmrA (also called BasR), and a sensor kinase protein PmrB (also called BasS) (232). Mutations either in PmrA or in PmrB have been found to be responsible for polymyxin resistance in *E. coli* isolates recovered from poultry in Spain (236). However, most of the mutations leading to polymyxin resistance in that op-

eron or in others, such as the PhoPQ two-component system or its regulator MgrB, have been identified in human *E. coli* isolates. Ongoing studies are being conducted to evaluate whether the same mechanisms might be responsible for polymyxin resistance in animal isolates. In one such study, mutations in the genes *pmrA*, *pmrB*, *mgrB*, *phoP*, and *phoQ* of *E. coli* isolates from pigs were identified (237).

### Plasmid-Mediated Polymyxin Resistance

In November 2016, the first plasmid-borne polymyxin resistance gene was identified. This gene was designated *mcr-1*, and it encodes the MCR-1 phosphoethanolamine transferase (238). Production of MCR-1 leads to the modification of the lipid A moiety of the LPS, resulting in a more cationic LPS and, consequently, to resistance to polymyxins. Production of MCR-1 in *E. coli* leads to a 4- to 8-fold increase in the MICs of polymyxins (232).

The *mcr-1* gene has been detected mainly in *E. coli* isolates but also in other *Enterobacteriaceae* genera, such as *Salmonella*, *Shigella*, *Klebsiella*, and *Enterobacter* (239). This gene has now been identified worldwide, in both animal and human isolates. The *mcr-1* gene has been found to be located on plasmids of various incompatibility groups (IncI2, IncHI2, IncP, IncX4, IncY, IncFI, and IncFIB) and variable sizes (58 to 251 kb) (232). A few reports showed that it may be colocalized with ESBL-encoding genes and/or other resistance genes (71, 240–244); nonetheless, most of the reports identified *mcr-1* as the sole resistance gene on the respective plasmids. This may suggest that a polymyxin-related selective pressure is responsible for the *mcr-1* acquisition, with corresponding plasmids providing no other obvious selective advantage. Upstream of the *mcr-1* gene, the IS*Apl1* insertion sequence element is frequently identified, although it is often, but not always, also identified downstream of it. Recent studies demonstrated that the *mcr-1* gene is mobilized by transposition when bracketed by two copies of IS*Apl1* that form a composite transposon structure (242, 245). So far, 11 variants of the *mcr-1* gene, designated *mcr-1.2* to *mcr-1.12* have been identified, with *mcr-1.3* being found in *E. coli* from chickens in China (246), *mcr-1.8* in *E. coli* from poultry in Brunei (GenBank accession no. KY683842.1), *mcr-1.9* in *E. coli* from swine in Portugal (KY964067.1), and *mcr-1.12* in *E. coli* from pork in Japan (LC337668.1).

Recently, the plasmid-mediated colistin-resistance *mcr-2* gene was identified in *E. coli* isolates recovered from piglets in Belgium (247). It shared 77% nucleotide

sequence identity with *mcr-1* and was located on an IncX4 plasmid. The *mcr-2* gene has been sporadically identified so far (248). In addition, further *mcr* genes—*mcr-3* to *mcr-7*—and variants thereof have been described. Among them, the *mcr-3* gene was initially identified together with 18 additional resistance genes on the 261-kb IncHI2-type plasmid pWJ1 from porcine *E. coli* (249). The *mcr-3* gene showed 45.0% and 47.0% nucleotide sequence identity to *mcr-1* and *mcr-2*, respectively. So far, ten variants of *mcr-3*, designated *mcr-3.2* to *mcr-3.11*, have been identified, with the *mcr-3.2* gene being originally detected in *E. coli* from cattle in Spain (250). A recent study in France reported the spread of a single *E. coli* clone harboring *mcr-3* in the veal calves sector from 2011 to 2016 (251). The combination in those isolates of *mcr-3* and *bla*<sub>CTX-M-55</sub>, an ESBL gene that is highly prevalent in Asian countries and rarely detected in Europe, may suggest the introduction and further dissemination of *mcr-3* in that specific animal setting due to international trade. The *mcr-4* gene was detected among *E. coli* from pigs in Spain and Belgium that suffered from postweaning diarrhea (252). The gene *mcr-5* and a variant, designated *mcr-5.2*, have recently been found in *E. coli* from pigs (253).

### Epidemiology of *mcr-1*

The *mcr-1* gene is a resistance gene identified in human and animal *E. coli* isolates. Its occurrence in animal isolates is quite elevated (232), and it has been identified worldwide. MCR-1-producing *E. coli* isolates have been identified in several food-producing animals and meat, including chickens and chicken meat, pigs and piglets, cattle, calves, and turkeys (254, 255) (Table 4). Those isolates are from many Asian countries (Cambodia, China, Japan, Laos, Malaysia, Taiwan, Singapore, Vietnam, India, Pakistan, South Korea), from Europe (Belgium, Denmark, France, Germany, Portugal, Italy, the Netherlands, Spain, Sweden, Switzerland, the UK), the Americas (Argentina, Brazil, Canada, the U.S., Ecuador, Bolivia, Venezuela), Australia, and Africa (Algeria, Egypt, South Africa, Tunisia). Worryingly, a recent study performed in China identified a series of MCR-1-producing *E. coli* isolates recovered from poultry, with many of the isolates coproducing the carbapenemase NDM-1 (71). In addition, such multi-drug-resistant isolates were recovered from flies and dogs present in the same farm environment, thus highlighting that those latter animals might also constitute sources of transmission (71). Additionally, some studies highlighted that *mcr-1*-positive *E. coli* may be also present in the environment or in food, being, for in-



**TABLE 4** Examples of acquired *mcr* genes in *E. coli* of animal origin from Europe, North and South America, and Asia

<i>mcr</i> gene	Geographical origin	Source	Sequence type(s)	Reference
<i>mcr-1</i>	China	Pig		<a href="#">238</a>
	China	Pig		<a href="#">242</a>
	China	Pig	48, 54, 90, 156, 165, 167, 410, 1114, 1178, 1437, 2439, 3331, 4429, 4463, 4656	<a href="#">277</a>
	China	Poultry	10, 48, 58, 77, 88, 101, 117, 178, 215, 361, 501, 542, 616, 617, 648, 744, 761, 870, 873, 952, 971, 1290, 1431, 1642, 2345, 2491, 2599, 3044, 3133, 3481, 3944, 5542, 5815, 5865, 5879, 5909, 6050,	<a href="#">246</a>
	Vietnam	Reptiles	117, 1011	<a href="#">282</a>
	South Korea	Poultry, pig	1, 10, 88, 101, 156, 162, 226, 410, 1141, 2732	<a href="#">283</a>
	Germany	Pig	1, 10, 846	<a href="#">240</a>
	Germany	Pig (manure), fly, dog	10, 342, 1011, 5281	<a href="#">256</a>
	France	Cattle		<a href="#">241</a>
	Italy	Poultry (meat)	602	<a href="#">243</a>
	U.S.	Pig	132, 3234	<a href="#">284</a>
	Venezuela	Pig	452	<a href="#">285</a>
	Brazil	Magellanic penguin	10	<a href="#">286</a>
	<i>mcr-1.3</i>	China	Poultry	155
<i>mcr-1.8</i>	Brunei	Poultry	101	KY683842.1 <sup>a</sup>
<i>mcr-1.9</i>	Portugal	Pig		KY964067.1 <sup>a</sup>
<i>mcr-1.12</i>	Japan	Pig		LC337668.1 <sup>a</sup>
<i>mcr-2</i>	Belgium	Pig, cattle	10, 167	<a href="#">247</a>
<i>mcr-3</i>	China	Pig	1642	<a href="#">249</a>
	France	Cattle	744	<a href="#">251</a>
<i>mcr-3.2</i>	Spain	Cattle	533	<a href="#">250</a>
<i>mcr-4</i>	Spain, Belgium	Pig	10, 7029	<a href="#">252</a>
<i>mcr-5</i>	Germany	Pig	29, 349	<a href="#">253</a>
<i>mcr-5.2</i>	Germany	Pig	1494	<a href="#">253</a>

<sup>a</sup>GenBank accession number.

stance, identified in rivers but also in Asian imported vegetables in Switzerland ([243](#)). The environmental emission of MCR-1-producing and multiresistant *E. coli* isolates was recently stressed by studying the close surroundings of pig farms in Germany ([256](#)).

Dating the emergence of *mcr-1*-positive *E. coli* isolates remains difficult, although a Chinese study retrospectively identified *mcr-1*-positive isolates from chickens in the 1980s ([255](#)) and as early as 2005 in veal calves in France ([254](#)). It seems, therefore, that the emergence of *mcr*-positive isolates, at least in animals, is not a recent event. Very likely, there has been some silent dissemination of *mcr* genes through the past decades, and the current situation shows ongoing further dissemination rather than an emerging phenomenon.

## CONCLUSIONS

Antimicrobial resistance in *E. coli* is an issue of the utmost importance since it occurs in both the human and animal sectors in a One Health perspective. In animals,

multidrug resistance in *E. coli* may lead to difficult-to-treat infections, but even more importantly, it constitutes a major and shared reservoir of resistance determinants to most families of antimicrobial agents across a vast number of animal species, including humans. Even though the different transmission pathways of resistant *E. coli* isolates from animals to humans remain to be clarified and their relative importance quantified, some data may support the role of the food chain since those bacteria have been demonstrated as common colonizers of foodstuffs at retail in many countries and continents. Other routes of transmission may include direct contacts with animals or indirect transfers through the environment. Since *E. coli* is a bacterium that is widely spread in all sectors, antimicrobial resistance in *E. coli* in animals has led to numerous cross-sectorial and joint initiatives, encompassing translational research, epidemiology, and surveillance in both human and veterinary medicine. It is now considered that the battle against the increased occurrence of antimicrobial resistance in *E. coli* from humans cannot be won without acting on a very large

scale. To tone down some current and alarming speculations, and in view of all the studies that have been conducted during recent years, it is, however, likely that the occurrence of carbapenemase-producing *E. coli* in animals does not represent a significant threat for human health (31). In contrast, recent data have demonstrated that animals are very significant reservoirs of plasmid-mediated colistin resistance genes—mostly present in *E. coli* isolates—which may represent a further risk for humans.

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#### REFERENCES

- Kaper JB, Nataro JP, Mobley HL. 2004. Pathogenic *Escherichia coli*. *Nat Rev Microbiol* 2:123–140 <http://dx.doi.org/10.1038/nrmicro818>.
- Köhler CD, Dobrindt U. 2011. What defines extraintestinal pathogenic *Escherichia coli*? *Int J Med Microbiol* 301:642–647 <http://dx.doi.org/10.1016/j.ijmm.2011.09.006>.
- Johnson JR, Russo TA. 2005. Molecular epidemiology of extraintestinal pathogenic (uropathogenic) *Escherichia coli*. *Int J Med Microbiol* 295:383–404 <http://dx.doi.org/10.1016/j.ijmm.2005.07.005>.
- Izzo MM, Kirkland PD, Mohler VL, Perkins NR, Gunn AA, House JK. 2011. Prevalence of major enteric pathogens in Australian dairy calves with diarrhoea. *Aust Vet J* 89:167–173 <http://dx.doi.org/10.1111/j.1751-0813.2011.00692.x>.
- Kolenda R, Burdukiewicz M, Schierack P. 2015. A systematic review and meta-analysis of the epidemiology of pathogenic *Escherichia coli* of calves and the role of calves as reservoirs for human pathogenic *E. coli*. *Front Cell Infect Microbiol* 5:23 <http://dx.doi.org/10.3389/fcimb.2015.00023>.
- Bouillon J, Snead E, Caswell J, Feng C, Hélie P, Lemetayer J. 2018. Pyelonephritis in dogs: retrospective study of 47 histologically diagnosed cases (2005–2015). *J Vet Intern Med* 32:249–259 <http://dx.doi.org/10.1111/jvim.14836>.
- Hutton TA, Innes GK, Harel J, Garneau P, Cucchiara A, Schifferli DM, Rankin SC. 2018. Phylogroup and virulence gene association with clinical characteristics of *Escherichia coli* urinary tract infections from dogs and cats. *J Vet Diagn Invest* 30:64–70 <http://dx.doi.org/10.1177/1040638717729395>.
- Antão EM, Glodde S, Li G, Sharifi R, Homeier T, Laternus C, Diehl I, Bethe A, Philipp HC, Preisinger R, Wieler LH, Ewers C. 2008. The chicken as a natural model for extraintestinal infections caused by avian pathogenic *Escherichia coli* (APEC). *Microb Pathog* 45:361–369 <http://dx.doi.org/10.1016/j.micpath.2008.08.005>.
- Ruegg PL. 2017. A 100-year review: mastitis detection, management, and prevention. *J Dairy Sci* 100:10381–10397 <http://dx.doi.org/10.3168/jds.2017-13023>.
- Taponen S, Liski E, Heikkilä AM, Pyörälä S. 2017. Factors associated with intramammary infection in dairy cows caused by coagulase-negative staphylococci, *Staphylococcus aureus*, *Streptococcus uberis*, *Streptococcus dysgalactiae*, *Corynebacterium bovis*, or *Escherichia coli*. *J Dairy Sci* 100:493–503 <http://dx.doi.org/10.3168/jds.2016-11465>.
- Shpigiel NY, Elazar S, Rosenshine I. 2008. Mammary pathogenic *Escherichia coli*. *Curr Opin Microbiol* 11:60–65 <http://dx.doi.org/10.1016/j.mib.2008.01.004>.
- Suojala L, Kaartinen L, Pyörälä S. 2013. Treatment for bovine *Escherichia coli* mastitis: an evidence-based approach. *J Vet Pharmacol Ther* 36:521–531 <http://dx.doi.org/10.1111/jvp.12057>.
- Dahmen S, Métayer V, Gay E, Madec JY, Haenni M. 2013. Characterization of extended-spectrum  $\beta$ -lactamase (ESBL)-carrying plasmids and clones of *Enterobacteriaceae* causing cattle mastitis in France. *Vet Microbiol* 162:793–799 <http://dx.doi.org/10.1016/j.vetmic.2012.10.015>.
- Freitag C, Michael GB, Kadlec K, Hassel M, Schwarz S. 2017. Detection of plasmid-borne extended-spectrum  $\beta$ -lactamase (ESBL) genes in *Escherichia coli* isolates from bovine mastitis. *Vet Microbiol* 200:151–156 <http://dx.doi.org/10.1016/j.vetmic.2016.08.010>.
- Su Y, Yu CY, Tsai Y, Wang SH, Lee C, Chu C. 2016. Fluoroquinolone-resistant and extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli* from the milk of cows with clinical mastitis in southern Taiwan. *J Microbiol Immunol Infect* 49:892–901 <http://dx.doi.org/10.1016/j.jmii.2014.10.003>.
- Timofte D, Maciua IE, Evans NJ, Williams H, Wattret A, Fick JC, Williams NJ. 2014. Detection and molecular characterization of *Escherichia coli* CTX-M-15 and *Klebsiella pneumoniae* SHV-12  $\beta$ -lactamases from bovine mastitis isolates in the United Kingdom. *Antimicrob Agents Chemother* 58:789–794 <http://dx.doi.org/10.1128/AAC.00752-13>.
- Pempek JA, Holder E, Proudfoot KL, Masterson M, Habing G. 2018. Short communication: investigation of antibiotic alternatives to improve health and growth of veal calves. *J Dairy Sci* 101:4473–4478 <http://dx.doi.org/10.3168/jds.2017-14055>.
- Meganck V, Hoflack G, Opsomer G. 2014. Advances in prevention and therapy of neonatal dairy calf diarrhoea: a systematic review with emphasis on colostrum management and fluid therapy. *Acta Vet Scand* 56:75 <http://dx.doi.org/10.1186/s13028-014-0075-x>.
- Dierikx CM, van der Goot JA, Smith HE, Kant A, Mevius DJ. 2013. Presence of ESBL/AmpC-producing *Escherichia coli* in the broiler production pyramid: a descriptive study. *PLoS One* 8:e79005 <http://dx.doi.org/10.1371/journal.pone.0079005>.
- Haenni M, Châte P, Métayer V, Bour M, Signol E, Madec JY, Gay E. 2014. Comparative prevalence and characterization of ESBL-producing *Enterobacteriaceae* in dominant versus subdominant enteric flora in veal calves at slaughterhouse, France. *Vet Microbiol* 171:321–327 <http://dx.doi.org/10.1016/j.vetmic.2014.02.023>.
- Hordijk J, Mevius DJ, Kant A, Bos ME, Graveland H, Bosman AB, Hartskeerl CM, Heederik DJ, Wagenaar JA. 2013. Within-farm dynamics of ESBL/AmpC-producing *Escherichia coli* in veal calves: a longitudinal approach. *J Antimicrob Chemother* 68:2468–2476 <http://dx.doi.org/10.1093/jac/dkt219>.
- Ambler RP. 1980. The structure of  $\beta$ -lactamases. *Philos Trans R Soc Lond B Biol Sci* 289:321–331 <http://dx.doi.org/10.1098/rstb.1980.0049>.
- Bush K, Jacoby GA. 2010. Updated functional classification of  $\beta$ -lactamases. *Antimicrob Agents Chemother* 54:969–976 <http://dx.doi.org/10.1128/AAC.01009-09>.
- Ewers C, Bethe A, Semmler T, Guenther S, Wieler LH. 2012. Extended-spectrum  $\beta$ -lactamase-producing and AmpC-producing *Escherichia coli* from livestock and companion animals, and their putative impact on public health: a global perspective. *Clin Microbiol Infect* 18:646–655 <http://dx.doi.org/10.1111/j.1469-0691.2012.03850.x>.
- Madec JY, Haenni M, Nordmann P, Poirel L. 2017. Extended-spectrum  $\beta$ -lactamase/AmpC- and carbapenemase-producing *Enterobacteriaceae* in animals: a threat for humans? *Clin Microbiol Infect* 23:826–833 <http://dx.doi.org/10.1016/j.cmi.2017.01.013>.
- Hordijk J, Schoormans A, Kwakernaak M, Duim B, Broens E, Dierikx C, Mevius D, Wagenaar JA. 2013. High prevalence of fecal carriage of extended spectrum  $\beta$ -lactamase/AmpC-producing *Enterobacteriaceae* in cats and dogs. *Front Microbiol* 4:242–247 <http://dx.doi.org/10.3389/fmicb.2013.00242>.
- Lalak A, Wasyl D, Zając M, Skarżyńska M, Hoszowski A, Samcik I, Woźniakowski G, Szulowski K. 2016. Mechanisms of cephalosporin resistance in indicator *Escherichia coli* isolated from food animals. *Vet Microbiol* 194:69–73 <http://dx.doi.org/10.1016/j.vetmic.2016.01.023>.

28. Schaufler K, Bethe A, Lübke-Becker A, Ewers C, Kohn B, Wieler LH, Guenther S. 2015. Putative connection between zoonotic multiresistant extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Escherichia coli* in dog feces from a veterinary campus and clinical isolates from dogs. *Infect Ecol Epidemiol* 5:25334–25339 <http://dx.doi.org/10.3402/iee.v5.25334>.
29. Tian GB, Wang HN, Zhang AY, Zhang Y, Fan WQ, Xu CW, Zeng B, Guan ZB, Zou LK. 2012. Detection of clinically important  $\beta$ -lactamases in commensal *Escherichia coli* of human and swine origin in western China. *J Med Microbiol* 61:233–238 <http://dx.doi.org/10.1099/jmm.0.036806-0>.
30. Guenther S, Ewers C, Wieler LH. 2011. Extended-spectrum  $\beta$ -lactamases producing *E. coli* in wildlife, yet another form of environmental pollution? *Front Microbiol* 2:246–259 <http://dx.doi.org/10.3389/fmicb.2011.00246>.
31. Karim A, Poirel L, Nagarajan S, Nordmann P. 2001. Plasmid-mediated extended-spectrum  $\beta$ -lactamase (CTX-M-3 like) from India and gene association with insertion sequence ISEcp1. *FEMS Microbiol Lett* 201:237–241 <https://doi.org/10.1111/j.1574-6968.2001.tb10762.x>.
32. Pitout JD, Nordmann P, Laupland KB, Poirel L. 2005. Emergence of *Enterobacteriaceae* producing extended-spectrum  $\beta$ -lactamases (ESBLs) in the community. *J Antimicrob Chemother* 56:52–59 <http://dx.doi.org/10.1093/jac/dki166>.
33. Michael GB, Freitag C, Wendlandt S, Eidam C, Fefler AT, Lopes GV, Kadlec K, Schwarz S. 2015. Emerging issues in antimicrobial resistance of bacteria from food-producing animals. *Future Microbiol* 10:427–443 <http://dx.doi.org/10.2217/fmb.14.93>.
34. EFSA. 2011. Panel on Biological Hazards (BIOHAZ); scientific opinion on the public health risks of bacterial strains producing extended-spectrum  $\beta$ -lactamases and/or AmpC  $\beta$ -lactamases in food and food-producing animals. *EFSA J* 9:2322–2417 <http://dx.doi.org/10.2903/j.efsa.2011.2322>.
35. Michael GB, Kaspar H, Siqueira AK, de Freitas Costa E, Corbellini LG, Kadlec K, Schwarz S. 2017. Extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Escherichia coli* isolates collected from diseased food-producing animals in the GERM-Vet monitoring program 2008–2014. *Vet Microbiol* 200:142–150 <http://dx.doi.org/10.1016/j.vetmic.2016.08.023>.
36. Day MJ, Rodríguez I, van Essen-Zandbergen A, Dierikx C, Kadlec K, Schink AK, Wu G, Chattaway MA, DoNascimento V, Wain J, Helmuth R, Guerra B, Schwarz S, Threlfall J, Woodward MJ, Coldham N, Mevius D, Woodford N. 2016. Diversity of STs, plasmids and ESBL genes among *Escherichia coli* from humans, animals and food in Germany, the Netherlands and the UK. *J Antimicrob Chemother* 71:1178–1182 <http://dx.doi.org/10.1093/jac/dkv485>.
37. Schmiedel J, Falgenhauer L, Domann E, Bauerfeind R, Prenger-Berninghoff E, Imirzalioglu C, Chakraborty T. 2014. Multiresistant extended-spectrum  $\beta$ -lactamase-producing *Enterobacteriaceae* from humans, companion animals and horses in central Hesse, Germany. *BMC Microbiol* 14:187–200 <http://dx.doi.org/10.1186/1471-2180-14-187>.
38. Shaheen BW, Nayak R, Foley SL, Kweon O, Deck J, Park M, Rafii F, Boothe DM. 2011. Molecular characterization of resistance to extended-spectrum cephalosporins in clinical *Escherichia coli* isolates from companion animals in the United States. *Antimicrob Agents Chemother* 55:5666–5675 <http://dx.doi.org/10.1128/AAC.00656-11>.
39. Alonso CA, Michael GB, Li J, Somalo S, Simón C, Wang Y, Kaspar H, Kadlec K, Torres C, Schwarz S. 2017. Analysis of *bla*<sub>SHV-12</sub>-carrying *Escherichia coli* clones and plasmids from human, animal and food sources. *J Antimicrob Chemother* 72:1589–1596 <http://dx.doi.org/10.1093/jac/dkx024>.
40. Peirano G, Pitout JD. 2010. Molecular epidemiology of *Escherichia coli* producing CTX-M beta-lactamases: the worldwide emergence of clone ST131 O25:H4. *Int J Antimicrob Agents* 35:316–321 <http://dx.doi.org/10.1016/j.ijantimicag.2009.11.003>.
41. Albrechtova K, Dolejska M, Cizek A, Tausova D, Klimes J, Beborá L, Literak I. 2012. Dogs of nomadic pastoralists in northern Kenya are reservoirs of plasmid-mediated cephalosporin- and quinolone-resistant *Escherichia coli*, including pandemic clone B2-O25-ST131. *Antimicrob Agents Chemother* 56:4013–4017 <http://dx.doi.org/10.1128/AAC.05859-11>.
42. Marques C, Belas A, Franco A, Aboim C, Gama LT, Pombo C. 2018. Increase in antimicrobial resistance and emergence of major international high-risk clonal lineages in dogs and cats with urinary tract infection: 16 year retrospective study. *J Antimicrob Chemother* 73:377–384 <http://dx.doi.org/10.1093/jac/dkx401>.
43. Schink AK, Kadlec K, Kaspar H, Mankertz J, Schwarz S. 2013. Analysis of extended-spectrum- $\beta$ -lactamase-producing *Escherichia coli* isolates collected in the GERM-Vet monitoring programme. *J Antimicrob Chemother* 68:1741–1749 <http://dx.doi.org/10.1093/jac/dkt123>.
44. Wieler LH, Ewers C, Guenther S, Walther B, Lübke-Becker A. 2011. Methicillin-resistant staphylococci (MRS) and extended-spectrum  $\beta$ -lactamases (ESBL)-producing *Enterobacteriaceae* in companion animals: nosocomial infections as one reason for the rising prevalence of these potential zoonotic pathogens in clinical samples. *Int J Med Microbiol* 301:635–641 <http://dx.doi.org/10.1016/j.ijmm.2011.09.009>.
45. Cantón R, González-Alba JM, Galán JC. 2012. CTX-M enzymes: origin and diffusion. *Front Microbiol* 3:110–129 <http://dx.doi.org/10.3389/fmicb.2012.00110>.
46. Poirel L, Naas T, Nordmann P. 2008. Genetic support of extended-spectrum  $\beta$ -lactamases. *Clin Microbiol Infect* 14(Suppl 1):75–81 <http://dx.doi.org/10.1111/j.1469-0691.2007.01865.x>.
47. Carattoli A. 2013. Plasmids and the spread of resistance. *Int J Med Microbiol* 303:298–304 <http://dx.doi.org/10.1016/j.ijmm.2013.02.001>.
48. Ferreira JC, Penha Filho RA, Andrade LN, Berchieri A Jr, Darini AL. 2014. Detection of chromosomal *bla*<sub>(CTX-M-2)</sub> in diverse *Escherichia coli* isolates from healthy broiler chickens. *Clin Microbiol Infect* 20:O623–O626 <http://dx.doi.org/10.1111/1469-0691.12531>.
49. Guenther S, Semmler T, Stubbe A, Stubbe M, Wieler LH, Schaufler K. 2017. Chromosomally encoded ESBL genes in *Escherichia coli* of ST38 from Mongolian wild birds. *J Antimicrob Chemother* 72:1310–1313 <http://dx.doi.org/10.1093/jac/dkx006>.
50. Valentin L, Sharp H, Hille K, Seibt U, Fischer J, Pfeifer Y, Michael GB, Nickel S, Schmiedel J, Falgenhauer L, Friese A, Bauerfeind R, Roesler U, Imirzalioglu C, Chakraborty T, Helmuth R, Valenza G, Werner G, Schwarz S, Guerra B, Appel B, Kreienbrock L, Käsböhrer A. 2014. Subgrouping of ESBL-producing *Escherichia coli* from animal and human sources: an approach to quantify the distribution of ESBL types between different reservoirs. *Int J Med Microbiol* 304:805–816 <http://dx.doi.org/10.1016/j.ijmm.2014.07.015>.
51. Wu G, Day MJ, Mafura MT, Nunez-Garcia J, Fenner JJ, Sharma M, van Essen-Zandbergen A, Rodríguez I, Dierikx C, Kadlec K, Schink AK, Chattaway M, Wain J, Helmuth R, Guerra B, Schwarz S, Threlfall J, Woodward MJ, Woodford N, Coldham N, Mevius D. 2013. Comparative analysis of ESBL-positive *Escherichia coli* isolates from animals and humans from the UK, The Netherlands and Germany. *PLoS One* 8:e75392–e75402 <http://dx.doi.org/10.1371/journal.pone.0075392>.
52. Leverstein-van Hall MA, Dierikx CM, Cohen Stuart J, Voets GM, van den Munckhof MP, van Essen-Zandbergen A, Platteel T, Fluit AC, van de Sande-Bruinsma N, Scharinga J, Bonten MJ, Mevius DJ, National ESBL Surveillance Group. 2011. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. *Clin Microbiol Infect* 17:873–880 <http://dx.doi.org/10.1111/j.1469-0691.2011.03497.x>.
53. Casella T, Nogueira MCL, Saras E, Haenni M, Maded JY. 2017. High prevalence of ESBLs in retail chicken meat despite reduced use of antimicrobials in chicken production, France. *Int J Food Microbiol* 257:271–275 <http://dx.doi.org/10.1016/j.ijfoodmicro.2017.07.005>.
54. Jacoby GA. 2009. AmpC  $\beta$ -lactamases. *Clin Microbiol Rev* 22:161–182 <http://dx.doi.org/10.1128/CMR.00036-08>.
55. Philippon A, Arlet G, Jacoby GA. 2002. Plasmid-determined AmpC-type  $\beta$ -lactamases. *Antimicrob Agents Chemother* 46:1–11 <http://dx.doi.org/10.1128/AAC.46.1.1-11.2002>.

56. Liebana E, Carattoli A, Coque TM, Hasman H, Magiorakos AP, Mevius D, Peixe L, Poirel L, Schuepbach-Regula G, Torneke K, Torren-Edo J, Torres C, Threlfall J. 2013. Public health risks of enterobacterial isolates producing extended-spectrum  $\beta$ -lactamases or AmpC  $\beta$ -lactamases in food and food-producing animals: an EU perspective of epidemiology, analytical methods, risk factors, and control options. *Clin Infect Dis* 56: 1030–1037 <http://dx.doi.org/10.1093/cid/cis1043>.
57. Hansen KH, Bortolaia V, Nielsen CA, Nielsen JB, Schønning K, Agersø Y, Guardabassi L. 2016. Host-specific patterns of genetic diversity among *Incl1*-Igamma and IncK plasmids encoding CMY-2  $\beta$ -lactamase in *Escherichia coli* isolates from humans, poultry meat, poultry, and dogs in Denmark. *Appl Environ Microbiol* 82:4705–4714 <http://dx.doi.org/10.1128/AEM.00495-16>.
58. Börjesson S, Ny S, Egervärn M, Bergström J, Rosengren Å, Englund S, Löfmark S, Byfors S. 2016. Limited dissemination of extended-spectrum  $\beta$ -lactamase- and plasmid-encoded AmpC-producing *Escherichia coli* from food and farm animals, Sweden. *Emerg Infect Dis* 22:634–640 <http://dx.doi.org/10.3201/eid2204.151142>.
59. Nilsson O, Börjesson S, Landén A, Bengtsson B. 2014. Vertical transmission of *Escherichia coli* carrying plasmid-mediated AmpC (pAmpC) through the broiler production pyramid. *J Antimicrob Chemother* 69: 1497–1500 <http://dx.doi.org/10.1093/jac/dku030>.
60. Lončarić I, Stalder GL, Mehinagic K, Rosengarten R, Hoelzl F, Knauer F, Walzer C. 2013. Comparison of ESBL- and AmpC producing *Enterobacteriaceae* and methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from migratory and resident population of rooks (*Corvus frugilegus*) in Austria. *PLoS One* 8:e84048 <http://dx.doi.org/10.1371/journal.pone.0084048>.
61. Poirel L, Potron A, De La Cuesta C, Cleary T, Nordmann P, Munoz-Price LS. 2012. Wild coastline birds as reservoirs of broad-spectrum- $\beta$ -lactamase-producing *Enterobacteriaceae* in Miami Beach, Florida. *Antimicrob Agents Chemother* 56:2756–2758 <http://dx.doi.org/10.1128/AAC.05982-11>.
62. Báez J, Hernández-García M, Guamparito C, Díaz S, Olave A, Guerrero K, Cantón R, Baquero F, Gahona J, Valenzuela N, Del Campo R, Silva J. 2015. Molecular characterization and genetic diversity of ESBL-producing *Escherichia coli* colonizing the migratory Franklin's gulls (*Leucophaeus pipixcan*) in Antofagasta, North of Chile. *Microb Drug Resist* 21:111–116 <http://dx.doi.org/10.1089/mdr.2014.0158>.
63. Simões RR, Poirel L, Da Costa PM, Nordmann P. 2010. Seagulls and beaches as reservoirs for multidrug-resistant *Escherichia coli*. *Emerg Infect Dis* 16:110–112 <http://dx.doi.org/10.3201/eid1601.090896>.
64. Köck R, Daniels-Haardt I, Becker K, Mellmann A, Friedrich AW, Mevius D, Schwarz S, Jurke A. 2018. Carbapenem-resistant *Enterobacteriaceae* in wildlife, food-producing, and companion animals: a systematic review. *Clin Microbiol Infect*. Epub ahead of print. doi:10.1016/j.cmi.2018.04.004.
65. Poirel L, Stephan R, Perreten V, Nordmann P. 2014. The carbapenemase threat in the animal world: the wrong culprit. *J Antimicrob Chemother* 69:2007–2008 <http://dx.doi.org/10.1093/jac/dku054>.
66. Woodford N, Wareham DW, Guerra B, Teale C. 2014. Carbapenemase-producing *Enterobacteriaceae* and non-*Enterobacteriaceae* from animals and the environment: an emerging public health risk of our own making? *J Antimicrob Chemother* 69:287–291 <http://dx.doi.org/10.1093/jac/dkt392>.
67. Fischer J, San José M, Roschanski N, Schmoger S, Baumann B, Irrgang A, Friese A, Roesler U, Helmuth R, Guerra B. 2017. Spread and persistence of VIM-1 carbapenemase-producing *Enterobacteriaceae* in three German swine farms in 2011 and 2012. *Vet Microbiol* 200:118–123 <http://dx.doi.org/10.1016/j.vetmic.2016.04.026>.
68. Fischer J, Rodríguez I, Schmoger S, Friese A, Roesler U, Helmuth R, Guerra B. 2012. *Escherichia coli* producing VIM-1 carbapenemase isolated on a pig farm. *J Antimicrob Chemother* 67:1793–1795 <http://dx.doi.org/10.1093/jac/dks108>.
69. Guerra B, Fischer J, Helmuth R. 2014. An emerging public health problem: acquired carbapenemase-producing microorganisms are present in food-producing animals, their environment, companion animals and wild birds. *Vet Microbiol* 171:290–297 <http://dx.doi.org/10.1016/j.vetmic.2014.02.001>.
70. Shaheen BW, Nayak R, Boothe DM. 2013. Emergence of a New Delhi metallo- $\beta$ -lactamase (NDM-1)-encoding gene in clinical *Escherichia coli* isolates recovered from companion animals in the United States. *Antimicrob Agents Chemother* 57:2902–2903 <http://dx.doi.org/10.1128/AAC.02028-12>.
71. Wang Y, Zhang R, Li J, Wu Z, Yin W, Schwarz S, Tyrrell JM, Zheng Y, Wang S, Shen Z, Liu Z, Liu J, Lei L, Li M, Zhang Q, Wu C, Zhang Q, Wu Y, Walsh TR, Shen J. 2017. Comprehensive resistome analysis reveals the prevalence of NDM and MCR-1 in Chinese poultry production. *Nat Microbiol* 2:16260 <http://dx.doi.org/10.1038/nmicrobiol.2016.260>.
72. Liu Z, Wang Y, Walsh TR, Liu D, Shen Z, Zhang R, Yin W, Yao H, Li J, Shen J. 2017. Plasmid-mediated novel *bla*<sub>NDM-17</sub> gene encoding a carbapenemase with enhanced activity in a sequence type 48 *Escherichia coli* strain. *Antimicrob Agents Chemother* 61:e02233-16.
73. Singh AS, Lekshmi M, Nayak BB, Kumar SH. 2016. Isolation of *Escherichia coli* harboring *bla*<sub>NDM-5</sub> from fresh fish in India. *J Microbiol Immunol Infect* 49:822–823 <http://dx.doi.org/10.1016/j.jmii.2014.11.004>.
74. Yang RS, Feng Y, Lv XY, Duan JH, Chen J, Fang LX, Xia J, Liao XP, Sun J, Liu YH. 2016. Emergence of NDM-5- and MCR-1-producing *Escherichia coli* clones ST648 and ST156 from a single Muscovy duck (*Cairina moschata*). *Antimicrob Agents Chemother* 60:6899–6902 <http://dx.doi.org/10.1128/AAC.01365-16>.
75. Yousfi M, Touati A, Mairi A, Brasme L, Gharout-Sait A, Guillard T, De Champs C. 2016. Emergence of carbapenemase-producing *Escherichia coli* isolated from companion animals in Algeria. *Microb Drug Resist* 22:342–346 <http://dx.doi.org/10.1089/mdr.2015.0196>.
76. Dolejska M, Masarikova M, Dobiasova H, Jamborova I, Karpiskova R, Havlicek M, Carlile N, Priddel D, Cizek A, Literak I. 2016. High prevalence of *Salmonella* and IMP-4-producing *Enterobacteriaceae* in the silver gull on Five Islands, Australia. *J Antimicrob Chemother* 71:63–70 <http://dx.doi.org/10.1093/jac/dkv306>.
77. Al Bayssari C, Olaitan AO, Dabboussi F, Hamze M, Rolain JM. 2015. Emergence of OXA-48-producing *Escherichia coli* clone ST38 in fowl. *Antimicrob Agents Chemother* 59:745–746 <http://dx.doi.org/10.1128/AAC.03552-14>.
78. Melo LC, Boisson MN, Saras E, Médaille C, Boulouis HJ, Madec JY, Haenni M. 2017. OXA-48-producing ST372 *Escherichia coli* in a French dog. *J Antimicrob Chemother* 72:1256–1258.
79. Stolle I, Prenger-Berninghoff E, Stamm I, Scheufen S, Hassdenteufel E, Guenther S, Bethe A, Pfeifer Y, Ewers C. 2013. Emergence of OXA-48 carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae* in dogs. *J Antimicrob Chemother* 68:2802–2808 <http://dx.doi.org/10.1093/jac/dkt259>.
80. Pulss S, Semmler T, Prenger-Berninghoff E, Bauerfeind R, Ewers C. 2017. First report of an *Escherichia coli* strain from swine carrying an OXA-181 carbapenemase and the colistin resistance determinant MCR-1. *Int J Antimicrob Agents* 50:232–236 <http://dx.doi.org/10.1016/j.ijantimicag.2017.03.014>.
81. Mollenkopf DF, Stull JW, Mathys DA, Bowman AS, Feicht SM, Grooters SV, Daniels JB, Wittum TE. 2017. Carbapenemase-producing *Enterobacteriaceae* recovered from the environment of a swine farrow-to-finish operation in the United States. *Antimicrob Agents Chemother* 61: e01298-16 <http://dx.doi.org/10.1128/AAC.01298-16>.
82. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, Cornaglia G, Garau J, Gniadkowski M, Hayden MK, Kumarasamy K, Livermore DM, Maya JJ, Nordmann P, Patel JB, Paterson DL, Pitout J, Villegas MV, Wang H, Woodford N, Quinn JP. 2013. Clinical epidemiology of the global expansion of *Klebsiella pneu-*

- moniae* carbapenemases. *Lancet Infect Dis* 13:785–796 [http://dx.doi.org/10.1016/S1473-3099\(13\)70190-7](http://dx.doi.org/10.1016/S1473-3099(13)70190-7).
83. Hopkins KL, Davies RH, Threlfall EJ. 2005. Mechanisms of quinolone resistance in *Escherichia coli* and *Salmonella*: recent developments. *Int J Antimicrob Agents* 25:358–373 <http://dx.doi.org/10.1016/j.ijantimicag.2005.02.006>.
84. de Jong A, Muggeo A, El Garch F, Moyaert H, de Champs C, Guillard T. 2018. Characterization of quinolone resistance mechanisms in *Enterobacteriaceae* isolated from companion animals in Europe (ComPath II study). *Vet Microbiol* 216:159–167 <http://dx.doi.org/10.1016/j.vetmic.2018.02.002>.
85. Schink AK, Kadlec K, Hauschild T, Brenner Michael G, Dörner JC, Ludwig C, Werckenthin C, Hehnen HR, Stephan B, Schwarz S. 2013. Susceptibility of canine and feline bacterial pathogens to pradofloxacin and comparison with other fluoroquinolones approved for companion animals. *Vet Microbiol* 162:119–126 <http://dx.doi.org/10.1016/j.vetmic.2012.08.001>.
86. Liu BT, Liao XP, Yang SS, Wang XM, Li LL, Sun J, Yang YR, Fang LX, Li L, Zhao DH, Liu YH. 2012. Detection of mutations in the *gyrA* and *parC* genes in *Escherichia coli* isolates carrying plasmid-mediated quinolone resistance genes from diseased food-producing animals. *J Med Microbiol* 61:1591–1599 <http://dx.doi.org/10.1099/jmm.0.043307-0>.
87. Redgrave LS, Sutton SB, Webber MA, Piddock LJ. 2014. Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success. *Trends Microbiol* 22:438–445 <http://dx.doi.org/10.1016/j.tim.2014.04.007>.
88. Cattoir V, Nordmann P. 2009. Plasmid-mediated quinolone resistance in Gram-negative bacterial species: an update. *Curr Med Chem* 16:1028–1046 <http://dx.doi.org/10.2174/092986709787581879>.
89. Rodríguez-Martínez JM, Machuca J, Cano ME, Calvo J, Martínez-Martínez L, Pascual A. 2016. Plasmid-mediated quinolone resistance: two decades on. *Drug Resist Updat* 29:13–29 <http://dx.doi.org/10.1016/j.drup.2016.09.001>.
90. Ma J, Zeng Z, Chen Z, Xu X, Wang X, Deng Y, Lü D, Huang L, Zhang Y, Liu J, Wang M. 2009. High prevalence of plasmid-mediated quinolone resistance determinants *qnr*, *aac(6)-Ib-cr*, and *qepA* among ceftiofur-resistant *Enterobacteriaceae* isolates from companion and food-producing animals. *Antimicrob Agents Chemother* 53:519–524 <http://dx.doi.org/10.1128/AAC.00886-08>.
91. Huang SY, Dai L, Xia LN, Du XD, Qi YH, Liu HB, Wu CM, Shen JZ. 2009. Increased prevalence of plasmid-mediated quinolone resistance determinants in chicken *Escherichia coli* isolates from 2001 to 2007. *Foodborne Pathog Dis* 6:1203–1209 <http://dx.doi.org/10.1089/fpd.2009.0348>.
92. Veldman K, Cavaco LM, Mevius D, Battisti A, Franco A, Botteldoorn N, Bruneau M, Perrin-Guyomard A, Cerny T, De Frutos Escobar C, Guerra B, Schroeter A, Gutierrez M, Hopkins K, Myllyniemi AL, Sunde M, Wasyl D, Aarestrup FM. 2011. International collaborative study on the occurrence of plasmid-mediated quinolone resistance in *Salmonella enterica* and *Escherichia coli* isolated from animals, humans, food and the environment in 13 European countries. *J Antimicrob Chemother* 66:1278–1286 <http://dx.doi.org/10.1093/jac/dkr084>.
93. Dolejska M, Duskova E, Rybarikova J, Janoszowska D, Roubalova E, Dibdakova K, Maceckova G, Kohoutova L, Literak I, Smola J, Cizek A. 2011. Plasmids carrying *bla*<sub>CTX-M-1</sub> and *qnr* genes in *Escherichia coli* isolates from an equine clinic and a horseback riding centre. *J Antimicrob Chemother* 66:757–764 <http://dx.doi.org/10.1093/jac/dkq500>.
94. Schink AK, Kadlec K, Schwarz S. 2012. Detection of *qnr* genes among *Escherichia coli* isolates of animal origin and complete sequence of the conjugative *qnrB19*-carrying plasmid pQNR2078. *J Antimicrob Chemother* 67:1099–1102 <http://dx.doi.org/10.1093/jac/dks024>.
95. Hordijk J, Bosman AB, van Essen-Zandbergen A, Veldman K, Dierikx C, Wagenaar JA, Mevius D. 2011. *qnrB19* gene bracketed by IS26 on a 40-kilobase IncR plasmid from an *Escherichia coli* isolate from a veal calf. *Antimicrob Agents Chemother* 55:453–454 <http://dx.doi.org/10.1128/AAC.00866-10>.
96. Ewers C, Bethe A, Stamm I, Grobbel M, Kopp PA, Guerra B, Stubbe M, Doi Y, Zong Z, Kola A, Schaufler K, Semmler T, Fruth A, Wieler LH, Guenther S. 2014. CTX-M-15-D-ST648 *Escherichia coli* from companion animals and horses: another pandemic clone combining multiresistance and extraintestinal virulence? *J Antimicrob Chemother* 69:1224–1230 <http://dx.doi.org/10.1093/jac/dkt516>.
97. Liu X, Liu H, Li Y, Hao C. 2016. High prevalence of  $\beta$ -lactamase and plasmid-mediated quinolone resistance genes in extended-spectrum cephalosporin-resistant *Escherichia coli* from dogs in Shaanxi, China. *Front Microbiol* 7:1843–1852 <http://dx.doi.org/10.3389/fmicb.2016.01843>.
98. Pomba C, da Fonseca JD, Baptista BC, Correia JD, Martínez-Martínez L. 2009. Detection of the pandemic O25-ST131 human virulent *Escherichia coli* CTX-M-15-producing clone harboring the *qnrB2* and *aac(6)-Ib-cr* genes in a dog. *Antimicrob Agents Chemother* 53:327–328 <http://dx.doi.org/10.1128/AAC.00896-08>.
99. Timofte D, Maciuca IE, Williams NJ, Wattret A, Schmidt V. 2016. Veterinary hospital dissemination of CTX-M-15 extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli* ST410 in the United Kingdom. *Microb Drug Resist* 22:609–615 <http://dx.doi.org/10.1089/mdr.2016.0036>.
100. Madec JY, Poirel L, Saras E, Gourguechon A, Girlich D, Nordmann P, Haenni M. 2012. Non-ST131 *Escherichia coli* from cattle harbouring human-like *bla*<sub>(CTX-M-15)</sub>-carrying plasmids. *J Antimicrob Chemother* 67:578–581 <http://dx.doi.org/10.1093/jac/dkr542>.
101. Chen X, He L, Li Y, Zeng Z, Deng Y, Liu Y, Liu JH. 2014. Complete sequence of a F2:A-B- plasmid pHN3A11 carrying *rmtB* and *qepA*, and its dissemination in China. *Vet Microbiol* 174:267–271 <http://dx.doi.org/10.1016/j.vetmic.2014.08.023>.
102. Liu BT, Yang QE, Li L, Sun J, Liao XP, Fang LX, Yang SS, Deng H, Liu YH. 2013. Dissemination and characterization of plasmids carrying *oqxAB-bla*<sub>CTX-M</sub> genes in *Escherichia coli* isolates from food-producing animals. *PLoS One* 8:e73947 <http://dx.doi.org/10.1371/journal.pone.0073947>.
103. Hansen LH, Jensen LB, Sørensen HI, Sørensen SJ. 2007. Substrate specificity of the OqxAB multidrug resistance pump in *Escherichia coli* and selected enteric bacteria. *J Antimicrob Chemother* 60:145–147 <http://dx.doi.org/10.1093/jac/dkm167>.
104. Davies J, Wright GD. 1997. Bacterial resistance to aminoglycoside antibiotics. *Trends Microbiol* 5:234–240 [http://dx.doi.org/10.1016/S0966-842X\(97\)01033-0](http://dx.doi.org/10.1016/S0966-842X(97)01033-0).
105. Doi Y, Wachino JI, Arakawa Y. 2016. Aminoglycoside resistance: the emergence of acquired 16S ribosomal RNA methyltransferases. *Infect Dis Clin North Am* 30:523–537 <http://dx.doi.org/10.1016/j.idc.2016.02.011>.
106. Anonymous. 2014. Concept paper on the of aminoglycosides in animals in the European Union: development of resistance and impact on human and animal health. EMA/CVMP/AWP/158821/2014 1-4.
107. Fourmy D, Yoshizawa S, Puglisi JD. 1998. Paromomycin binding induces a local conformational change in the A-site of 16 S rRNA. *J Mol Biol* 277:333–345 <http://dx.doi.org/10.1006/jmbi.1997.1551>.
108. Bowers DR SAN, Tam VH. 2016. Aminoglycoside pharmacodynamics, p 199–220. In Rotschafer J, Andes D, Rodvold K (ed), *Antibiotic Pharmacodynamics. Methods in Pharmacology and Toxicology*. Humana Press, New York, NY.
109. Griffey RH, Hofstadler SA, Sannes-Lowery KA, Ecker DJ, Crooke ST. 1999. Determinants of aminoglycoside-binding specificity for rRNA by using mass spectrometry. *Proc Natl Acad Sci USA* 96:10129–10133 <http://dx.doi.org/10.1073/pnas.96.18.10129>.
110. Llano-Sotelo B, Hickerson RP, Lancaster L, Noller HF, Mankin AS. 2009. Fluorescently labeled ribosomes as a tool for analyzing antibiotic binding. *RNA* 15:1597–1604 <http://dx.doi.org/10.1261/rna.1681609>.

111. Galimand M, Courvalin P, Lambert T. 2003. Plasmid-mediated high-level resistance to aminoglycosides in *Enterobacteriaceae* due to 16S rRNA methylation. *Antimicrob Agents Chemother* 47:2565–2571 <http://dx.doi.org/10.1128/AAC.47.8.2565-2571.2003>.
112. Batah R, Loucif L, Olaitan AO, Boutefnouchet N, Allag H, Rolain JM. 2015. Outbreak of *Serratia marcescens* coproducing ArmA and CTX-M-15 mediated high levels of resistance to aminoglycoside and extended-spectrum  $\beta$ -lactamases, Algeria. *Microb Drug Resist* 21:470–476 <http://dx.doi.org/10.1089/mdr.2014.0240>.
113. Dolejska M, Villa L, Poirel L, Nordmann P, Carattoli A. 2013. Complete sequencing of an IncHI1 plasmid encoding the carbapenemase NDM-1, the ArmA 16S rRNA methylase and a resistance-nodulation-cell division/multidrug efflux pump. *J Antimicrob Chemother* 68:34–39 <http://dx.doi.org/10.1093/jac/dks357>.
114. Gurung M, Moon DC, Tamang MD, Kim J, Lee YC, Seol SY, Cho DT, Lee JC. 2010. Emergence of 16S rRNA methylase gene *armA* and cocarriage of *bla*<sub>(IMP-1)</sub> in *Pseudomonas aeruginosa* isolates from South Korea. *Diagn Microbiol Infect Dis* 68:468–470 <http://dx.doi.org/10.1016/j.diagmicrobio.2010.07.021>.
115. Wachino J, Yamane K, Shibayama K, Kurokawa H, Shibata N, Suzuki S, Doi Y, Kimura K, Ike Y, Arakawa Y. 2006. Novel plasmid-mediated 16S rRNA methylase, RmtC, found in a *Proteus mirabilis* isolate demonstrating extraordinary high-level resistance against various aminoglycosides. *Antimicrob Agents Chemother* 50:178–184 <http://dx.doi.org/10.1128/AAC.50.1.178-184.2006>.
116. Yu YS, Zhou H, Yang Q, Chen YG, Li LJ. 2007. Widespread occurrence of aminoglycoside resistance due to ArmA methylase in imipenem-resistant *Acinetobacter baumannii* isolates in China. *J Antimicrob Chemother* 60:454–455 <http://dx.doi.org/10.1093/jac/dkm208>.
117. Galimand M, Sabtcheva S, Courvalin P, Lambert T. 2005. World-wide disseminated *armA* aminoglycoside resistance methylase gene is borne by composite transposon Tn1548. *Antimicrob Agents Chemother* 49:2949–2953 <http://dx.doi.org/10.1128/AAC.49.7.2949-2953.2005>.
118. González-Zorn B, Teshager T, Casas M, Porrero MC, Moreno MA, Courvalin P, Domínguez L. 2005. *armA* and aminoglycoside resistance in *Escherichia coli*. *Emerg Infect Dis* 11:954–956 <http://dx.doi.org/10.3201/eid1106.040553>.
119. Chen L, Chen ZL, Liu JH, Zeng ZL, Ma JY, Jiang HX. 2007. Emergence of RmtB methylase-producing *Escherichia coli* and *Enterobacter cloacae* isolates from pigs in China. *J Antimicrob Chemother* 59:880–885 <http://dx.doi.org/10.1093/jac/dkm065>.
120. Du XD, Wu CM, Liu HB, Li XS, Beier RC, Xiao F, Qin SS, Huang SY, Shen JZ. 2009. Plasmid-mediated ArmA and RmtB 16S rRNA methylases in *Escherichia coli* isolated from chickens. *J Antimicrob Chemother* 64:1328–1330 <http://dx.doi.org/10.1093/jac/dkp354>.
121. Liu BT, Liao XP, Yue L, Chen XY, Li L, Yang SS, Sun J, Zhang S, Liao SD, Liu YH. 2013. Prevalence of  $\beta$ -lactamase and 16S rRNA methylase genes among clinical *Escherichia coli* isolates carrying plasmid-mediated quinolone resistance genes from animals. *Microb Drug Resist* 19:237–245 <http://dx.doi.org/10.1089/mdr.2012.0179>.
122. Yu T, He T, Yao H, Zhang JB, Li XN, Zhang RM, Wang GQ. 2015. Prevalence of 16S rRNA methylase gene *rmtB* among *Escherichia coli* isolated from bovine mastitis in Ningxia, China. *Foodborne Pathog Dis* 12:770–777 <http://dx.doi.org/10.1089/fpd.2015.1983>.
123. Yang Y, Zhang A, Lei C, Wang H, Guan Z, Xu C, Liu B, Zhang D, Li Q, Jiang W, Pan Y, Yang C. 2015. Characteristics of plasmids coharboring 16S rRNA methylases, CTX-M, and virulence factors in *Escherichia coli* and *Klebsiella pneumoniae* isolates from chickens in China. *Foodborne Pathog Dis* 12:873–880 <http://dx.doi.org/10.1089/fpd.2015.2025>.
124. Lupo A, Saras E, Madec JY, Haenni M. 2018. Emergence of *bla*<sub>CTX-M-55</sub> associated with *fosA*, *rmtB* and *mcr* gene variants in *Escherichia coli* from various animal species in France. *J Antimicrob Chemother* 73:867–872 <http://dx.doi.org/10.1093/jac/dkx489>.
125. Leigue L, Warth JF, Melo LC, Silva KC, Moura RA, Barbato L, Silva LC, Santos AC, Silva RM, Lincopan N. 2015. MDR ST2179-CTX-M-15 *Escherichia coli* co-producing RmtD and AAC(6)-Ib-cr in a horse with extraintestinal infection, Brazil. *J Antimicrob Chemother* 70:1263–1265.
126. Lee CS, Hu F, Rivera JI, Doi Y. 2014. *Escherichia coli* sequence type 354 coproducing CMY-2 cephalosporinase and RmtE 16S rRNA methyltransferase. *Antimicrob Agents Chemother* 58:4246–4247 <http://dx.doi.org/10.1128/AAC.02627-14>.
127. Xia J, Sun J, Li L, Fang LX, Deng H, Yang RS, Li XP, Liao XP, Liu YH. 2015. First report of the IncI1/ST898 conjugative plasmid carrying *rmtE2* 16S rRNA methyltransferase gene in *Escherichia coli*. *Antimicrob Agents Chemother* 59:7921–7922 <http://dx.doi.org/10.1128/AAC.01235-15>.
128. Zou W, Li C, Yang X, Wang Y, Cheng G, Zeng J, Zhang X, Chen Y, Cai R, Huang Q, Feng L, Wang H, Li D, Zhang G, Chen Y, Zhang Z, Zhang H. 2018. Frequency of antimicrobial resistance and integron gene cassettes in *Escherichia coli* isolated from giant pandas (*Ailuropoda melanoleuca*) in China. *Microb Pathog* 116:173–179 <http://dx.doi.org/10.1016/j.micpath.2018.01.034>.
129. Gutierrez B, Escudero JA, San Millan A, Hidalgo L, Carrilero L, Ovejero CM, Santos-Lopez A, Thomas-Lopez D, Gonzalez-Zorn B. 2012. Fitness cost and interference of Arm/Rmt aminoglycoside resistance with the RsmF housekeeping methyltransferases. *Antimicrob Agents Chemother* 56:2335–2341 <http://dx.doi.org/10.1128/AAC.06066-11>.
130. Lioy VS, Goussard S, Guerineau V, Yoon EJ, Courvalin P, Galimand M, Grillot-Courvalin C. 2014. Aminoglycoside resistance 16S rRNA methyltransferases block endogenous methylation, affect translation efficiency and fitness of the host. *RNA* 20:382–391 <http://dx.doi.org/10.1261/rna.042572.113>.
131. Ramirez MS, Tolmasky ME. 2010. Aminoglycoside modifying enzymes. *Drug Resist Updat* 13:151–171 <http://dx.doi.org/10.1016/j.drug.2010.08.003>.
132. Choi MJ, Lim SK, Nam HM, Kim AR, Jung SC, Kim MN. 2011. Apramycin and gentamicin resistances in indicator and clinical *Escherichia coli* isolates from farm animals in Korea. *Foodborne Pathog Dis* 8:119–123 <http://dx.doi.org/10.1089/fpd.2010.0641>.
133. Costa D, Poeta P, Sáenz Y, Vinué L, Coelho AC, Matos M, Rojo-Bezares B, Rodrigues J, Torres C. 2008. Mechanisms of antibiotic resistance in *Escherichia coli* isolates recovered from wild animals. *Microb Drug Resist* 14:71–77 <http://dx.doi.org/10.1089/mdr.2008.0795>.
134. Haldorsen BC, Simonsen GS, Sundsfjord A, Samuelsen O, Norwegian Study Group on Aminoglycoside Resistance. 2014. Increased prevalence of aminoglycoside resistance in clinical isolates of *Escherichia coli* and *Klebsiella* spp. in Norway is associated with the acquisition of AAC(3)-II and AAC(6)-Ib. *Diagn Microbiol Infect Dis* 78:66–69 <http://dx.doi.org/10.1016/j.diagmicrobio.2013.10.001>.
135. Medina A, Horcajo P, Jurado S, De la Fuente R, Ruiz-Santa-Quiteria JA, Domínguez-Bernal G, Orden JA. 2011. Phenotypic and genotypic characterization of antimicrobial resistance in enterohemorrhagic *Escherichia coli* and atypical enteropathogenic *E. coli* strains from ruminants. *J Vet Diagn Invest* 23:91–95 <http://dx.doi.org/10.1177/104063871102300114>.
136. Radhouani H, Poeta P, Gonçalves A, Pacheco R, Sargo R, Igrejas G. 2012. Wild birds as biological indicators of environmental pollution: antimicrobial resistance patterns of *Escherichia coli* and enterococci isolated from common buzzards (*Buteo buteo*). *J Med Microbiol* 61:837–843 <http://dx.doi.org/10.1099/jmm.0.038364-0>.
137. Radhouani H, Poeta P, Igrejas G, Gonçalves A, Vinué L, Torres C. 2009. Antimicrobial resistance and phylogenetic groups in isolates of *Escherichia coli* from seagulls at the Berlengas nature reserve. *Vet Rec* 165:138–142 <http://dx.doi.org/10.1136/vr.165.5.138>.
138. Rocha-Gracia RC, Cortés-Cortés G, Lozano-Zarain P, Bello F, Martínez-Laguna Y, Torres C. 2015. Faecal *Escherichia coli* isolates from

- healthy dogs harbour CTX-M-15 and CMY-2  $\beta$ -lactamases. *Vet J* 203: 315–319 <http://dx.doi.org/10.1016/j.tvjl.2014.12.026>.
139. Silva N, Igrejas G, Figueiredo N, Gonçalves A, Radhouani H, Rodrigues J, Poeta P. 2010. Molecular characterization of antimicrobial resistance in enterococci and *Escherichia coli* isolates from European wild rabbit (*Oryctolagus cuniculus*). *Sci Total Environ* 408:4871–4876 <http://dx.doi.org/10.1016/j.scitotenv.2010.06.046>.
140. Xiao Y, Hu Y. 2012. The major aminoglycoside-modifying enzyme AAC(3)-II found in *Escherichia coli* determines a significant disparity in its resistance to gentamicin and amikacin in China. *Microb Drug Resist* 18:42–46 <http://dx.doi.org/10.1089/mdr.2010.0190>.
141. Allen SE, Boerlin P, Janecko N, Lumsden JS, Barker IK, Pearl DL, Reid-Smith RJ, Jardine C. 2011. Antimicrobial resistance in generic *Escherichia coli* isolates from wild small mammals living in swine farm, residential, landfill, and natural environments in southern Ontario, Canada. *Appl Environ Microbiol* 77:882–888 <http://dx.doi.org/10.1128/AEM.01111-10>.
142. Gonçalves A, Igrejas G, Radhouani H, Correia S, Pacheco R, Santos T, Monteiro R, Guerra A, Petrucci-Fonseca F, Brito F, Torres C, Poeta P. 2013. Antimicrobial resistance in faecal enterococci and *Escherichia coli* isolates recovered from Iberian wolf. *Lett Appl Microbiol* 56:268–274 <http://dx.doi.org/10.1111/lam.12044>.
143. Gonçalves A, Igrejas G, Radhouani H, Santos T, Monteiro R, Pacheco R, Alcaide E, Zorrilla I, Serra R, Torres C, Poeta P. 2013. Detection of antibiotic resistant enterococci and *Escherichia coli* in free range Iberian Lynx (*Lynx pardinus*). *Sci Total Environ* 456–457:115–119 <http://dx.doi.org/10.1016/j.scitotenv.2013.03.073>.
144. Marchant M, Vinué L, Torres C, Moreno MA. 2013. Change of integrons over time in *Escherichia coli* isolates recovered from healthy pigs and chickens. *Vet Microbiol* 163:124–132 <http://dx.doi.org/10.1016/j.vetmic.2012.12.011>.
145. Marinho C, Igrejas G, Gonçalves A, Silva N, Santos T, Monteiro R, Gonçalves D, Rodrigues T, Poeta P. 2014. Azorean wild rabbits as reservoirs of antimicrobial resistant *Escherichia coli*. *Anaerobe* 30:116–119 <http://dx.doi.org/10.1016/j.anaerobe.2014.09.009>.
146. Radhouani H, Igrejas G, Gonçalves A, Pacheco R, Monteiro R, Sargo R, Brito F, Torres C, Poeta P. 2013. Antimicrobial resistance and virulence genes in *Escherichia coli* and enterococci from red foxes (*Vulpes vulpes*). *Anaerobe* 23:82–86 <http://dx.doi.org/10.1016/j.anaerobe.2013.06.013>.
147. Sacristán C, Esperón F, Herrera-León S, Iglesias I, Neves E, Nogal V, Muñoz MJ, de la Torre A. 2014. Virulence genes, antibiotic resistance and integrons in *Escherichia coli* strains isolated from synanthropic birds from Spain. *Avian Pathol* 43:172–175 <http://dx.doi.org/10.1080/03079457.2014.897683>.
148. Santos T, Silva N, Igrejas G, Rodrigues P, Micael J, Rodrigues T, Resendes R, Gonçalves A, Marinho C, Gonçalves D, Cunha R, Poeta P. 2013. Dissemination of antibiotic resistant *Enterococcus* spp. and *Escherichia coli* from wild birds of Azores Archipelago. *Anaerobe* 24:25–31 <http://dx.doi.org/10.1016/j.anaerobe.2013.09.004>.
149. Karczmarczyk M, Abbott Y, Walsh C, Leonard N, Fanning S. 2011. Characterization of multidrug-resistant *Escherichia coli* isolates from animals presenting at a university veterinary hospital. *Appl Environ Microbiol* 77:7104–7112 <http://dx.doi.org/10.1128/AEM.00599-11>.
150. Shin SW, Byun JW, Jung M, Shin MK, Yoo HS. 2014. Antimicrobial resistance, virulence genes and PFGE-profiling of *Escherichia coli* isolates from South Korean cattle farms. *J Microbiol* 52:785–793 <http://dx.doi.org/10.1007/s12275-014-4166-1>.
151. Toszeghy M, Phillips N, Reeves H, Wu G, Teale C, Coldham N, Randall L. 2012. Molecular and phenotypic characterisation of extended spectrum  $\beta$ -lactamase CTX-M *Escherichia coli* from farm animals in Great Britain. *Res Vet Sci* 93:1142–1150 <http://dx.doi.org/10.1016/j.rvsc.2012.05.001>.
152. Yamamoto S, Iwabuchi E, Hasegawa M, Esaki H, Muramatsu M, Hirayama N, Hirai K. 2013. Prevalence and molecular epidemiological characterization of antimicrobial-resistant *Escherichia coli* isolates from Japanese black beef cattle. *J Food Prot* 76:394–404 <http://dx.doi.org/10.4315/0362-028X.JFP-12-273>.
153. Adelowo OO, Fagade OE, Agersø Y. 2014. Antibiotic resistance and resistance genes in *Escherichia coli* from poultry farms, southwest Nigeria. *J Infect Dev Ctries* 8:1103–1112 <http://dx.doi.org/10.3855/jidc.4222>.
154. Zhang FY, Huo SY, Li YR, Xie R, Wu XJ, Chen LG, Gao YH. 2014. A survey of the frequency of aminoglycoside antibiotic-resistant genotypes and phenotypes in *Escherichia coli* in broilers with septicaemia in Hebei, China. *Br Poult Sci* 55:305–310 <http://dx.doi.org/10.1080/00071668.2014.891096>.
155. Gonçalves A, Torres C, Silva N, Carneiro C, Radhouani H, Coelho C, Araújo C, Rodrigues J, Vinué L, Somalo S, Poeta P, Igrejas G. 2010. Genetic characterization of extended-spectrum  $\beta$ -lactamases in *Escherichia coli* isolates of pigs from a Portuguese intensive swine farm. *Foodborne Pathog Dis* 7:1569–1573 <http://dx.doi.org/10.1089/fpd.2010.0598>.
156. Tang X, Tan C, Zhang X, Zhao Z, Xia X, Wu B, Guo A, Zhou R, Chen H. 2011. Antimicrobial resistances of extraintestinal pathogenic *Escherichia coli* isolates from swine in China. *Microb Pathog* 50:207–212 <http://dx.doi.org/10.1016/j.micpath.2011.01.004>.
157. Zhang WJ, Xu XR, Schwarz S, Wang XM, Dai L, Zheng HJ, Liu S. 2014. Characterization of the IncA/C plasmid pSCEC2 from *Escherichia coli* of swine origin that harbours the multiresistance gene *cf*. *J Antimicrob Chemother* 69:385–389 <http://dx.doi.org/10.1093/jac/dkt355>.
158. Falagas ME, Vouloumanou EK, Samonis G, Vardakas KZ. 2016. Fosfomicin. *Clin Microbiol Rev* 29:321–347 <http://dx.doi.org/10.1128/CMR.00068-15>.
159. Pérez DS, Tapia MO, Soraci AL. 2014. Fosfomicin: uses and potentialities in veterinary medicine. *Open Vet J* 4:26–43.
160. Silver LL. 2017. Fosfomicin: mechanism and resistance. *Cold Spring Harb Perspect Med* 7:7 <http://dx.doi.org/10.1101/cshperspect.a025262>.
161. Wang X, Zhu Y, Hua X, Chen F, Wang C, Zhang Y, Liu S, Zhang W. 2018. F14:A-B- and IncX4 Inc group *cf*-positive plasmids circulating in *Escherichia coli* of animal origin in Northeast China. *Vet Microbiol* 217:53–57 <http://dx.doi.org/10.1016/j.vetmic.2018.02.003>.
162. Wang XM, Dong Z, Schwarz S, Zhu Y, Hua X, Zhang Y, Liu S, Zhang WJ. 2017. Plasmids of diverse Inc groups disseminate the fosfomicin resistance gene *fosA3* among *Escherichia coli* isolates from pigs, chickens, and dairy cows in northeast China. *Antimicrob Agents Chemother* 61:e00859–e00817 <http://dx.doi.org/10.1128/AAC.00859-17>.
163. Hou J, Huang X, Deng Y, He L, Yang T, Zeng Z, Chen Z, Liu JH. 2012. Dissemination of the fosfomicin resistance gene *fosA3* with CTX-M  $\beta$ -lactamase genes and *rmtB* carried on IncFII plasmids among *Escherichia coli* isolates from pets in China. *Antimicrob Agents Chemother* 56:2135–2138 <http://dx.doi.org/10.1128/AAC.05104-11>.
164. Yao H, Wu D, Lei L, Shen Z, Wang Y, Liao K. 2016. The detection of fosfomicin resistance genes in *Enterobacteriaceae* from pets and their owners. *Vet Microbiol* 193:67–71 <http://dx.doi.org/10.1016/j.vetmic.2016.07.019>.
165. Xie M, Lin D, Chen K, Chan EW, Yao W, Chen S. 2016. Molecular characterization of *Escherichia coli* strains isolated from retail meat that harbor *bla*<sub>CTX-M</sub> and *fosA3* genes. *Antimicrob Agents Chemother* 60:2450–2455 <http://dx.doi.org/10.1128/AAC.03101-15>.
166. He L, Partridge SR, Yang X, Hou J, Deng Y, Yao Q, Zeng Z, Chen Z, Liu JH. 2013. Complete nucleotide sequence of pHN7A8, an F33:A-B-type epidemic plasmid carrying *bla*<sub>CTX-M-65</sub>, *fosA3* and *rmtB* from China. *J Antimicrob Chemother* 68:46–50 <http://dx.doi.org/10.1093/jac/dks369>.
167. Ho PL, Chan J, Lo WU, Law PY, Chow KH. 2013. Plasmid-mediated fosfomicin resistance in *Escherichia coli* isolated from pig. *Vet Microbiol* 162:964–967 <http://dx.doi.org/10.1016/j.vetmic.2012.09.023>.

168. Sun H, Li S, Xie Z, Yang F, Sun Y, Zhu Y, Zhao X, Jiang S. 2012. A novel multidrug resistance plasmid isolated from an *Escherichia coli* strain resistant to aminoglycosides. *J Antimicrob Chemother* 67:1635–1638 <http://dx.doi.org/10.1093/jac/dks107>.
169. Pan YS, Yuan L, Zong ZY, Liu JH, Wang LF, Hu GZ. 2014. A multidrug-resistance region containing *bla*<sub>CTX-M-65</sub>, *fosA3* and *rmtB* on conjugative IncFII plasmids in *Escherichia coli* ST117 isolates from chicken. *J Med Microbiol* 63:485–488 <http://dx.doi.org/10.1099/jmm.0.070664-0>.
170. Hou J, Yang X, Zeng Z, Lv L, Yang T, Lin D, Liu JH. 2013. Detection of the plasmid-encoded fosfomycin resistance gene *fosA3* in *Escherichia coli* of food-animal origin. *J Antimicrob Chemother* 68:766–770 <http://dx.doi.org/10.1093/jac/dks465>.
171. Ho PL, Chan J, Lo WU, Law PY, Li Z, Lai EL, Chow KH. 2013. Dissemination of plasmid-mediated fosfomycin resistance *fosA3* among multidrug-resistant *Escherichia coli* from livestock and other animals. *J Appl Microbiol* 114:695–702 <http://dx.doi.org/10.1111/jam.12099>.
172. Tseng SP, Wang SF, Kuo CY, Huang JW, Hung WC, Ke GM, Lu PL. 2015. Characterization of fosfomycin resistant extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli* isolates from human and pig in Taiwan. *PLoS One* 10:e0135864 <http://dx.doi.org/10.1371/journal.pone.0135864>.
173. Grave K, Torren-Edo J, Muller A, Greko C, Moulin G, Mackay D, Group E, ESVAC Group. 2014. Variations in the sales and sales patterns of veterinary antimicrobial agents in 25 European countries. *J Antimicrob Chemother* 69:2284–2291 <http://dx.doi.org/10.1093/jac/dku106>.
174. Shin SW, Shin MK, Jung M, Belaynehe KM, Yoo HS. 2015. Prevalence of antimicrobial resistance and transfer of tetracycline resistance genes in *Escherichia coli* isolates from beef cattle. *Appl Environ Microbiol* 81:5560–5566 <http://dx.doi.org/10.1128/AEM.01511-15>.
175. Metzger SA, Hogan JS. 2013. Short communication: antimicrobial susceptibility and frequency of resistance genes in *Escherichia coli* isolated from bovine mastitis. *J Dairy Sci* 96:3044–3049 <http://dx.doi.org/10.3168/jds.2012-6402>.
176. Srinivasan V, Gillespie BE, Lewis MJ, Nguyen LT, Headrick SI, Schukken YH, Oliver SP. 2007. Phenotypic and genotypic antimicrobial resistance patterns of *Escherichia coli* isolated from dairy cows with mastitis. *Vet Microbiol* 124:319–328 <http://dx.doi.org/10.1016/j.vetmic.2007.04.040>.
177. Lanz R, Kuhnert P, Boerlin P. 2003. Antimicrobial resistance and resistance gene determinants in clinical *Escherichia coli* from different animal species in Switzerland. *Vet Microbiol* 91:73–84 [http://dx.doi.org/10.1016/S0378-1135\(02\)00263-8](http://dx.doi.org/10.1016/S0378-1135(02)00263-8).
178. Jurado-Rabadán S, de la Fuente R, Ruiz-Santa-Quiteria JA, Orden JA, de Vries LE, Agersø Y. 2014. Detection and linkage to mobile genetic elements of tetracycline resistance gene *tet(M)* in *Escherichia coli* isolates from pigs. *BMC Vet Res* 10:155–162 <http://dx.doi.org/10.1186/1746-6148-10-155>.
179. Hölzel CS, Harms KS, Bauer J, Bauer-Unkauf I, Hörmansdorfer S, Kämpf P, Mölle G, Oehme C, Preikschat P, Schwaiger K. 2012. Diversity of antimicrobial resistance genes and class-1-integrations in phylogenetically related porcine and human *Escherichia coli*. *Vet Microbiol* 160:403–412 <http://dx.doi.org/10.1016/j.vetmic.2012.06.010>.
180. Seifi S, Khoshbakht R. 2016. Prevalence of tetracycline resistance determinants in broiler isolated *Escherichia coli* in Iran. *Br Poult Sci* 57:729–733 <http://dx.doi.org/10.1080/00071668.2016.1232478>.
181. Costa D, Poeta P, Sáenz Y, Coelho AC, Matos M, Vinué L, Rodrigues J, Torres C. 2008. Prevalence of antimicrobial resistance and resistance genes in faecal *Escherichia coli* isolates recovered from healthy pets. *Vet Microbiol* 127:97–105 <http://dx.doi.org/10.1016/j.vetmic.2007.08.004>.
182. Bryan A, Shapir N, Sadowsky MJ. 2004. Frequency and distribution of tetracycline resistance genes in genetically diverse, nonselected, and nonclinical *Escherichia coli* strains isolated from diverse human and animal sources. *Appl Environ Microbiol* 70:2503–2507 <http://dx.doi.org/10.1128/AEM.70.4.2503-2507.2004>.
183. Allmeier H, Cresnar B, Greck M, Schmitt R. 1992. Complete nucleotide sequence of Tn1721: gene organization and a novel gene product with features of a chemotaxis protein. *Gene* 111:11–20 [http://dx.doi.org/10.1016/0378-1119\(92\)90597-1](http://dx.doi.org/10.1016/0378-1119(92)90597-1).
184. Chalmers R, Sewitz S, Lipkow K, Crellin P. 2000. Complete nucleotide sequence of Tn10. *J Bacteriol* 182:2970–2972 <http://dx.doi.org/10.1128/JB.182.10.2970-2972.2000>.
185. Siqueira AK, Michael GB, Domingos DF, Ferraz MM, Ribeiro MG, Schwarz S, Leite DS. 2016. Diversity of class 1 and 2 integrons detected in *Escherichia coli* isolates from diseased and apparently healthy dogs. *Vet Microbiol* 194:79–83 <http://dx.doi.org/10.1016/j.vetmic.2016.05.005>.
186. Huang SY, Zhu XQ, Wang Y, Liu HB, Dai L, He JK, Li BB, Wu CM, Shen JZ. 2012. Co-carriage of *qnrS1*, *floR*, and *bla*<sub>(CTX-M-14)</sub> on a multidrug-resistant plasmid in *Escherichia coli* isolated from pigs. *Foodborne Pathog Dis* 9:896–901 <http://dx.doi.org/10.1089/fpd.2012.1131>.
187. Schwarz S, Kehrenberg C, Doublet B, Cloeckaert A. 2004. Molecular basis of bacterial resistance to chloramphenicol and florfenicol. *FEMS Microbiol Rev* 28:519–542 <http://dx.doi.org/10.1016/j.femsre.2004.04.001>.
188. Wang XM, Liao XP, Liu SG, Zhang WJ, Jiang HX, Zhang MJ, Zhu HQ, Sun Y, Sun J, Li AX, Liu YH. 2011. Serotypes, virulence genes, and antimicrobial susceptibility of *Escherichia coli* isolates from pigs. *Foodborne Pathog Dis* 8:687–692 <http://dx.doi.org/10.1089/fpd.2010.0739>.
189. Travis RM, Gyles CL, Reid-Smith R, Poppe C, McEwen SA, Friendship R, Janecko N, Boerlin P. 2006. Chloramphenicol and kanamycin resistance among porcine *Escherichia coli* in Ontario. *J Antimicrob Chemother* 58:173–177 <http://dx.doi.org/10.1093/jac/dkl207>.
190. White DG, Hudson C, Maurer JJ, Ayers S, Zhao S, Lee MD, Bolton L, Foley T, Sherwood J. 2000. Characterization of chloramphenicol and florfenicol resistance in *Escherichia coli* associated with bovine diarrhea. *J Clin Microbiol* 38:4593–4598.
191. Guerra B, Junker E, Schroeter A, Malorny B, Lehmann S, Helmuth R. 2003. Phenotypic and genotypic characterization of antimicrobial resistance in German *Escherichia coli* isolates from cattle, swine and poultry. *J Antimicrob Chemother* 52:489–492 <http://dx.doi.org/10.1093/jac/dkg362>.
192. Awad A, Arafat N, Elhadidy M. 2016. Genetic elements associated with antimicrobial resistance among avian pathogenic *Escherichia coli*. *Ann Clin Microbiol Antimicrob* 15:59–67 <http://dx.doi.org/10.1186/s12941-016-0174-9>.
193. Ahmed MO, Clegg PD, Williams NJ, Baptiste KE, Bennett M. 2010. Antimicrobial resistance in equine faecal *Escherichia coli* isolates from North West England. *Ann Clin Microbiol Antimicrob* 9:12–19 <http://dx.doi.org/10.1186/1476-0711-9-12>.
194. Shaheen BW, Oyarzabal OA, Boothe DM. 2010. The role of class 1 and 2 integrons in mediating antimicrobial resistance among canine and feline clinical *E. coli* isolates from the US. *Vet Microbiol* 144:363–370 <http://dx.doi.org/10.1016/j.vetmic.2010.01.018>.
195. Derakhshandeh A, Eraghi V, Borojeni AM, Niaki MA, Zare S, Naziri Z. 2018. Virulence factors, antibiotic resistance genes and genetic relatedness of commensal *Escherichia coli* isolates from dogs and their owners. *Microb Pathog* 116:241–245 <http://dx.doi.org/10.1016/j.micpath.2018.01.041>.
196. Chang SK, Lo DY, Wei HW, Kuo HC. 2015. Antimicrobial resistance of *Escherichia coli* isolates from canine urinary tract infections. *J Vet Med Sci* 77:59–65 <http://dx.doi.org/10.1292/jvms.13-0281>.
197. Van TT, Chin J, Chapman T, Tran LT, Coloe PJ. 2008. Safety of raw meat and shellfish in Vietnam: an analysis of *Escherichia coli* isolations for antibiotic resistance and virulence genes. *Int J Food Microbiol* 124:217–223 <http://dx.doi.org/10.1016/j.ijfoodmicro.2008.03.029>.



198. Keyes K, Hudson C, Maurer JJ, Thayer S, White DG, Lee MD. 2000. Detection of florfenicol resistance genes in *Escherichia coli* isolated from sick chickens. *Antimicrob Agents Chemother* 44:421–424 <http://dx.doi.org/10.1128/AAC.44.2.421-424.2000>.
199. Bischoff KM, White DG, Hume ME, Poole TL, Nisbet DJ. 2005. The chloramphenicol resistance gene *cmlA* is disseminated on transferable plasmids that confer multiple-drug resistance in swine *Escherichia coli*. *FEMS Microbiol Lett* 243:285–291 <http://dx.doi.org/10.1016/j.femsle.2004.12.017>.
200. Blickwede M, Schwarz S. 2004. Molecular analysis of florfenicol-resistant *Escherichia coli* isolates from pigs. *J Antimicrob Chemother* 53:58–64 <http://dx.doi.org/10.1093/jac/dkh007>.
201. Cloeckaert A, Baucheron S, Flaujac G, Schwarz S, Kehrenberg C, Martel JL, Chaslus-Dancla E. 2000. Plasmid-mediated florfenicol resistance encoded by the *floR* gene in *Escherichia coli* isolated from cattle. *Antimicrob Agents Chemother* 44:2858–2860 <http://dx.doi.org/10.1128/AAC.44.10.2858-2860.2000>.
202. Shen J, Wang Y, Schwarz S. 2013. Presence and dissemination of the multiresistance gene *cfr* in Gram-positive and Gram-negative bacteria. *J Antimicrob Chemother* 68:1697–1706 <http://dx.doi.org/10.1093/jac/dkt092>.
203. Wang Y, He T, Schwarz S, Zhou D, Shen Z, Wu C, Wang Y, Ma L, Zhang Q, Shen J. 2012. Detection of the staphylococcal multiresistance gene *cfr* in *Escherichia coli* of domestic-animal origin. *J Antimicrob Chemother* 67:1094–1098 <http://dx.doi.org/10.1093/jac/dks020>.
204. Deng H, Sun J, Ma J, Li L, Fang LX, Zhang Q, Liu YH, Liao XP. 2014. Identification of the multi-resistance gene *cfr* in *Escherichia coli* isolates of animal origin. *PLoS One* 9:e102378 <http://dx.doi.org/10.1371/journal.pone.0102378>.
205. Sun J, Deng H, Li L, Chen MY, Fang LX, Yang QE, Liu YH, Liao XP. 2015. Complete nucleotide sequence of *cfr*-carrying IncX4 plasmid pSD11 from *Escherichia coli*. *Antimicrob Agents Chemother* 59:738–741 <http://dx.doi.org/10.1128/AAC.04388-14>.
206. Zhang WJ, Wang XM, Dai L, Hua X, Dong Z, Schwarz S, Liu S. 2015. Novel conjugative plasmid from *Escherichia coli* of swine origin that coharbors the multiresistance gene *cfr* and the extended-spectrum- $\beta$ -lactamase gene *bla<sub>CTX-M-14b</sub>*. *Antimicrob Agents Chemother* 59:1337–1340 <http://dx.doi.org/10.1128/AAC.04631-14>.
207. Zhang R, Sun B, Wang Y, Lei L, Schwarz S, Wu C. 2015. Characterization of a *cfr*-carrying plasmid from porcine *Escherichia coli* that closely resembles plasmid pEA3 from the plant pathogen *Erwinia amylovora*. *Antimicrob Agents Chemother* 60:658–661 <http://dx.doi.org/10.1128/AAC.02114-15>.
208. van Duijkeren E, Schink AK, Roberts MC, Wang Y, Schwarz S. 2018. Mechanisms of bacterial resistance to antimicrobial agents. *Microbiol Spectr* 6: <http://dx.doi.org/10.1128/microbiolspec.ARBA-0019-2017>.
209. Recchia GD, Hall RM. 1995. Gene cassettes: a new class of mobile element. *Microbiology* 141:3015–3027 <http://dx.doi.org/10.1099/13500872-141-12-3015>.
210. Kadlec K, Schwarz S. 2008. Analysis and distribution of class 1 and class 2 integrons and associated gene cassettes among *Escherichia coli* isolates from swine, horses, cats and dogs collected in the BfT-GermVet monitoring study. *J Antimicrob Chemother* 62:469–473 <http://dx.doi.org/10.1093/jac/dkn233>.
211. Bass L, Liebert CA, Lee MD, Summers AO, White DG, Thayer SG, Maurer JJ. 1999. Incidence and characterization of integrons, genetic elements mediating multiple-drug resistance, in avian *Escherichia coli*. *Antimicrob Agents Chemother* 43:2925–2929.
212. Waturangi DE, Suwanto A, Schwarz S, Erdelen W. 2003. Identification of class 1 integrons-associated gene cassettes in *Escherichia coli* isolated from *Varanus* spp. in Indonesia. *J Antimicrob Chemother* 51:175–177 <http://dx.doi.org/10.1093/jac/dkf253>.
213. Zhao S, White DG, Ge B, Ayers S, Friedman S, English L, Wagner D, Gaines S, Meng J. 2001. Identification and characterization of integron-mediated antibiotic resistance among Shiga toxin-producing *Escherichia coli* isolates. *Appl Environ Microbiol* 67:1558–1564 <http://dx.doi.org/10.1128/AEM.67.4.1558-1564.2001>.
214. Sunde M. 2005. Class I integron with a group II intron detected in an *Escherichia coli* strain from a free-range reindeer. *Antimicrob Agents Chemother* 49:2512–2514 <http://dx.doi.org/10.1128/AAC.49.6.2512-2514.2005>.
215. Du X, Shen Z, Wu B, Xia S, Shen J. 2005. Characterization of class 1 integrons-mediated antibiotic resistance among calf pathogenic *Escherichia coli*. *FEMS Microbiol Lett* 245:295–298 <http://dx.doi.org/10.1016/j.femsle.2005.03.021>.
216. Wu S, Dalsgaard A, Hammerum AM, Porsbo LJ, Jensen LB. 2010. Prevalence and characterization of plasmids carrying sulfonamide resistance genes among *Escherichia coli* from pigs, pig carcasses and human. *Acta Vet Scand* 52:47 <http://dx.doi.org/10.1186/1751-0147-52-47>.
217. Sidjabat HE, Townsend KM, Hanson ND, Bell JM, Stokes HW, Gobius KS, Moss SM, Trott DJ. 2006. Identification of *bla<sub>(CMY-7)</sub>* and associated plasmid-mediated resistance genes in multidrug-resistant *Escherichia coli* isolated from dogs at a veterinary teaching hospital in Australia. *J Antimicrob Chemother* 57:840–848 <http://dx.doi.org/10.1093/jac/dkl057>.
218. van Essen-Zandbergen A, Smith H, Veldman K, Mevius D. 2009. *In vivo* transfer of an incFIB plasmid harbouring a class 1 integron with gene cassettes *dfrA1-aadA1*. *Vet Microbiol* 137:402–407 <http://dx.doi.org/10.1016/j.vetmic.2009.02.004>.
219. Boerlin P, Travis R, Gyles CL, Reid-Smith R, Janecko N, Lim H, Nicholson V, McEwen SA, Friendship R, Archambault M. 2005. Antimicrobial resistance and virulence genes of *Escherichia coli* isolates from swine in Ontario. *Appl Environ Microbiol* 71:6753–6761 <http://dx.doi.org/10.1128/AEM.71.11.6753-6761.2005>.
220. Kikvi GM, Schwarz S, Ombui JN, Mitema ES, Kehrenberg C. 2007. Streptomycin and chloramphenicol resistance genes in *Escherichia coli* isolates from cattle, pigs, and chicken in Kenya. *Microb Drug Resist* 13:62–68 <http://dx.doi.org/10.1089/mdr.2006.9998>.
221. Ojo OE, Schwarz S, Michael GB. 2016. Detection and characterization of extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli* from chicken production chains in Nigeria. *Vet Microbiol* 194:62–68 <http://dx.doi.org/10.1016/j.vetmic.2016.04.022>.
222. Schwaiger K, Bauer J, Hölzel CS. 2013. Selection and persistence of antimicrobial-resistant *Escherichia coli* including extended-spectrum  $\beta$ -lactamase producers in different poultry flocks on one chicken farm. *Microb Drug Resist* 19:498–506 <http://dx.doi.org/10.1089/mdr.2012.0257>.
223. Touzain F, Le Devendec L, de Boissésion C, Baron S, Jouy E, Perrin-Guyomard A, Blanchard Y, Kempf I. 2018. Characterization of plasmids harboring *bla<sub>CTX-M</sub>* and *bla<sub>CMY</sub>* genes in *E. coli* from French broilers. *PLoS One* 13:e0188768 <http://dx.doi.org/10.1371/journal.pone.0188768>.
224. Perreten V, Boerlin P. 2003. A new sulfonamide resistance gene (*sul3*) in *Escherichia coli* is widespread in the pig population of Switzerland. *Antimicrob Agents Chemother* 47:1169–1172 <http://dx.doi.org/10.1128/AAC.47.3.1169-1172.2003>.
225. Liu J, Keelan P, Bennett PM, Enne VI. 2009. Characterization of a novel macrolide efflux gene, *mef(B)*, found linked to *sul3* in porcine *Escherichia coli*. *J Antimicrob Chemother* 63:423–426 <http://dx.doi.org/10.1093/jac/dkn523>.
226. Sunde M, Solheim H, Sletteemåns JS. 2008. Genetic linkage between class 1 integrons with the *dfrA12-orfF-aadA2* cassette array and *sul3* in *Escherichia coli*. *Vet Microbiol* 130:422–425 <http://dx.doi.org/10.1016/j.vetmic.2008.02.001>.
227. Pattishall KH, Acar J, Burchall JJ, Goldstein FW, Harvey RJ. 1977. Two distinct types of trimethoprim-resistant dihydrofolate reductase specified by R-plasmids of different compatibility groups. *J Biol Chem* 252:2319–2323.
228. Reid CJ, Wyrsh ER, Roy Chowdhury P, Zingali T, Liu M, Darling AE, Chapman TA, Djordjevic SP. 2017. Porcine commensal *Escherichia*

- coli*: a reservoir for class 1 integrons associated with IS26. *Microb Genom* 3:3 <http://dx.doi.org/10.1099/mgen.0.000143>.
229. Seputienė V, Povilonis J, Ruzauskas M, Pavilonis A, Suziedėlienė E. 2010. Prevalence of trimethoprim resistance genes in *Escherichia coli* isolates of human and animal origin in Lithuania. *J Med Microbiol* 59: 315–322 <http://dx.doi.org/10.1099/jmm.0.015008-0>.
230. Delport TC, Harcourt RG, Beaumont LJ, Webster KN, Power ML. 2015. Molecular detection of antibiotic-resistance determinants in *Escherichia coli* isolated from the endangered Australian sea lion (*Neophoca cinerea*). *J Wildl Dis* 51:555–563 <http://dx.doi.org/10.7589/2014-08-200>.
231. Ojo KK, Kehrenberg C, Schwarz S, Odelola HA. 2002. Identification of a complete *dfrA14* gene cassette integrated at a secondary site in a resistance plasmid of uropathogenic *Escherichia coli* from Nigeria. *Antimicrob Agents Chemother* 46:2054–2055 <http://dx.doi.org/10.1128/AAC.46.6.2054-2055.2002>.
232. Poirel L, Jayol A, Nordmann P. 2017. Polymyxins: antibacterial activity, susceptibility testing, and resistance mechanisms encoded by plasmids or chromosomes. *Clin Microbiol Rev* 30:557–596 <http://dx.doi.org/10.1128/CMR.00064-16>.
233. Rhouma M, Beaudry F, Thériault W, Letellier A. 2016. Colistin in pig production: chemistry, mechanism of antibacterial action, microbial resistance emergence, and One Health perspectives. *Front Microbiol* 7:1789 <http://dx.doi.org/10.3389/fmicb.2016.01789>.
234. Anonymous. 2016. European Medicines Agency. Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health. EMA/CVMP/CHMP/231573.1-56.
235. Walsh TR, Wu Y. 2016. China bans colistin as a feed additive for animals. *Lancet Infect Dis* 16:1102–1103 [http://dx.doi.org/10.1016/S1473-3099\(16\)30329-2](http://dx.doi.org/10.1016/S1473-3099(16)30329-2).
236. Quesada A, Porrero MC, Téllez S, Palomo G, García M, Domínguez L. 2015. Polymorphism of genes encoding PmrAB in colistin-resistant strains of *Escherichia coli* and *Salmonella enterica* isolated from poultry and swine. *J Antimicrob Chemother* 70:71–74 <http://dx.doi.org/10.1093/jac/dku320>.
237. Delannoy S, Le Devendec L, Jouy E, Fach P, Drider D, Kempf I. 2017. Characterization of colistin-resistant *Escherichia coli* isolated from diseased pigs in France. *Front Microbiol* 8:2278 <http://dx.doi.org/10.3389/fmicb.2017.02278>.
238. Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, Doi Y, Tian G, Dong B, Huang X, Yu LF, Gu D, Ren H, Chen X, Lv L, He D, Zhou H, Liang Z, Liu JH, Shen J. 2016. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *Lancet Infect Dis* 16:161–168 [http://dx.doi.org/10.1016/S1473-3099\(15\)00424-7](http://dx.doi.org/10.1016/S1473-3099(15)00424-7).
239. Schwarz S, Johnson AP. 2016. Transferable resistance to colistin: a new but old threat. *J Antimicrob Chemother* 71:2066–2070 <http://dx.doi.org/10.1093/jac/dkw274>.
240. Falgenhauer L, Waezsada SE, Yao Y, Imirzalioglu C, Käsbohrer A, Roesler U, Michael GB, Schwarz S, Werner G, Kreienbrock L, Chakraborty T, RESET consortium. 2016. Colistin resistance gene *mcr-1* in extended-spectrum  $\beta$ -lactamase-producing and carbapenemase-producing Gram-negative bacteria in Germany. *Lancet Infect Dis* 16:282–283 [http://dx.doi.org/10.1016/S1473-3099\(16\)00009-8](http://dx.doi.org/10.1016/S1473-3099(16)00009-8).
241. Haenni M, Poirel L, Kieffer N, Châtre P, Saras E, Métayer V, Dumoulin R, Nordmann P, Madec JY. 2016. Co-occurrence of extended spectrum  $\beta$  lactamase and MCR-1 encoding genes on plasmids. *Lancet Infect Dis* 16:281–282 [http://dx.doi.org/10.1016/S1473-3099\(16\)00007-4](http://dx.doi.org/10.1016/S1473-3099(16)00007-4).
242. Li R, Xie M, Zhang J, Yang Z, Liu L, Liu X, Zheng Z, Chan EW, Chen S. 2017. Genetic characterization of *mcr-1*-bearing plasmids to depict molecular mechanisms underlying dissemination of the colistin resistance determinant. *J Antimicrob Chemother* 72:393–401 <http://dx.doi.org/10.1093/jac/dkw411>.
243. Zurfluh K, Klumpp J, Nüesch-Inderbilen M, Stephan R. 2016. Full-length nucleotide sequences of *mcr-1*-harboring plasmids isolated from extended-spectrum- $\beta$ -lactamase-producing *Escherichia coli* isolates of different origins. *Antimicrob Agents Chemother* 60:5589–5591 <http://dx.doi.org/10.1128/AAC.00935-16>.
244. Zurfluh K, Poirel L, Nordmann P, Nüesch-Inderbilen M, Hächler H, Stephan R. 2016. Occurrence of the plasmid-borne *mcr-1* colistin resistance gene in extended-spectrum- $\beta$ -lactamase-producing *Enterobacteriaceae* in river water and imported vegetable samples in Switzerland. *Antimicrob Agents Chemother* 60:2594–2595 <http://dx.doi.org/10.1128/AAC.00066-16>.
245. Poirel L, Kieffer N, Nordmann P. 2017. *In vitro* study of IS*ApI1*-mediated mobilization of the colistin resistance gene *mcr-1*. *Antimicrob Agents Chemother* 61:61 <http://dx.doi.org/10.1128/AAC.00127-17>.
246. Yang YQ, Li YX, Song T, Yang YX, Jiang W, Zhang AY, Guo XY, Liu BH, Wang YX, Lei CW, Xiang R, Wang HN. 2017. Colistin resistance gene *mcr-1* and its variant in *Escherichia coli* isolates from chickens in China. *Antimicrob Agents Chemother* 61:e01204-16.
247. Xavier BB, Lammens C, Ruhel R, Kumar-Singh S, Butaye P, Goossens H, Malhotra-Kumar S. 2016. Identification of a novel plasmid-mediated colistin-resistance gene, *mcr-2*, in *Escherichia coli*, Belgium, June 2016. *Euro Surveill* 21:30280.
248. Zhang J, Chen L, Wang J, Yassin AK, Butaye P, Kelly P, Gong J, Guo W, Li J, Li M, Yang F, Feng Z, Jiang P, Song C, Wang Y, You J, Yang Y, Price S, Qi K, Kang Y, Wang C. 2018. Molecular detection of colistin resistance genes (*mcr-1*, *mcr-2* and *mcr-3*) in nasal/oropharyngeal and anal/coloanal swabs from pigs and poultry. *Sci Rep* 8:3705 <http://dx.doi.org/10.1038/s41598-018-22084-4>.
249. Yin W, Li H, Shen Y, Liu Z, Wang S, Shen Z, Zhang R, Walsh TR, Shen J, Wang Y. 2017. Novel plasmid-mediated colistin resistance gene *mcr-3* in *Escherichia coli*. *MBio* 8:e00543-17 <http://dx.doi.org/10.1128/mBio.00543-17>.
250. Hernández M, Iglesias MR, Rodríguez-Lázaro D, Gallardo A, Quijada N, Miguela-Villoldo P, Campos MJ, Píriz S, López-Orozco G, de Frutos C, Sáez JL, Ugarte-Ruiz M, Domínguez L, Quesada A. 2017. Co-occurrence of colistin-resistance genes *mcr-1* and *mcr-3* among multidrug-resistant *Escherichia coli* isolated from cattle, Spain, September 2015. *Euro Surveill* 22:30586 <http://dx.doi.org/10.2807/1560-7917.ES.2017.22.31.30586>.
251. Haenni M, Beyrouthy R, Lupo A, Châtre P, Madec JY, Bonnet R. 2018. Epidemic spread of *Escherichia coli* ST744 isolates carrying *mcr-3* and *bla*<sub>CTX-M-55</sub> in cattle in France. *J Antimicrob Chemother* 73:533–536 <http://dx.doi.org/10.1093/jac/dkx418>.
252. Carattoli A, Villa L, Feudi C, Curcio L, Orsini S, Luppi A, Pezzotti G, Magistrali CF. 2017. Novel plasmid-mediated colistin resistance *mcr-4* gene in *Salmonella* and *Escherichia coli*, Italy 2013, Spain and Belgium, 2015 to 2016. *Euro Surveill* 22:30589 <http://dx.doi.org/10.2807/1560-7917.ES.2017.22.31.30589>.
253. Hammerl JA, Borowiak M, Schmogger S, Shamoun D, Grobbel M, Malorny B, Tenhagen BA, Käsbohrer A. 2018. *mcr-5* and a novel *mcr-5.2* variant in *Escherichia coli* isolates from food and food-producing animals, Germany, 2010 to 2017. *J Antimicrob Chemother* 73:1433–1435 <http://dx.doi.org/10.1093/jac/dky020>.
254. Haenni M, Métayer V, Gay E, Madec JY. 2016. Increasing trends in *mcr-1* prevalence among extended-spectrum- $\beta$ -lactamase-producing *Escherichia coli* isolates from French calves despite decreasing exposure to colistin. *Antimicrob Agents Chemother* 60:6433–6434 <http://dx.doi.org/10.1128/AAC.01147-16>.
255. Shen Z, Wang Y, Shen Y, Wu C. 2016. Early emergence of *mcr-1* in *Escherichia coli* from food-producing animals. *Lancet Infect Dis* 16:293 [http://dx.doi.org/10.1016/S1473-3099\(16\)00061-X](http://dx.doi.org/10.1016/S1473-3099(16)00061-X).
256. Guenther S, Falgenhauer L, Semmler T, Imirzalioglu C, Chakraborty T, Roesler U, Roschanski N. 2017. Environmental emission of multi-resistant *Escherichia coli* carrying the colistin resistance gene *mcr-1* from

- German swine farms. *J Antimicrob Chemother* 72:1289–1292 <http://dx.doi.org/10.1093/jac/dkw585>.
257. Hammerum AM, Larsen J, Andersen VD, Lester CH, Skovgaard Skytte TS, Hansen F, Olsen SS, Mordhorst H, Skov RL, Aarestrup FM, Agersø Y. 2014. Characterization of extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Escherichia coli* obtained from Danish pigs, pig farmers and their families from farms with high or no consumption of third- or fourth-generation cephalosporins. *J Antimicrob Chemother* 69:2650–2657 <http://dx.doi.org/10.1093/jac/dku180>.
258. Börjesson S, Bengtsson B, Jernberg C, Englund S. 2013. Spread of extended-spectrum  $\beta$ -lactamase producing *Escherichia coli* isolates in Swedish broilers mediated by an *incl* plasmid carrying *bla*(CTX-M-1). *Acta Vet Scand* 55:3 <http://dx.doi.org/10.1186/1751-0147-55-3>.
259. Randall LP, Clouting C, Horton RA, Coldham NG, Wu G, Clifton-Hadley FA, Davies RH, Teale CJ. 2011. Prevalence of *Escherichia coli* carrying extended-spectrum  $\beta$ -lactamases (CTX-M and TEM-52) from broiler chickens and turkeys in Great Britain between 2006 and 2009. *J Antimicrob Chemother* 66:86–95 <http://dx.doi.org/10.1093/jac/dkq396>.
260. Endimiani A, Rossano A, Kunz D, Overesch G, Perreten V. 2012. First countrywide survey of third-generation cephalosporin-resistant *Escherichia coli* from broilers, swine, and cattle in Switzerland. *Diagn Microbiol Infect Dis* 73:31–38 <http://dx.doi.org/10.1016/j.diagmicrobio.2012.01.004>.
261. Liu X, Thungrat K, Boothe DM. 2016. Occurrence of OXA-48 carbapenemase and other  $\beta$ -lactamase genes in ESBL-producing multidrug resistant *Escherichia coli* from dogs and cats in the United States, 2009–2013. *Front Microbiol* 7:1057 <http://dx.doi.org/10.3389/fmicb.2016.01057>.
262. Liao XP, Xia J, Yang L, Li L, Sun J, Liu YH, Jiang HX. 2015. Characterization of CTX-M-14-producing *Escherichia coli* from food-producing animals. *Front Microbiol* 6:1136 <http://dx.doi.org/10.3389/fmicb.2015.01136>.
263. Falgenhauer L, Imirzalioglu C, Ghosh H, Gwozdinski K, Schmiedel J, Gentil K, Bauerfeind R, Kämpfer B, Seifert H, Michael GB, Schwarz S, Pfeifer Y, Werner G, Pietsch M, Roesler U, Guerra B, Fischer J, Sharp H, Käsböhrer A, Goesmann A, Hille K, Kreienbrock L, Chakraborty T. 2016. Circulation of clonal populations of fluoroquinolone-resistant CTX-M-15-producing *Escherichia coli* ST410 in humans and animals in Germany. *Int J Antimicrob Agents* 47:457–465 <http://dx.doi.org/10.1016/j.ijantimicag.2016.03.019>.
264. Ewers C, Grobbel M, Stamm I, Kopp PA, Diehl I, Semmler T, Fruth A, Beutlich J, Guerra B, Wieler LH, Guenther S. 2010. Emergence of human pandemic O25:H4-ST131 CTX-M-15 extended-spectrum- $\beta$ -lactamase-producing *Escherichia coli* among companion animals. *J Antimicrob Chemother* 65:651–660 <http://dx.doi.org/10.1093/jac/dkq004>.
265. Schill F, Abdulmawjoed A, Klein G, Reich F. 2017. Prevalence and characterization of extended-spectrum  $\beta$ -lactamase (ESBL) and AmpC  $\beta$ -lactamase producing *Enterobacteriaceae* in fresh pork meat at processing level in Germany. *Int J Food Microbiol* 257:58–66 <http://dx.doi.org/10.1016/j.ijfoodmicro.2017.06.010>.
266. Alcalá L, Alonso CA, Simón C, González-Esteban C, Orós J, Rezusta A, Ortega C, Torres C. 2016. Wild birds, frequent carriers of extended-spectrum  $\beta$ -lactamase (ESBL) producing *Escherichia coli* of CTX-M and SHV-12 types. *Microb Ecol* 72:861–869 <http://dx.doi.org/10.1007/s00248-015-0718-0>.
267. Jones-Dias D, Manageiro V, Martins AP, Ferreira E, Caniça M. 2016. New class 2 integron *In2-4* among *InclI*-positive *Escherichia coli* isolates carrying ESBL and PMA $\beta$  genes from food animals in Portugal. *Foodborne Pathog Dis* 13:36–39 <http://dx.doi.org/10.1089/fpd.2015.1972>.
268. Vogt D, Overesch G, Endimiani A, Collaud A, Thomann A, Perreten V. 2014. Occurrence and genetic characteristics of third-generation cephalosporin-resistant *Escherichia coli* in Swiss retail meat. *Microb Drug Resist* 20:485–494 <http://dx.doi.org/10.1089/mdr.2013.0210>.
269. Park YS, Adams-Haduch JM, Rivera JI, Curry SR, Harrison LH, Doi Y. 2012. *Escherichia coli* producing CMY-2  $\beta$ -lactamase in retail chicken, Pittsburgh, Pennsylvania, USA. *Emerg Infect Dis* 18:515–516 <http://dx.doi.org/10.3201/eid1803.111434>.
270. Cunha MP, Lincopan N, Cerdeira L, Esposito F, Dropa M, Franco LS, Moreno AM, Knobl T. 2017. Coexistence of CTX-M-2, CTX-M-55, CMY-2, FosA3, and QnrB19 in extraintestinal pathogenic *Escherichia coli* from poultry in Brazil. *Antimicrob Agents Chemother* 61:e02474-16 <http://dx.doi.org/10.1128/AAC.02474-16>.
271. Guo YF, Zhang WH, Ren SQ, Yang L, Lü DH, Zeng ZL, Liu YH, Jiang HX. 2014. *IncA/C* plasmid-mediated spread of CMY-2 in multi-drug-resistant *Escherichia coli* from food animals in China. *PLoS One* 9:e96738 <http://dx.doi.org/10.1371/journal.pone.0096738>.
272. Ohnishi M, Okatani AT, Esaki H, Harada K, Sawada T, Murakami M, Marumo K, Kato Y, Sato R, Shimura K, Hatanaka N, Takahashi T. 2013. Herd prevalence of *Enterobacteriaceae* producing CTX-M-type and CMY-2  $\beta$ -lactamases among Japanese dairy farms. *J Appl Microbiol* 115:282–289 <http://dx.doi.org/10.1111/jam.12211>.
273. Sato T, Yokota S, Okubo T, Usui M, Fujii N, Tamura Y. 2014. Phylogenetic association of fluoroquinolone and cephalosporin resistance of D-O1-ST648 *Escherichia coli* carrying *bla*<sub>CMY-2</sub> from faecal samples of dogs in Japan. *J Med Microbiol* 63:263–270 <http://dx.doi.org/10.1099/jmm.0.054676-0>.
274. Maamar E, Hammami S, Alonso CA, Dakhli N, Abbassi MS, Ferjani S, Hamzaoui Z, Saidani M, Torres C, Boutiba-Ben Boubaker I. 2016. High prevalence of extended-spectrum and plasmidic AmpC  $\beta$ -lactamase-producing *Escherichia coli* from poultry in Tunisia. *Int J Food Microbiol* 231:69–75 <http://dx.doi.org/10.1016/j.ijfoodmicro.2016.05.001>.
275. Cui L, Lei L, Lv Y, Zhang R, Liu X, Li M, Zhang F, Wang Y. 2017. *bla*<sub>NDM-1</sub>-producing multidrug-resistant *Escherichia coli* isolated from a companion dog in China. *J Glob Antimicrob Resist* 13:24–27 <http://dx.doi.org/10.1016/j.jgar.2017.10.021>.
276. Lin D, Xie M, Li R, Chen K, Chan EW, Chen S. 2016. *IncFII* conjugative plasmid-mediated transmission of *bla*<sub>NDM-1</sub> elements among animal-borne *Escherichia coli* strains. *Antimicrob Agents Chemother* 61:e02285-16 <http://dx.doi.org/10.1128/AAC.02285-16>.
277. Kong LH, Lei CW, Ma SZ, Jiang W, Liu BH, Wang YX, Guan R, Men S, Yuan QW, Cheng GY, Zhou WC, Wang HN. 2017. Various sequence types of *Escherichia coli* isolates cohabiting *bla*<sub>NDM-5</sub> and *mcr-1* genes from a commercial swine farm in China. *Antimicrob Agents Chemother* 61:e02167-16 <http://dx.doi.org/10.1128/AAC.02167-16>.
278. Purkait D, Ahuja A, Bhattacharjee U, Singha A, Rhetso K, Dey TK, Das S, Sanjukta RK, Puro K, Shakuntala I, Sen A, Banerjee A, Sharma I, Bhatta RS, Mawlong M, Guha C, Pradhan NR, Ghatak S. 2016. Molecular characterization and computational modelling of New Delhi metallo- $\beta$ -lactamase-5 from an *Escherichia coli* isolate (KOE3) of bovine origin. *Indian J Microbiol* 56:182–189 <http://dx.doi.org/10.1007/s12088-016-0569-5>.
279. Yaici L, Haenni M, Saras E, Boudehouche W, Touati A, Madec JY. 2016. *bla*<sub>NDM-5</sub>-carrying *IncX3* plasmid in *Escherichia coli* ST1284 isolated from raw milk collected in a dairy farm in Algeria. *J Antimicrob Chemother* 71:2671–2672 <http://dx.doi.org/10.1093/jac/dkw160>.
280. Roschanski N, Friese A, von Salviati-Claudius C, Hering J, Kaesbohrer A, Kreienbrock L, Roesler U. 2017. Prevalence of carbapenemase producing *Enterobacteriaceae* isolated from German pig-fattening farms during the years 2011–2013. *Vet Microbiol* 200:124–129 <http://dx.doi.org/10.1016/j.vetmic.2015.11.030>.
281. Roschanski N, Guenther S, Vu TTT, Fischer J, Semmler T, Huehn S, Alter T, Roesler U. 2017. VIM-1 carbapenemase-producing *Escherichia coli* isolated from retail seafood, Germany 2016. *Euro Surveill* 22:17-00032 <http://dx.doi.org/10.2807/1560-7917.ES.2017.22.43.17-00032>.
282. Unger F, Eisenberg T, Prenger-Berninghoff E, Leidner U, Ludwig ML, Rothe M, Semmler T, Ewers C. 2017. Imported reptiles as a risk

- factor for the global distribution of *Escherichia coli* harbouring the colistin resistance gene *mcr-1*. *Int J Antimicrob Agents* 49:122–123 <http://dx.doi.org/10.1016/j.ijantimicag.2016.10.007>.
283. Lim SK, Kang HY, Lee K, Moon DC, Lee HS, Jung SC. 2016. First detection of the *mcr-1* gene in *Escherichia coli* isolated from livestock between 2013 and 2015 in South Korea. *Antimicrob Agents Chemother* 60:6991–6993 <http://dx.doi.org/10.1128/AAC.01472-16>.
284. Meinersmann RJ, Ladely SR, Plumlee JR, Cook KL, Thacker E. 2017. Prevalence of *mcr-1* in the cecal contents of food animals in the United States. *Antimicrob Agents Chemother* 61:e02244-16 <http://dx.doi.org/10.1128/AAC.02244-16>.
285. Delgado-Blas JF, Ovejero CM, Abadia-Patiño L, Gonzalez-Zorn B. 2016. Coexistence of *mcr-1* and *bla*<sub>NDM-1</sub> in *Escherichia coli* from Venezuela. *Antimicrob Agents Chemother* 60:6356–6358 <http://dx.doi.org/10.1128/AAC.01319-16>.
286. Sellera FP, Fernandes MR, Sartori L, Carvalho MP, Esposito F, Nascimento CL, Dutra GH, Mamizuka EM, Pérez-Chaparro PJ, McCulloch JA, Lincopan N. 2017. *Escherichia coli* carrying IncX4 plasmid-mediated *mcr-1* and *bla*<sub>CTX-M</sub> genes in infected migratory Magellanic penguins (*Spheniscus magellanicus*). *J Antimicrob Chemother* 72:1255–1256 <http://dx.doi.org/10.1093/jac/dkw543>.
287. Sellera FP, Fernandes MR, Ruiz R, Falleiros ACM, Rodrigues FP, Cerdeira L, Lincopan N. 2018. Identification of KPC-2-producing *Escherichia coli* in a companion animal: a new challenge for veterinary clinicians. *J Antimicrob Chemother* [Epub ahead of print] <http://dx.doi.org/10.1093/jac/dky173>.