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Antimicrobial Resistance in *Acinetobacter* spp. and *Pseudomonas* spp.

AGNESE LUPO, MARISA HAENNI, and JEAN-YVES MADEC
Université de Lyon–ANSES, Unité Antibiorésistance et Virulence Bactériennes, Lyon, France

ABSTRACT The nonfermenting bacteria belonging to *Acinetobacter* spp. and *Pseudomonas* spp. are capable of colonizing both humans and animals and can also be opportunistic pathogens. More specifically, the species *Acinetobacter baumannii* and *Pseudomonas aeruginosa* have been recurrently reported as multidrug-resistant and even pandrug-resistant in clinical isolates. Both species were categorized among the ESKAPE pathogens, ESKAPE standing for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* species. These six pathogens are the major cause of nosocomial infections in the United States and are a threat all over the world because of their capacity to become increasingly resistant to all available antibiotics. *A. baumannii* and *P. aeruginosa* are both intrinsically resistant to many antibiotics due to complementary mechanisms, the main ones being the low permeability of their outer membrane, the production of the AmpC beta-lactamase, and the production of several efflux systems belonging to the resistance-nodulation-cell division family. In addition, they are both capable of acquiring multiple resistance determinants, such as beta-lactamases or carbapenemases. Even if such enzymes have rarely been identified in bacteria of animal origin, they may sooner or later spread to this reservoir. The goal of this article is to give an overview of the resistance phenotypes described in these pathogens and to provide a comprehensive analysis of all data that have been reported on *Acinetobacter* spp. and *Pseudomonas* spp. from animal hosts.

ACINETOBACTER SPP.

The *Acinetobacter* genus includes 50 species of nonmotile Gram-negative rods that are strictly aerobic, adapted to a wide range of temperatures, and able to survive on abiotic surfaces. Many species belonging to the *Acinetobacter* genus are able to cause infections, favored by the presence of indwelling devices, in immune-compromised human hosts (1). The lethality of *Acinetobacter* infections is elevated in more than 50% of cases (2). Among the *Acinetobacter* spp., *A. baumannii* is the most prevalent, responsible for 95% of infections and outbreaks in hospitals, followed by *A. nosocomialis* and *A. pittii*. The ability of *A. baumannii* to survive in the hospital environment promotes its diffusion by outbreaks and epidemics. To date, several global epidemics have occurred, sustained by a few strains belonging to successful lineages, namely, clonal complex I-III, as characterized by multilocus sequence typing (3). Recently, another lineage with the potential for global diffusion, delineated as sequence type (ST) 25, has emerged (4). Preventing the introduction of *A. baumannii* into hospital settings could contribute to preventing the further spread of multidrug-resistant isolates. Although its reservoir remains unknown, this organism has been found in soil, water, and food, including fish, milk, raw vegetables, and meat, which has earned it the definition of "ubiquitous." The presence in retail meat samples of *A. baumannii* isolates belonging to a clonal complex commonly associated

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Correspondence: Agnese Lupo, agnese.lupo@anses.fr

with multidrug-resistant clones invites the speculation that food may carry organisms into hospital settings. A highly selective pressure exerted by antimicrobial usage may positively select those isolates able to acquire and/or develop resistance mechanisms (5). Unfortunately, *Acinetobacter* spp. can also be pathogenic for animals. In the following paragraphs, an overview of the infections, the principal mechanisms of antibiotic resistance, and their epidemiology in *Acinetobacter* spp. among animals will be presented.

Acinetobacter Infections in Animal Hosts

Acinetobacter species are commensals of several body sites in many animal hosts. *A. baumannii* is frequently isolated from the eyes of horses. It is also isolated from the fecal flora of cattle, equids, and rabbits; from lice and ked of cattle, sheep and dogs; and from the mouths of dogs and cats, with a reported prevalence of 6.5% (9/138) in Reunion Island (6–12). Besides commensalism, the pathogenic role of *Acinetobacter* in animals cannot be neglected, with infections occurring that are similar to those observed in humans. The presence of foreign bodies in critically ill animals represents a risk factor for developing *Acinetobacter* spp. infections (13, 14). Furthermore, propagation of multidrug-resistant isolates may occur that are similar to the outbreaks generated in human clinics (15, 16). In the effort to understand the relevance of *Acinetobacter* as an animal pathogen, Mathewson and Simpson analyzed 347 animal specimens. Although the analysis was conducted on a phenotypic basis, they found *Acinetobacter* to be prevalent in as many as 14.5% (50/347) of isolates, principally from equine hosts (27%) followed by canine (17%), feline (2%), bovine (2%), and various other hosts (2%) (17). *Acinetobacter* spp. have also been associated with wound and respiratory tract infections in horses (18, 19) and with urinary tract and respiratory infections and sepsis in dogs and cats (20, 21). Less frequently, *Acinetobacter* spp. have been found in association with other animal diseases such as bovine mastitis (22, 23) and skin and mucous diseases in birds.

Besides the veterinary relevance of *Acinetobacter* spp. and, in particular, *A. baumannii* as an infective agent, many investigations have been conducted with an anthropocentric perspective, studying animals as a reservoir of antimicrobial-resistant bacteria and a source of infections for humans. Indeed, sporadic investigations of animals infected by multidrug-resistant isolates of *Acinetobacter* spp. have been reported and their epidemiology discussed. In the following section, the most common antimicrobial resistance mechanisms detected in *Acinetobacter* spp. will be described.

Antimicrobial Resistance in *Acinetobacter* spp.

A. baumannii poses a public health concern because of its propensity to develop multidrug resistance. In particular, the acquisition of carbapenem resistance poses a serious threat of therapeutic failures (1). The occurrence of *Acinetobacter* spp. infections in animal hosts poses principally two issues: first, treating such infections is challenging because *Acinetobacter* spp. isolates are often naturally resistant to many of the antibiotics authorized for use in veterinary medicine; second, the presence and/or the development of multidrug-resistant isolates in animal hosts may serve as reservoir of multidrug-resistant isolates for humans.

Intrinsic resistance

A. baumannii exhibits an intrinsic reduced susceptibility to several antibiotic classes, including beta-lactams, macrolides, trimethoprim, and fosfomycin (24). The mechanisms underlying such intrinsic resistances consist of natural membrane impermeability, basal efflux activity, and the presence of two chromosomally encoded beta-lactamases, an ADC cephalosporinase and an OXA-51 oxacillinase (25). To date, three efflux systems belonging to the resistance-nodulation-division family have been characterized in *A. baumannii*, encoded by the *adeABC*, *adeFGH*, and *adeIJK* operons (26). Homologs of these operons have been recovered in other *Acinetobacter* spp. such as *A. calcoaceticus*, *A. nosocomialis*, and *A. pittii*, among others (27–29). The AdeIJK efflux system is constitutively expressed and contributes to a basal resistance to beta-lactams, tetracyclines, macrolides and lincosamides, phenicols, fusidic acid, and fluoroquinolones.

Acquired resistance

The development of acquired resistance can occur by two processes: mutation in chromosomal structures and the acquisition of exogenous genes by horizontal gene transfer. Mutations in the two-component regulatory system AdeRS and in the regulators AdeL and AdeN have been shown to lead to the overproduction of the efflux pumps AdeABC, AdeFGH, and AdeIJK, respectively, and consequently to an increase in resistance. In particular, overproduction of AdeABC contributes to an increase of resistance to beta-lactams, aminoglycosides, fluoroquinolones, tetracyclines and tigecycline, macrolides and lincosamides, and chloramphenicol, whereas overproduction of AdeFGH contributes to resistance to quinolones, antifolates, and chloramphenicol (27).

Resistance to beta-lactams in *A. baumannii*

Certain insertion sequences, including IS*AbaI* among others, can provide a strong promoter for the overexpression of the genes located downstream. This phenomenon can be responsible for the overproduction of ADC and OXA-51, leading to the development of high-level resistance to third- and fourth-generation cephalosporins in the first case and of carbapenem resistance in the second case (30, 31). Other insertion sequences, such as IS*Aba125* and IS*Aba825*, are able to insert into porin-encoding genes, causing the inactivation of the porins and subsequent resistance to carbapenems (32).

Resistance to third- and/or fourth-generation cephalosporins, other than penicillins and their derivatives, can also be mediated by the acquisition of genes coding for exogenous enzymes such as the class A beta-lactamases TEM and SHV in the extended-spectrum variants CTX-M, PER, GES, and VEB (33, 34). Among *A. baumannii* isolates from human infections, the most common mechanism of carbapenem resistance is mediated by the acquisition of OXAs hydrolyzing carbapenems. The enzymes OXA-23 and OXA-58 are frequently identified in clinical isolates, whereas OXA-24/40 and OXA-143 are rarer. The insertion sequence IS*AbaI* can mediate the overexpression of the acquired bla_{OXAs}, leading to high-level resistance to carbapenems (35). The presence of class B metallo-beta-lactamases such as SIM, IMP, VIM, and NDM-1 has also been reported (36).

Resistance to aminoglycosides in *A. baumannii*

Frequently, resistance to carbapenems is associated with aminoglycoside resistance. This is classically mediated by aminoglycoside-modifying enzymes, which catalyze reactions of acetylation, phosphorylation, or O-nucleotidyl transfer. Among such enzymes, AAC(6′)-I is cryptic in several *Acinetobacter* spp. and confers, when the relative gene is expressed, resistance to netilmicin, tobramycin, gentamicin, and amikacin. Acquired aminoglycoside-modifying enzymes have been frequently detected in *A. baumannii*, with AAC(3)-I, APH (3′)-VI, and ANT(2″)-I being the most prevalent (37). More recently, 16S rRNA methylases have been described as another mechanism conferring resistance to aminoglycosides (38, 39). This mechanism confers high-level resistance to amikacin, gentamicin, netilmicin, tobramycin, and kanamycin. Among the known methylases, ArmA is the only one to be reported in *A. baumannii* clinical human isolates, whereas no report exists from animals (40, 41).

Resistance to fluoroquinolones in *A. baumannii*

In contrast to beta-lactam and aminoglycoside resistances, which are mostly based on the acquisition of exogenous determinants, the development of fluoroquinolone resistances is mainly due to point mutations of the gyrase and topoisomerase enzymes. Of particular importance for high-level resistance are GyrA Ser83Leu together with ParC Ser80Leu and Glu84Lys amino acid substitutions (42, 43).

Resistance to other antibiotics in *A. baumannii*

Certain antibiotic classes are of limited therapeutic interest for the treatment of *A. baumannii* infections, mainly because of their toxicity in humans. However, in certain circumstances some of these antibiotics' properties are fundamental, as in the case of rifampicin, which is able to easily penetrate tissues. Resistance to this antibiotic occurs principally by mutation of the *rpoB* gene and acquisition of an enzyme that modifies the rifampicin, encoded by the *arr-2* gene, and that is usually located on class I integrons (44). The development of multidrug resistance has forced intensified usage of "old antibiotics" such as colistin. Resistance to colistin is mediated by mutation in the proteins PmrAB, a two-component system in *A. baumannii* (45). Colistin resistance in animal isolates has never been reported. Tigecycline is considered a last-resort treatment of infections caused by multidrug-resistant *Acinetobacter* spp. Emergence of resistant isolates, mainly overexpressing efflux pumps, has been reported among human patients (46). Furthermore, coselection of tigecycline resistance by usage of other antibiotics, including tetracycline, has been demonstrated in enterococci (47). This is a concern, considering that tigecycline is not allowed in veterinary practice, whereas tetracycline could contribute to the development of a potential reservoir for human contamination. Recently, Ewers et al. reported two tigecycline-resistant *A. baumannii* isolates from two dogs in Germany (48).

Most common mobile genetic elements in *A. baumannii*

All the described acquired resistance mechanisms can be located on the chromosome or on plasmids, eventually associated with transposons. For instance, $bla_{\text{OXA-23}}$ has been found located on several transposon structures containing IS*AbaI*, such as Tn*2006*, Tn*2007*, Tn*2008*, Tn*2008B*, and Tn*2009* (49). A very successful strategy for *A. baumannii* to develop multidrug resistance is the acquisition of the so-called resistance islands, such as *AbaR*. The acquisition of such islands seems to be con-

secutive to a transposition event in a hot-spot sequence, the ATPase encoding gene. Several *AbaR* islands have been described, with *AbaR1* containing as many as 25 genes encoding mechanisms conferring resistance to several antimicrobial classes (50, 51). This brief overview of resistance mechanisms encountered in *A. baumannii* is far from exhaustive but highlights the potential and the propensity for multidrug resistance development. Therefore, understanding the epidemiology of this species and the intersection of its different habitats and hosts is a high priority. In the following section, we will focus on reports concerning resistance to carbapenems, aminoglycosides, and fluoroquinolones in *A. baumannii* from animal settings.

Antimicrobial Resistance in *Acinetobacter* spp. from Food-Producing Animals

The first evidence of carbapenemase-producing *Acinetobacter* spp. of animal origin dates back to 2010, when Poirel et al. (52) investigated the carriage of carbapenem-resistant Gram-negative organisms in a dairy farm in France. In this investigation, nine isolates sampled from 50 cows were identified as *Acinetobacter* genomospecies 15TU, a close relative of the species *Acinetobacter lwoffii*, and all isolates were resistant to carbapenems, harboring a $bla_{\text{OXA-23}}$ gene located on a Tn*2008* transposon. The isolates demonstrated resistance not to fluoroquinolones but to kanamycin. Later, an *A. lwoffii* isolate producing NDM-1 was found in a chicken in China. The isolate was multidrug-resistant, and the $bla_{\text{NDM-1}}$ gene was located on a conjugative plasmid (53). Later, a sporadic *A. baumannii* isolate was found in China in a survey conducted in 2011 to 2012 for carbapenem resistance in Gram-negative organisms from food-producing animals. The isolates harbored $bla_{\text{NDM-1}}$ located on a plasmid that revealed similarity to plasmids found in isolates of human origin; furthermore, it demonstrated coresistance to aminoglycosides, with the exception of amikacin, and fluoroquinolones. Unfortunately, the sequence type of the isolate was not determined (54). The presence of *A. baumannii* isolates producing OXA-23 has been documented in wild fish from the Mediterranean Sea. In these isolates, also demonstrating multidrug resistance, the *aac(6')-Ib* and *aac(3')-I* genes coding for aminoglycoside-modifying enzymes were found. The isolates belonged to ST2, the most widely spread clone in human clinics with which multidrug-resistant isolates are associated. Further investigations revealed that the isolates found in fish were similar to the isolates found contemporaneously in human clinical infections (55). Most likely, the fish were colonized after exposure of water contaminated with clinical waste. Contemporaneously, Al Bayssari et al. (56) reported the presence of *A. baumannii* demonstrating high-level resistance to imipenem in livestock in Lebanon. The isolates (n = 5) were found in cattle, pigs, and fowls, and all of them harbored the $bla_{\text{OXA-23}}$ gene. One isolate coharbored $bla_{\text{OXA-58}}$. Sequence type determination revealed that among the isolates, one belonged to ST2 and another to ST20, the first being globally spread in human clinics and the second also found in dogs in Switzerland (13). Recently, a report from Pailhoriès et al. (57) revealed the presence of $bla_{\text{OXA-24}}$ in *A. baumannii* in healthy cattle in Reunion Island. The $bla_{\text{OXA-24}}$ gene occurred in an ST that had never been reported before, suggesting that carbapenem resistance can emerge and disseminate among animals independently from human cross-contamination. The presence of OXA-23 in species other than *A. baumannii* is quite infrequent, but Klotz et al. (58) has reported the emergence of $bla_{\text{OXA-23}}$ located on Tn*2008* in two isolates identified as *Acinetobacter indicus* colonizing two calves in Germany.

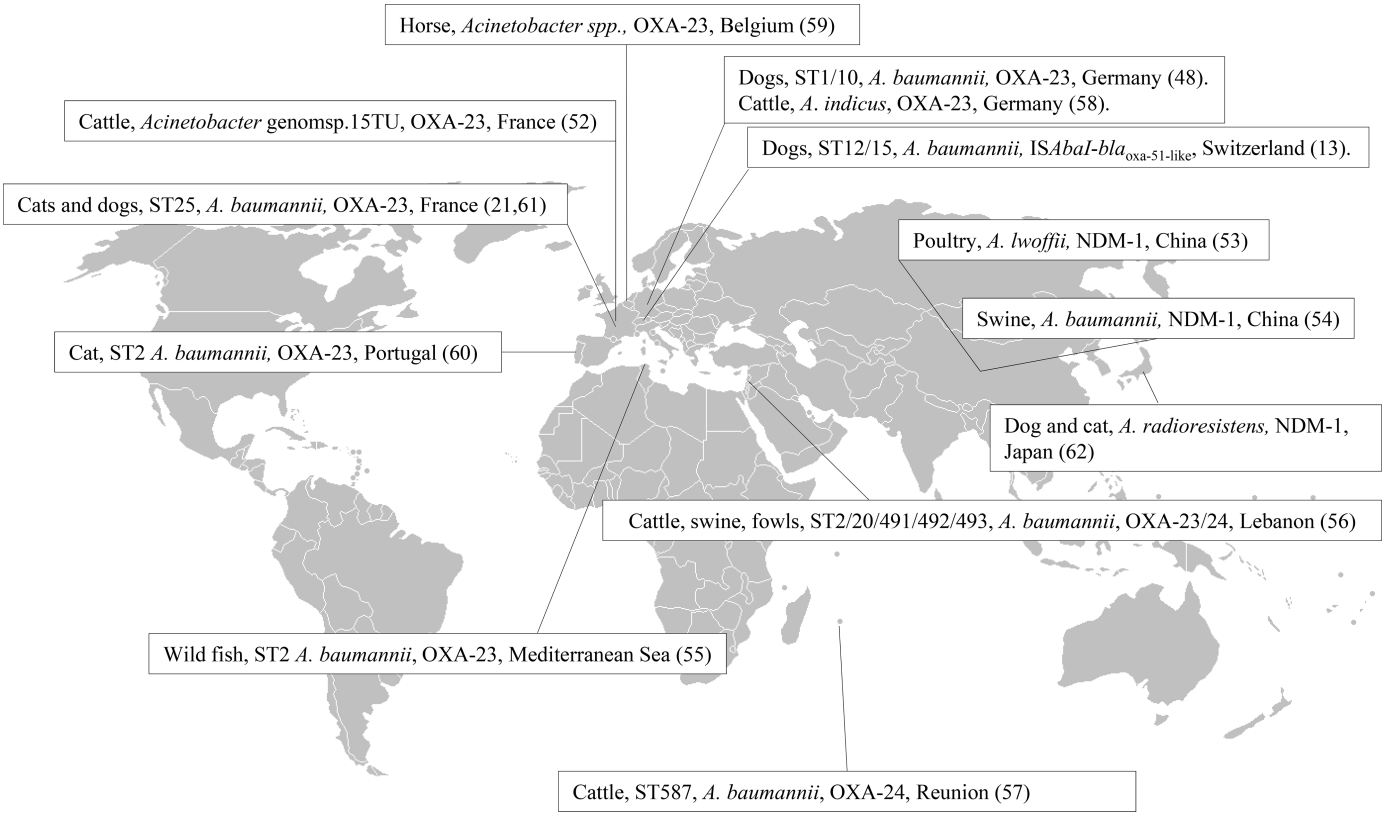
Antimicrobial Resistance in *Acinetobacter* spp. from Companion Animals

In 2011, a study conducted in Switzerland demonstrated the presence of *A. baumannii* isolates (n = 19) in infections of pets and horses (13). The majority of these isolates (n = 12) were resistant to fluoroquinolones and harbored the GyrA Ser83Leu and ParC Ser80Leu mutations. Seventeen isolates were resistant to aminoglycosides, and among those the genes *aacC2*, *aacC1*, and *aadA1* were present. Three isolates in this study, identified in three diseased dogs, demonstrated reduced susceptibility to carbapenems and harbored an IS*AbaI* inserted upstream from the $bla_{\text{OXA-51}}$ gene. These isolates belonged to ST12 and ST15, which are common among human isolates. An even more worrisome finding has been the detection of *Acinetobacter* spp. harboring $bla_{\text{OXA-23}}$ in companion animals. The first report dates from 2012 from a screening of fecal carriage in hospitalized horses. On this occasion Smet et al. (59) found two multidrug-resistant *Acinetobacter* spp. harboring $bla_{\text{OXA-23}}$ located on a Tn*2008* transposon. The second report concerned a single isolate associated with a urinary tract infection in a cat in Portugal in 2009. In this isolate, $bla_{\text{OXA-23}}$ was located on a Tn*2006* transposon that was chromosomally located. Furthermore, an IS*AbaI* copy was located upstream from bla_{ADC}, and mutations conferring fluoroquinolone resistance were detected, as well (60). This isolate also belonged to ST2, reinforcing the hypothesis that a cross-transmission among humans and pets could be at the base of the

animal colonization. In our recent study (21) conducted in the framework of Resapath, the French network for the surveillance of antimicrobial resistance in diseased animals, we analyzed 49 *Acinetobacter* spp. isolates collected from 2011 to 2015. Among those isolates, the majority were identified as *A. baumannii* (n = 41), three as *A. lwoffii*, and one each as *A. haemolyticus*, *A. radioresistens*, *A. schindleri*, *A. johnsonii*, and *A. junii*. Among the *A. baumannii* isolates, seven isolated from the urine of dogs and cats affected by urinary tract infections demonstrated multidrug resistance with high-level resistance to carbapenems. All these isolates harbored a $bla_{\text{OXA-23}}$ located on a chromosomal Tn*2008B*-like transposon and belonged to ST25. This finding was quite surprising since all previously described *A. baumannii* isolates of animal origin that were resistant to carbapenems by OXA enzymes production have been reported as belonging to ST2. We also demonstrated that this clone was able to propagate in two regions of France and persist for at least two years among diseased pets. Our study was amplified by a contemporaneous report from the Nantes region, where two dogs were found to be colonized by ST25 *A. baumannii* harboring $bla_{\text{OXA-23}}$ (61). During a 13-year (2000 to 2013) investigation conducted in Germany by Ewers et al. (48) on diagnostic veterinary samples, three out of 223 *A. baumannii* isolates harbored $bla_{\text{OXA-23}}$ on a Tn*2008* transposon located on a plasmid. These isolates belonged to ST10 and to ST1, two multidrug-resistant sequence types associated with isolates responsible for human infections. In Japan, two isolates of *A. radioresistens* have been isolated from a diseased cat and dog. The isolates were resistant to carbapenems and harbored a $bla_{\text{OXA-23}}$ gene, which *A. radioresistens* is considered to be the source of, and a $bla_{\text{IMP-1}}$ gene, together with genes encoding aminoglycoside-modifying enzymes (62). A summary of all the reports described at time of writing is provided in Figure 1.

Overall, recovering carbapenem-resistant *A. baumannii* in animal hosts continues to be surprising when considering that usage of carbapenems is not allowed in veterinary medicine. However, coselective pressure on OXA enzymes by the usage of other beta-lactams can be speculated, similalry to the role of other environmental factors.

FIGURE 1 Overview of *Acinetobacter* spp., sequence types, and acquired carbapenem resistance mechanisms.



PSEUDOMONAS spp.

Pseudomonas spp. are Gram-negative bacteria comprising more than 200 species at the time of writing (http://www.bacterio.net/pseudomonas.html) that can be ubiquitously found in humans, animals, soil, and plants (63, 64). *Pseudomonas* spp. were extensively studied for their beneficial or deleterious associations with plants (*P. putida*, *P. syringae*, *P. fluorescens*, etc.) but also for their roles in soil bioremediation due to specific biodegradation properties (*P. putida*, *P. stutzeri*, *P. alcaligenes*, etc.) (65–67). Only a few species are of clinical interest in either humans or animals, and *P. aeruginosa* is by far the most frequently reported pathogen. For this reason, this section will focus on this unique species, which is also the only one in which antibiotic resistance was reported in animal hosts.

P. aeruginosa Infections in Animal Hosts

P. aeruginosa is a ubiquitous bacterium normally found in water and soil, but also an opportunistic pathogen of humans, animals, and plants (68). In humans, *P. aeruginosa* is mostly nosocomial, causing severe infections in patients with underlying conditions. Immunosuppressed or intubated-ventilated patients presenting compromised host defenses are particularly vulnerable to this pathogen. It is primarily associated with burn victims and cystic fibrosis patients (69, 70).

P. aeruginosa has not been extensively studied in infections of animal origin since this bacterium is more often considered an environmental contaminant rather than a true pathogen. Apart from sporadic descriptions, it has mostly been reported in cats and dogs, where it is an important pathogen causing otitis externa and otitis media (71–74). Together with *Staphylococcus pseudintermedius*, it is one of the two main ear pathogens, and its prevalence ranges from 6.5 to 27.8% depending on the study (71, 72, 75, 76). However, *P. aeruginosa* is also implicated in skin infections, including deep pyoderma, often in association with other bacterial pathogens (72, 77, 78).

More surprisingly, *P. aeruginosa* infections have been recurrently described in fur animals, where it seems to be particularly virulent (79, 80). The first victims are minks (*Neovison vison*). These mammalian carnivores of the *Mustelidae* family are raised for fur production, principally in Denmark, China, the Netherlands, Poland, and the United States. First described in 1953, the acute and fatal hemorrhagic pneumonia caused by *P. aeruginosa* can decimate farmed minks and lead to high economic losses (81). The second victims are chinchillas, a rodent species which is raised for both pets and laboratory animals—but not for fur. The infections, mainly otitis, are often due to uncleaned water and cage environment and are favored by a weak immunity of this animal species. Since *P. aeruginosa* has a particular capacity of dissemination between these animals, it is very important to rapidly isolate the diseased individuals.

P. aeruginosa is much less reported in livestock animals. It is an opportunistic pathogen that is very rarely reported in etiological surveys of bovine mastitis (82–86). However, several case reports suggest that, though unusual, outbreaks of *P. aeruginosa* can be severe and spread either clonally or nonclonally in different herds (87–90). The origin of the infection is often contaminated liquids, teat dips, or even a contaminated antibiotic preparation (91, 92). One study also reports its implication in 12% of the urinary tract infections in cattle in Israel (93).

Antimicrobial Resistance in *P. aeruginosa*

P. aeruginosa is one of the ESKAPE bacteria (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* spp.), for which the therapeutic options are increasingly limited (94). In addition to its capacity to form biofilms, *P. aeruginosa* is intrinsically resistant to many antibiotics, including beta-lactams (penicillin G, aminopenicillins alone or in combination with inhibitors, first- and second-generation cephalosporins, cefixime, cefuroxime, cefotaxime, ceftriaxone, ertapenem), kanamycin, tetracycline, chloramphenicol, trimethoprim, and quinolones (95). *P. aeruginosa* is also known for its capacity to rapidly acquire additional resistances, so that the combination of intrinsic and acquired resistances can lead to therapeutic failures (96).

Intrinsic resistance

It is commonly admitted that in *P. aeruginosa*, intrinsic resistance is mainly mediated by a combination of impermeability, production of the inducible AmpC cephalosporinase, and the presence of efflux pumps (97). On the one hand, the permeability of the outer membrane is up to 100-fold lower in *P. aeruginosa* than in *Escherichia coli* (97), and on the other hand, two constitutively expressed drug efflux systems, MexAB-OprM and MexXY-OprM, directly participate in intrinsic resistance. Both systems belong to the resistance-nodulation-division family and were identified in the laboratory strain PAO1 (98). MexAB-OprM confers resistance to beta-lactams (with the exception of imipenem), fluoroquinolones, trimethoprim-sulfonamides, chloramphenicol, and tetracyclines, while MexXY-OprM is involved

in resistance to cefepime, aminoglycosides, fluoroquinolones, tetracyclines, chloramphenicol, trimethoprim-sulfonamides, and macrolides. Ten other efflux systems were also described in *P. aeruginosa*, none of which plays a role in intrinsic resistance. Finally, *P. aeruginosa* harbors two beta-lactamase encoding genes. The first one is the constitutively expressed bla_{OXA-50} oxacillinase, which only plays a minor role in beta-lactam resistance (99). The second is the inducible AmpC beta-lactamase, which confers resistance to beta-lactams, including cefuroxime and ceftriaxone, even though this mechanism may be redundant with the MexAB-OprM efflux system (100, 101).

Like many bacterial species, *P. aeruginosa* can live either as planktonic cells or as organized communities called biofilms (102). Quorum-sensing, the cell-to-cell communication mechanism involving the Las, Rhl, and PQS systems in *P. aeruginosa*, was shown to be involved in biofilm formation, particularly through the Rhl system (103, 104). An important characteristic of biofilms is their tolerance to different external stresses, including antibiotic treatment (105). Tolerance is a physiological state of the bacteria that does not involve any acquired mutation and cannot be transmitted to the progeny of a mother cell. For example, tolerance to aminoglycosides (gentamicin, tobramycin), tetracyclines, and colistin has been described (93, 106). Colistin targets different zones of the biofilm compared to other molecules, so that combined treatment with colistin/gentamicin or colistin/tetracycline is more appropriate to eradicate the majority of the cells composing the biofilm (106).

Acquired resistance

Besides intrinsic resistance, *P. aeruginosa* is capable of acquiring numerous additional resistances, either through point mutations in pre-existing genes or through horizontal transfer of resistance determinants (96). The use of specific antibiotics during treatment can readily select for point mutations which lead to the overexpression of one or another efflux system. Depending on the affected system (MexAB-OprM, MexXY-OprM, MexCD-OprJ, or MexEF-OprN), elevated resistance levels toward their specific antibiotic substrates are observed (98, 107). Overproduction of AmpC can also be obtained through mutations in regulatory genes. The porin OprD can also be modified, which is the preferential pathway toward carbapenem resistance in human clinical isolates of *P. aeruginosa*. And finally, mutations in the target genes *gyrA*/*gyrB* and *parC*/*parD* confer resistance to fluoroquinolones (see below).

In parallel, a large number of acquired enzymes conferring beta-lactam resistance were identified in *P. aeruginosa* (108). These include extended-spectrum beta-lactamases of the PER, SHV, PME, GES, and VEB families, as well as the CTX-M enzymes typically found in *Enterobacteriaceae*. Metallo-beta-lactamases conferring resistance to carbapenems were also reported, mainly IMP and VIM enzymes, even though carbapenem resistance in *P. aeruginosa* is mostly due to the *oprD* gene, which can be repressed, mutated, or deleted (108). These enzymes are increasingly found in human clinical isolates but have not been reported yet in animal isolates.

Antimicrobial Resistance in *Pseudomonas* spp. in Cats and Dogs

P. aeruginosa is one of the main pathogens causing otitis externa and otitis media (71–74) but is also implicated in skin infections (72, 77, 78). The treatment of such infections starts by a thorough cleaning (deep ear flush in the case of otitis) and a topical disinfection, which is often followed by an antibiotic treatment using mainly fluoroquinolones, aminoglycosides or polymyxins. In this respect, monitoring of antimicrobial resistance in *P. aeruginosa* is clearly needed. However, most of the clinically relevant antibiotics do not have referenced clinical breakpoints, which is a serious data gap for effective surveillance that will have to be filled in in the near future.

Resistance to fluoroquinolones

Ciprofloxacin is considered the most active fluoroquinolone against *P. aeruginosa* (109). The prevalence of resistance to this molecule in *P. aeruginosa* of animal origin ranges from very low to high rates (Table 1). Indeed, variable resistance rates have been reported, ranging from 3.7% in China in 2009 to 2010 and 8.7% in Croatia (2007 to 2009) to 16% in Canada (2003 to 2006), 4.8% and 20% in two Brazilian studies, and 21% in the United States (73, 74, 78, 110–113), and even reaching 63% in France between 2008 and 2011. These divergences may be due to the methodology (MICs versus disk diffusion), the levels of fluoroquinolone usage in the countries where strains were collected, or the type of sampling (otitis versus skin infection or mild versus severe infections).

The importance of resistance to ciprofloxacin also has to be put into perspective here since this molecule is not used in veterinary medicine. Nevertheless, among the three main fluoroquinolones prescribed in animals (enrofloxacin, marbofloxacin, and the more recent pradofloxacin), the most frequently tested is enrofloxacin, which presents high rates of resistance (Table 1). Indeed, 18.2% of isolates collected throughout Europe were resistant (and 81.8% presented an intermediate pheno-

TABLE 1 Antimicrobial susceptibility to fluoroquinolones and aminoglycosides in *P. aeruginosa* isolates of animal origin

Country	Year	Animal host	Pathology	No. of isolates	Method	Percentage (%) of resistance[d]				Reference
						CIP	ENR	GEN	AMI	
US.	1998–2003	Dogs/cats	Otitis	319	Sensititre	–[e]	38.0	15.0	11.0	71
U.S.	1992–2005	Dogs	Pyoderma	20	Disk diffusion	25.0	40.0	5.0	5.0	78
Europe[a]	2008–2010	Dogs	SSTI[f]	160	Agar dilution	–	16.9	18.8	–	114
		Cats	SSTI	11		–	18.2	9.0	–	
Croatia	2007–2009	Dogs	Otitis	104	Etest	8.7	51.9	43.3	–	74
Croatia	1998–2000	Dogs	Otitis	183	Agar dilution	3.8	26.2	10.9	7.6	116
Canada	2003–2006	Dogs	SSTI	106	Sensititre	16.0	31.0	7.0	3.0	73
China	2009–2010	Dogs	SSTI	27	Broth microdilution	14.8	–	14.8	11.1	110
Germany	2004–2006	Dogs/cats	SSTI	71	Broth microdilution	–	24.0	27.0	–	115
			Urinary/genital tract	28		–	11.0	11.0	–	
France	2008–2011	Dogs	SSTI	46	Agar dilution	63.0	–	56.5	15.2	124
		Horses	Diverse[b]	10		0.0	–	10.0	0.0	
		Cows	Diverse[c]	12		0.0	–	8.4	0.0	
Brazil	2010–2012	Dogs	Otitis, pyoderma	104	Disk diffusion	4.8	26.0	4.8	2.9	113
Japan	2005–2007	Cows	Mastitis	116	Broth microdilution	0.0	31.0	4.3	1.7	154
Japan	Unknown	Chinchillas	Healthy	22		4.5	81.0	0.0	0.0	150
Denmark	2002–2005	Minks	Hemorrhagic pneumonia	39	Sensititre	–	5.1	0.0	–	144
China	2010–2011	Minks	Hemorrhagic pneumonia	30	VITEK-2	13.3	–	0.0	0.0	146

[a]Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Spain, Sweden, and the United Kingdom.
[b]Respiratory infections, skin or eye infections, metritis.
[c]Mastitis, digestive and respiratory infections.
[d]CIP, ciprofloxacin; ENR, enrofloxacin; GEN, gentamicin; AMI, amikacin.
[e]–, Not performed.
[f]SSTI, Skin and Soft Tissues Infections.

type), as were 24% in Germany (49% intermediately resistant), 26.2% in Croatia, 31% and 38% in two Canadian studies, 49% in the United States, and 26.0% and 70% in two Brazilian studies (71, 73, 76, 111, 112, 114–116). On the other hand, even though ciprofloxacin is the major active metabolite of enrofloxacin, divergences in the prevalence of resistance are observed when both antibiotics are tested on the same collection of isolates (116). This may be because of the different *in vitro* activities of enrofloxacin, marbofloxacin, and ciprofloxacin. Globally, there is a lack of harmonized studies to clarify the clinical relevance of those discrepancies in the resistance of *P. aeruginosa* to the major fluoroquinolones used in routine veterinary practice.

The targets of quinolones and fluoroquinolones are the DNA gyrase and the DNA topoisomerase IV, which are both constituted of two subunits, named GyrA/GyrB and ParC/ParE, respectively (117). The main resistance mechanism in both Gram-positive and Gram-negative bacteria involves mutations in these targets. In *P. aeruginosa*, GyrA and ParC mutations were identified (though not systematically) in ciprofloxacin-resistant clinical isolates, while GyrB mutations are thought to confer only moderate resistance (118). Such point mutations were also reported in veterinary isolates, and the most frequent ones, namely Thr83Ile in GyrA and Ser87Leu in ParC, were also reported in human isolates (73, 110, 118, 119). Efflux pumps have also been identified as a key mechanism in fluoroquinolone resistance, notably through the MexAB-OprM or MexF-OprN systems (108, 120–122). Only one study reported the overexpression of these efflux systems in veterinary isolates (123). However, this subject should definitely be further explored in *P. aeruginosa* of animal origin, since overproduction of efflux pumps is easily selected by usage of veterinary -licensed antibiotics, conferring resistance to several antibiotics including aminoglycosides and even a few carbapenems due to their wide substrate specificity (98).

Resistance to aminoglycosides

Resistances to gentamicin and amikacin are often reported, probably because they are used as first- and second-line antibiotics for the treatment of otitis but also of pyoderma and corneal ulcers in cats and dogs.

Precautions need to be taken with this family of antibiotics because of their nephro- and ototoxicity.

The prevalence of resistance to gentamicin is systematically higher than resistance to amikacin (Table 1). Gentamicin resistance was reported from dogs in two studies of soft tissue infections in the United States (5% and 7%), in ophthalmic infections in Brazil (10%), in otitis in Canada (15%), in diverse infectious contexts in Germany (11%) and Brazil (4.8%), in soft tissue infections in China and in Europe (14.8% and 18.8%), in otitis in Croatia (16.9% and 43.3% in two studies, respectively), and in otitis in France (56.5%) (71, 73, 74, 78, 110–112, 114–116, 124). On the other hand, amikacin resistance rates observed in the same studies (when available) ranged from 5% and 3% in the United States, 10% (ophthalmic infections) and 2.9% (otitis and pyoderma) in Brazil, 11% in Canada, 11.1% in China, 12.6% in Croatia, and 15.2% in France. The divergences between the two antibiotics may have the same causes as cited above for fluoroquinolones.

Aminoglycoside resistance in *P. aeruginosa* is principally mediated by the MexXY-OprM multidrug efflux system. This system is constitutively expressed and implicated in the intrinsic resistance of *P. aeruginosa* to aminoglycosides (112). However, its overexpression can easily be induced by the use of its substrate antibiotics, thus conferring an elevated resistance to these very same antibiotics, including aminoglycosides (98, 125). The role of MexXY-OprM in animal strains was studied by Chuanchuen et al. in pets and bovine mastitis (see below) (126, 127). The role of the MexXY efflux pump in aminoglycoside resistance was evidenced in cats and dogs sampled in Thailand and the United States (123, 127), in addition to the presence of aminoglycoside-modifying enzymes, which have also been reported in isolates from the United States and Canada (73, 110). Aminoglycoside resistance can be achieved by inactivation of these antibiotics through specific modifications mediated by enzymes of the AAC, APH, and ANT families (128). The nature of the modifications and the spectrum of inactivated molecules depend on the modifying enzyme implicated (128). Finally, three methylases—which bind to the target site of the aminoglycosides and confer high-resistance phenotypes to several molecules, including gentamicin and amikacin—have been described in *P. aeruginosa*, namely ArmA, RmtA, and RmtD (129–131), none of which have been reported yet in veterinary isolates.

Resistance to polymyxins

Polymyxin B is one of the first-line antibiotic treatments in cases of otitis and eye infections in cats and dogs (132). Antimicrobial susceptibility data on this molecule are still rare, but when data are available, polymyxin B is always the most efficient antibiotic. Indeed, no resistant isolate was described in the United States (78), in Canada (71), or in Brazil (112). Polymyxin-resistant veterinary isolates were nonetheless reported in Germany—where four isolates (4/71, 5.6%) from soft tissue infections and two isolates (2/28, 7.1%) from urinary/genital tract infections presented an MIC to colistin of >2 mg/liter—and recently in Brazil, where 3/10 isolates from ophthalmic infections showed polymyxin B resistance (111, 115). However, the molecular basis of these resistant phenotypes remains unknown.

The discovery of a plasmidic gene, *mcr-1*, conferring resistance to *Enterobacteriaceae* has shed new light on colistin resistance (133). Interestingly, this gene has been successfully transferred *in vitro* to *P. aeruginosa*, but no field strain of *mcr-1*-carrying *P. aeruginosa* has been reported yet. Colistin-resistance can also be achieved under laboratory conditions in a reversible manner by repeated exposure to subinhibitory concentrations of colistin (134). Colistin is a last-resort antibiotic in cases of multidrug-resistant strains, but colistin resistance is fortunately still very rare in human clinical isolates (135). When studied molecularly, these resistant isolates mostly present modifications in the lipopolysaccharide (136–138).

Resistance to carbapenems

Carbapenem use is forbidden in veterinary medicine, including in companion animals. Consequently, the occurrence of carbapenem-resistant pathogens in animals has only sporadically been described. In 2014, an IMP-45-producing *P. aeruginosa* strain was detected in a dog during routine surveillance for carbapenem resistance (139). Recently, a study was performed in France on 30 isolates from cats and dogs (including one cattle isolate) presenting a decreased susceptibility to imipenem and/or meropenem (140). No carbapenemase gene was detected, and only a few isolates showed an altered OprD (6/30), which is a major cause of carbapenem resistance in humans. On the contrary, most of the isolates displayed alterations in efflux pumps (MexAB-OprM [n = 12], MexEF-OprN [n = 4], MexXY [n = 8], and CzcCBA [n = 3]). Since these efflux pumps also confer resistances to antibiotics that are used in veterinary medicine (notably fluoroquinolones and aminoglycosides), the observed decreased susceptibility to carbapenems is thus probably a consequence of noncarbapenem antibiotic use. In Brazil, carbapenem-resistant isolates were also reported (7.7% of isolates resistant to imipenem, 1.0% to meropenem), but no molecular characterization was performed (112).

Antimicrobial Resistance in *Pseudomonas* spp. in Minks

P. aeruginosa is especially virulent in minks, where it is a major cause of hemorrhagic pneumonia. This infection is decimating farmed minks (*N. vison*) and causes high economic losses (81). *P. aeruginosa* dissemination is due to local outbreaks of clonal strains, but clones vary between outbreaks (79, 141, 142). The origin of the contamination is mostly environmental, and clones spread in farms due to contaminated water containers or food, standing water, and uncleaned cages (79). Prevention of hemorrhagic pneumonia mostly relies on multivalent vaccines, but their expensive price and short protection period leads to innovative research such as research in phages (79, 142, 143).

Antibiotics are used to treat minks. Penicillins, aminoglycosides, and macrolides are the main families of molecules used to treat fur animals in Denmark, independent of the pathology and the pathogen identified. Their use steadily increased between 2001 and 2006 (144) and increased significantly (102% increase) from 2007 to 2012 (145). However, data on antimicrobial resistance in *P. aeruginosa* from hemorrhagic pneumonia were only reported in three studies, which showed an overall high susceptibility of most of the isolates. The first study included 39 isolates collected in Denmark between 2000 and 2005 (144), the second one comprised 30 isolates originating from China from 2010 to 2011 (146), and the third one included 41 isolates collected in Denmark between 2014 and 2016 (147). Danish isolates from the first sampling period (2000 to 2005) were susceptible to gentamicin and colistin, while 5.1% were resistant to enrofloxacin. Resistance to aminoglycosides was suspected in both collections, but no proportions can be inferred because of the lack of referenced breakpoints. Isolates from the same country but the second sampling period (2014 to 2016) were also susceptible to gentamicin and ciprofloxacin, while 17% were resistant to colistin. Unfortunately, colistin resistance was only inferred by MIC results, but no molecular characterization was performed. Chinese isolates were more resistant to fluoroquinolones (13.3%) and also presented resistance to ticarcillin/clavulanic acid. However, no resistance was observed to aminoglycosides. The differences in resistance may reflect local specificities in terms of antibiotic treatment.

Antimicrobial Resistance in *Pseudomonas* spp. in Chinchillas

P. aeruginosa is the main cause of infections in chinchillas, often due to uncleaned water and cages. Chinchillas have been extensively studied as models of middle ear infections (148), but studies dedicated to otitis media in this animal species are scarce (149).

Antibiotic susceptibility has only been reported once, in 67 chinchillas in Japan (150), of which 23 were raised as pets and 21 as laboratory animals. A total of 22 *P. aeruginosa* isolates were identified, which clustered in seven pulsed-field gel electrophoresis patterns. No resistance phenotype was observed for aminoglycosides, even though nine isolates presented a decreased susceptibility to gentamicin and one to amikacin. One isolate was resistant to ciprofloxacin, while MICs for enrofloxacin—the major veterinary fluoroquinolone—were much higher than those to ciprofloxacin. Finally, six isolates showed intermediate resistance to ceftazidime and five to imipenem. The number of isolates presenting reduced susceptibilities should undoubtedly prompt further studies in these animals which are in close contact with humans.

Antimicrobial Resistance in *Pseudomonas* spp. in Food-Producing Animals

Cattle are the only food-producing animals for which substantial data on antimicrobial resistance in *P. aeruginosa* are available. Data for chickens and pigs are very scarce and mostly describe *Pseudomonas* spp. as environmental contaminants (151, 152). Only two studies specifically designed for the detection of carbapenem-resistant isolates reported the presence of VIM-2 in *P. aeruginosa* in fowl in Lebanon and VIM-1 in *Pseudomonas putida* in chicken cloacal swabs as well as in their environment in China (56, 153).

In cattle, only three articles reported on resistance phenotypes in *P. aeruginosa* isolates from bovine mastitis. Ohnishi et al. studied 116 *P. aeruginosa* strains collected from the milk of 115 cows in Japan between 2005 and 2007 (154). *P. aeruginosa* was found in 0.65% of the milk isolates that had been under control and caused moderate to severe infections in half of the cases. Isolates presented high susceptibility rates toward piperacillin, ceftazidime, cefepime, imipenem, ciprofloxacin, amikacin, and tobramycin. Amikacin resistance was suspected in two isolates and carbapenem-resistance in two others, but this could not be confirmed molecularly. This is considerably different from what has been seen in Japan in human isolates, where multidrug-resistant and carbapenemase-producing strains were recurrently found. Haenni et al. also reported 12 isolates from cattle in France in 2010 (124), which all belonged to nonhuman clones. In parallel, *P. aeruginosa* was recovered in 0.61% of the bovine isolates collected the same year through the Resapath network (www.resapath.anses.fr).

Isolates originated from mastitis and respiratory tract infections and were susceptible to the majority of antibiotics tested, except fosfomycin (9/12, 75%) and ticarcillin (3/12, 25%). Thus, these results confirm the low incidence of *P. aeruginosa* in bovine mastitis in both countries, suggest that clones circulating in animals differ from the ones isolated in humans, and prove their capacity to cause severe infections.

Chuanchuen et al. reported a molecular study of the MexXY efflux pumps in 18 *P. aeruginosa* isolates collected from bovine mastitis in Thailand (126). All of these field isolates presented decreased susceptibility to a variety of aminoglycosides, and three displayed an MIC to gentamicin higher than those of the PAO1 control strains. These decreased susceptibilities to aminoglycosides were partly attributed to overexpression of the MexXY efflux system but also to the presence of genes coding for aminoglycoside-modifying genes, such as *aph(3')-IIb* and *aac(6')-IIb*. Finally, two carbapenem-resistant isolates producing the VIM-2 enzyme were reported in Lebanon (56).

Antimicrobial Resistance in *Pseudomonas* spp. in Horses

P. aeruginosa is a rare pathogen in horses, sporadically causing skin or respiratory infections. It is more frequently associated with genital tract infections such as endometritis, which can lead to reduced fertility or even sterility. Horse-to-horse transmission is a potential source of transmission since nonpathogenic isolates may be incidentally introduced into the vagina of the mare during coitus (155). However, a wide variety of clones was identified in certain studies, suggesting transmission through contaminated material during artificial insemination or opportunistic growth of bacteria from environmental sources if conditions are favorable (156–158).

Only two limited studies from France and Brazil reported the antimicrobial susceptibility of *P. aeruginosa* isolates from horses (111, 124). No multiresistant isolates were reported in France among the 10 animals sampled, and only fosfomycin resistance was prevalent (6/10, 60%). Interestingly, two strains belonged to clones ST155 and ST27, which are associated with human outbreaks and sometimes display multiresistance phenotypes. In Brazil, only three animals were included in the study, and two out of the three *P. aeruginosa* isolates studied presented multiple resistances to fluoroquinolones and aminoglycosides.

The paucity of infections due to *P. aeruginosa* in horses may explain the lack of information on antimicrobial resistance in such isolates. However, the spread of resistance in all reservoirs (human, animal, and environmental) and the need for data on all potential niches will probably prompt scientists to explore this field.

CONCLUSION

A. baumannii and *P. aeruginosa* are two major nosocomial pathogens in humans, and increasingly resistant strains are being characterized all over the world. In contrast, they are more rarely found in animals, as is evidenced by the low number of publications in the veterinary field. However, when considering taking measures to avoid further spread of antimicrobial-resistant organisms or emergence of further resistance, the intersections of all the ecological domains must be explored. The crossroads of humans and animals is especially important—on the one hand for protection of professionals, as in the case of breeders and livestock farmers, and on the other hand, for physical proximity, adoption of pets in Europe being a growing phenomenon with 75 million pet-owing households. In this context, the emergence of multidrug-resistant bacteria from animals is worrisome: first, because the therapeutic options for animals are dramatically diminishing and, second, because the animal reservoir of multidrug-resistant bacteria is gaining in prevalence and complexity. The process contributing to such development is articulated, consisting of cross-contamination between human and animals, selective and coselective pressure by antimicrobial usage, and the spread of multidrug-resistant organisms in intensive breeding frameworks. Considering this context, studies dedicated to *Acinetobacter* spp. and *Pseudomonas* spp. on farms or generally in animal hosts are both limited in number and quite sparse in their geographical distribution, thus impeding the elaboration of a general picture of the modality of the spread of certain clones and the emergence of resistance mechanisms. Ideally, concerted investigations between human and veterinary clinics would provide useful keys to understanding such phenomena. To this end, global and vigilant surveys are priorities to preserve public health.

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