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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 β-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 β-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,

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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 β-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 β-LACTAMS

There are numerous genes in *E. coli* of human and animal origin that confer resistance to β-lactams. Some of them, such as $bla_{\text{TEM-1}}$, are widespread in *E. coli* from animals but code only for narrow-spectrum β-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 β-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 β-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

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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 β-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 $bla_{\text{CTX-M-1}}$, $bla_{\text{CTX-M-14}}$, $bla_{\text{TEM-52}}$, and $bla_{\text{SHV-12}}$ were identified as the most common ones along with a wide range of other $bla_{\text{CTX-M}}$, bla_{TEM}, and bla_{SHV} 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
$bla_{\text{CTX-M-1}}$	Denmark	Pig	10, 189, 206, 453, 542, 744, 910, 1406, 1684 2739, 4048, 4052, 4053, 4056,	257
	Sweden	Poultry	57, 135, 155, 219, 602, 752, 1594, 1640	258
	Great Britain	Poultry	4, 10, 57, 88, 155, 371, 1515, 1517, 1518, 1549, 1550	259
	Switzerland	Poultry, cattle, pig	48, 83, 305, 525, 528, 529, 533, 534, 536, 540	260
	The Netherlands	Veal calves	10, 58, 88, 117, 162, 224, 354, 448, 617, 648, 744, 973	21
	France	Dairy cattle	23, 58	13
	Germany	Dairy cattle	10, 117, 540, 1431, 5447	14
	Germany	Swine, cattle, poultry, horse	10, 23, 83, 100, 131, 167, 362, 453, 648, 925, 973, 1684, 2699	43
	Germany	Dog	10, 23, 69, 160, 224	28
	U.S.	Dog, cat	23, 38, 44, 68, 69, 131, 167, 405, 410, 443, 648, 1011, 1088, 5174, 5206, 5220	261
$bla_{\text{CTX-M-14}}$	The Netherlands	Veal calves	10, 57, 952	21
	France	Dairy cattle	10, 23, 45, 58	13
	China	Pig, poultry	10, 155, 206, 224, 359, 405, 602, 648, 2929, 2930, 2962	262
	China	Dog	10, 38, 104, 131, 167, 405, 648, 146, 3630	97
$bla_{\text{CTX-M-15}}$	UK	Poultry	57, 156	259
	UK	Dog	131, 410, 1284, 2348, 4184	99
	The Netherlands	Veal calves	58, 59, 88, 361, 410, 648	21
	Germany	Livestock	10, 88, 90, 167, 410, 617, 648	263
	Germany	Dairy cattle	10, 361, 1508	14
	Germany, Denmark, Spain, France, the Netherlands	Dog, horse	131	264
	Germany, Italy	Dog, cat, cattle, horse	648	96
	Germany	Dog	410, 3018	28
	U.S.	Dog, cat	23, 38, 44, 68, 69, 131, 167, 405, 410, 443, 617, 648, 1011, 1088, 5174, 5206, 5220	261
	Mexico	Dog	410, 617	138
	China	Dog	10, 38, 44, 69, 73, 75, 131, 302, 405, 648, 1700, 2375	97
	Nigeria	Poultry	10, 405	221
$bla_{\text{SHV-12}}$	Spain, Germany	Wild bird, dog, poultry	23, 57, 117, 155, 362, 371, 453, 616, 1564, 2001	39
	China	Dog	10, 75, 131, 167, 405, 648, 2375, 3058	97

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food-producing animals in the GERM-Vet monitoring program from 2008 to 2014 (35). This study detected the gene $bla_{CTX-M-1}$ in 69.9% of the ESBL producers, followed by $bla_{CTX-M-15}$ in 13.6%, $bla_{CTX-M-14}$ in 11.7%, bla_{TEM-52} in 1.9%, and bla_{SHV-12} in 1.4%. The genes $bla_{CTX-M-3}$ and $bla_{CTX-M-2}$ 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 $bla_{CTX-M-1}$ as the most common among bovine ESBL-producing *E. coli* from Germany, while the gene $bla_{CTX-M-15}$ 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 $bla_{CTX-M-1}$ was most common, but the gene $bla_{CTX-M-15}$ was also frequently identified (24, 37). In the United States, the gene $bla_{CTX-M-15}$ was predominant among ESBL-producing *E. coli* from urinary tract infections of companion animals (38). The gene $bla_{CTX-M-14}$ 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_{SHV-12} 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 $bla_{CTX-M-15}$, 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 IS*Ecp1*, IS*CR1*, IS*26*, and IS*10*, transposons such as Tn*2*, 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 $bla_{CTX-M-15}$ and belonging to the IncF family had been detected in the pandemic *E. coli* clone O25:H4-ST131 (47). The ESBL gene $bla_{CTX-M-1}$ was frequently identified on plasmids belonging to the IncN or IncI1 families, while $bla_{CTX-M-14}$ was detected on IncK plasmids, and $bla_{CTX-M-3}$ on IncL/M plasmids (47). IncI1, IncK, and IncX plasmids carried the ESBL gene bla_{SHV-12} (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 β-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).

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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 β-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 β-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_{CMY-2} was mainly due to the spread of IncI1-γ 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_{CMY-2} 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_{CMY-2} 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

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

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 β-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_{KPC-2}-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 β-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-

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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 $bla_{\text{CTX-M}}$ ESBL gene, usually $bla_{\text{CTX-M-15}}$, was often colocated (96, 98). Furthermore, *aac(6')Ib-cr* was described in *E. coli* isolates from the feces of French cattle, where it was also colocated with $bla_{\text{CTX-M-15}}$ 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 β-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

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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 Tn*1548*, 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 $bla_{\text{CMY-2}}$, $bla_{\text{OXA-181}}$, 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 $bla_{\text{CTX-M-55}}$ 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 $bla_{\text{CTX-M-15}}$ 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_3CO) to an amine group ($-NH_2$) 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).

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Among aminoglycosides, the nucleotidyltransferases ANT(2″) and ANT(3″) are most commonly found in Gram-negative bacteria. ANT(2″) and ANT(3″) 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″)-I/II* 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 ($bla_{\text{CTX-M-55}}$, $bla_{\text{CTX-M-15}}$, or $bla_{\text{CTX-M-123}}$) on plasmids of 78 to 138 kb in size. In a recent French study, the emergence of plasmids carrying multiple resistance determinants including *fosA3*, $bla_{\text{CTX-M-55}}$, *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 $bla_{\text{CTX-M-55}}$ 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$^-$:B$^-$-type epidemic plasmid that carried the resistance genes $bla_{\text{CTX-M-65}}$, *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 coharboring $bla_{\text{CTX-M-14}}$, *rmtB*, *aadA2*, and $bla_{\text{TEM-1}}$), pECB11 from chicken [92,545 bp, F33:A$^-$:B$^-$, and coharboring $bla_{\text{CTX-M-55}}$, *floR*, *cfr*, $bla_{\text{TEM-1}}$, *tet*(A), *strA*, and *strB*], and pECF12 from chicken [77,822 bp, F33:A$^-$:B$^-$, and coharboring $bla_{\text{CTX-M-3}}$, *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

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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, Tn*1721* [*tet*(A)] (183) and Tn*10* [*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 colocated 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 $bla_{\text{CTX-M-2}}$, $bla_{\text{TEM-1}}$, *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 $bla_{\text{SHV-12}}$, *aadA1*, *cmlA1*, and *aadA2* or the genes $bla_{\text{SHV-12}}$, *qacG*, and *aadA6* were identified in *E. coli* isolates from wild

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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 $bla_{CTX-M-2}$, *sul1*, *aadA29*, *strA*, and *strB*; (ii) a ca. 240-kb IncFIC plasmid that harbored the *tet*(A) gene together with the resistance genes bla_{CMY-2}, *cmlA*, *floR*, *strA*, *strB*, *sul1*, *sul3*, and *aadA7*; (iii) a 240-kb IncHI2 plasmid with the resistance genes $bla_{CTX-M-2}$, *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*, $bla_{CTX-M-14}$, bla_{TEM-1}, *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

Phenicols 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 azidamfenicol 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 *cfr*, 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 ≥16 mg/liter, 42 carried the *floR* gene. Twelve *E. coli* isolates were positive for *cmlA*, and their corresponding chloramphenicol MICs were ≥32 mg/liter. In addition, eight isolates were positive for *floR* and *cmlA*, and their florfenicol and chloramphenicol MICs were ≥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 *cfr* 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

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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_{CMY-2}, *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 $bla_{CTX-M-14b}$ 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^-: B^- 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 dihydropteorate 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

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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 Seputiené 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-

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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 colocated 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 $bla_{\text{CTX-M-55}}$, 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 multidrug-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-

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

mcr gene	Geographical origin	Source	Sequence type(s)	Reference
mcr-1	China	Pig		238
	China	Pig		242
	China	Pig	48, 54, 90, 156, 165, 167, 410, 1114, 1178, 1437, 2439, 3331, 4429, 4463, 4656	277
	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,	246
	Vietnam	Reptiles	117, 1011	282
	South Korea	Poultry, pig	1, 10, 88, 101, 156, 162, 226, 410, 1141, 2732	283
	Germany	Pig	1, 10, 846	240
	Germany	Pig (manure), fly, dog	10, 342, 1011, 5281	256
	France	Cattle		241
	Italy	Poultry (meat)	602	243
	U.S.	Pig	132, 3234	284
	Venezuela	Pig	452	285
	Brazil	Magellanic penguin	10	286
mcr-1.3	China	Poultry	155	246
mcr-1.8	Brunei	Poultry	101	KY683842.1[a]
mcr-1.9	Portugal	Pig		KY964067.1[a]
mcr-1.12	Japan	Pig		LC337668.1[a]
mcr-2	Belgium	Pig, cattle	10, 167	247
mcr-3	China	Pig	1642	249
	France	Cattle	744	251
mcr-3.2	Spain	Cattle	533	250
mcr-4	Spain, Belgium	Pig	10, 7029	252
mcr-5	Germany	Pig	29, 349	253
mcr-5.2	Germany	Pig	1494	253

[a]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

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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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