Chapter

Of Animal and Men: The Importance of Animal Environment to Antimicrobial Resistance: A One Health Approach

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Abstract

The contribution of the animal environments to the worsening of the global antimicrobial resistance framework is related to the use of antimicrobials in subtherapeutic doses and, for long periods, establishing ideal conditions for the circulation of resistance genes, which can be transmitted to pathogens adapted to the human microbiota. The study of the animal environment as conducive to the acceleration of resistance evolution is an emerging and critical area for understanding the development and dissemination of resistance genes among the circulating bacteria. The connection between people, animals, and the environment allows us to consider antimicrobial resistance in an approach within the "One Health" concept, which provides a global strategy for expanding collaboration and interdisciplinary communication. This chapter will highlight the emergence of colistin resistance, a great challenge in antimicrobial resistance field. Also, it will focus on some agents included in the priority list of superbugs of the World Health Organization (WHO) or correlated species already identified in veterinary medicine, such as the critical superbugs; priority level 1, Carbapenem-resistant *Acinetobacter baumannii*, Carbapenem-resistant *Pseudomonas aeruginosa*, and ESBL-producing Carbapenemic-resistant Enterobacteriaceae; and the high-priority, level 2, methicillin-resistant *Staphylococcus aureus* (MRSA).

Keywords: one health, *Staphylococcus pseudintermedius*, *Acinetobacter baumannii*, *mec*A gene, *mcr* genes, beta-lactamases

1. Introduction

Global antimicrobial resistance indices are the subject of concern once it has been predicted that nearly 10 million annual deaths will be attributable to resistant

pathogen infections by 2050 [1, 2]. The World Health Organization (WHO), the US Center for Disease Control and Prevention (CDC), and the European Center for Disease Prevention and Control (ECDC) classified the emergence and the spread of antimicrobial-resistant bacteria as one of the three major threats to public health in the twenty first century [3].

Importantly, the emergence of resistance is a natural evolutionary response to antimicrobial exposure. Over thousands of years, fungi and bacteria in the natural environment have developed complex mechanisms to prevent their destruction by toxic substances originating from the microbial competition, and these substances have made it possible to synthesize most antibiotics. Therefore, soils should be evaluated as potential reservoirs of antimicrobial-resistant bacteria and should be considered in assessing risk factors that contribute to the global spread of antimicrobial resistance. Moreover, the active collaboration of the human being in the propitiation of this emergency is undeniable due to the increased selection pressure, mainly given by the indiscriminate use of these drugs in human and veterinary medicine [4].

Antimicrobials not only kill sensitive and select resistant bacteria but also influence the mechanisms of genetic variation such as mutation, recombination, transposition, and gene exchange. Such phenomena can be observed from the soil to the intestinal microbiota of humans or animals exposed to antimicrobial underdosing, as the population of commensal microorganisms includes species that are naturally resistant to some antimicrobials. This selective pressure and subsequent imbalance due to the death of sensitive microorganisms allow bacteria with intrinsic or newly acquired resistance to survive and proliferate [5].

Despite this general understanding, the multifactorial origin of the current worldwide antimicrobial resistance scenario makes the picture complex and challenging to intervene. Although studies point to the hospital environment as the main reservoir for the resistance genes of bacteria that colonize and infect humans, the community environment indeed contributes to the establishment of a diverse set of resistance genes [3].

In 2012, Bhullar and colleagues [6] found multiresistant bacteria from an isolated cave microbiome over 4 million years ago in New Mexico, and some of the microorganisms were resistant to up to 14 commercial antibiotics. In another study, the ability of bacteria to use antibiotics as their sole carbon source was detected, making them a significant reservoir of antimicrobial resistance genes [7].

In this context, little is known about the contribution of animal production and veterinary hospital care environments in the maintenance of resistance genes and consequent resistance dissemination. The study of the contribution of various animal-related environments in accelerating the evolution of resistance is an emerging and critical area for understanding its development and as a model for the dissemination of resistance genes among the circulating bacteria. The connection between people, animals, and environment allows for the consideration of antimicrobial resistance within the One Health concept.

2. Distinct animal environment and its impact on antimicrobial resistance

2.1 The poultry production environment as a source of emerging colistin resistance

The increase in antibiotic resistance is now a global concern, including in food-producing animals. They can serve as a reservoir of antibiotic-resistant bacteria

and antibiotic resistance determinants that may be transferred to humans [8, 9]. The systematic use of antibiotics in food-producing animals has been increasing the selection pressure for antibiotic-resistant bacteria, especially in Enterobacteriales such as *Escherichia coli* [10]. Furthermore, the emergence of carbapenem-resistant bacteria worldwide and the increased use of polymyxins as "last-line" antibiotics to treat human infections may have contributed to the spread of its resistance [11, 12]. Due to its low price, colistin has been carried on for decades in the poultry industry, worsening this scenario. It is usually administered to the entire flock and mostly used for metaphylaxis and growth promotion in different countries [13].

2.1.1 The silent colistin transferable plasmid-mediated resistance dissemination

The chromosomal polymyxin resistance is most associated with the modification of the lipopolysaccharide (LPS) following the addition of 4-amino-4-deoxy-L-arabinose to lipid A. Modifications of Ara4N are regulated by two-component systems: PhoP/PhoQ, PmrA/PmrB, and MgrB regulator. Mutations in genes involved in the production of these systems may result in lower antibiotic fixation [14]. However, in 2015, a Chinese research group reported the emergence of a transferable plasmid-mediated resistance gene (mcr-1) from human, porcine, and poultry samples, shifting colistin resistance from a contained problem to a global issue [15]. After identification of mcr-1, full scientific attention led to the recognition of multiple mcr-1 variants [16–18] and eight additional mcr genes. Subsequently, the mcr-2 plasmid-mediated colistin resistance gene was detected from poultry, porcine, and bovine *E. coli* in Belgium [19]. A third mobile colistin resistance gene, mcr-3, has been reported in *E. coli*, *Aeromonas* spp., and *Salmonella* spp. isolates from human and animal samples in Asia and Europe [20]. The mcr-4 was detected in *Salmonella enterica* serovar Typhimurium and *E. coli* isolates from animal sources in Italy, Spain, and Belgium [21]. The mcr-5 was detected in poultry and poultry meat isolates of *S. enterica* serovar Paratyphi from porcine *E. coli* in Germany [22]. The sixth mobile colistin resistance gene, mcr-6, was detected in *Moraxella* sp. from porcine in the United Kingdom [23]. The mcr-7 gene was detected in *Klebsiella pneumoniae* in China [9], the mcr-8 gene in *K. pneumoniae* from porcine and human in China [24], and finally, the mcr-9 gene from human in the United States of America [25]. Despite all these reports, a retrospective analysis demonstrated that the mcr-1 gene had been circulating since the 1980s with the earliest isolates from poultry [26]. So, the plasmid-mediated colistin resistance had been around for about 35 years without being detected until 2015. The silent colistin resistance dissemination could partly be explained by the fact that China is by far the leading colistin producer and, at the same time, the largest consumer of its production [15].

Nevertheless, colistin is often added to feed at low doses and used as a growth promoter in different countries. This practice may be the leading cause of the high rate of colistin-resistant bacteria carrying the mcr genes isolated from food-producing animals compared with humans and accelerate the dissemination of mcr genes from animals to humans [15, 27]. Furthermore, the mcr genes may have originated from food-producing animals. The mcr-1 gene was associated with *ISApl1* insertion sequence element, which was first identified in the porcine pathogen *Actinobacillus pleuropneumoniae* [28], and finally, mcr-1-positive strains usually carry *floR* gene conferring resistance to florfenicol, a drug only used in veterinary medicine [10]. The mcr genes have also been found on diverse plasmid backbones (IncI2, IncHI2, IncX4, and pHNSHP45) with high in vitro transfer rates and often harbored together with other resistance determinants, such as β-lactamases [29]. The prevalence data on colistin resistance vary from different countries and continents. Data from two European AMR monitoring from 2014 to 2016 have reported low colistin

resistance rates for broilers and chicken meat in Nordic countries [29]. However, studies have shown moderate prevalence in turkey flocks, chicken and turkey meat in Germany [30] and Switzerland [31], and a high prevalence was found in Portugal [32]. In Asia, the prevalence of colistin resistance in poultry is higher than Europe. Different studies have been reported a remarkable increase in colistin resistance frequency in *E. coli* from porcine, poultry, and cattle in all geographic areas of China [33, 34].

2.1.2 Data on colistin resistance in Brazil

In 2015, Brazil overtook China as the world's second largest poultry producer. Nowadays, about 150 countries from all continents consume Brazilian broiler meat, according to the Brazilian Ministry of Agriculture Livestock and Farming [35]. It is noticeable that scientific and technological advancements have transformed poultry from rural farming to full-fledged industry in the last few decades. However, despite this significant expansion, the Brazilian poultry industry is still highly dependent on antibiotic prescription. Prevalence data on colistin resistance in poultry and broiler are overall scarce in South America, including Brazil, in particular, data regarding the plasmid-mediated resistance to colistin [36–38]. In 2016, a Brazilian research group developed a retrospective antimicrobial resistance study and screened 4.620 Enterobacteriales strains isolated from human, animal, food, and environmental samples for the presence of the *mcr*-1 gene. Samples were collected from 2000 to 2016. In this study, *mcr*-1 gene was detected in 16 *E. coli* strains from poultry and porcine isolated between 2012 and 2013. This surveillance showed evidence that *mcr*-1-harboring *E. coli* has been circulating in food-producing animals in Brazil since 2012 [36]. In 2017, the same research group detected the presence of *mcr*-1-harboring *E. coli* strains isolated from commercial chicken meat sold in markets in São Paulo, southeastern Brazil. Most *E. coli* strains exhibited an MDR phenotype and carried IncX4 plasmids, previously identified in human and animal isolates [38].

Furthermore, between 2015 and 2016, Pimenta [39] also detected a high prevalence of *mcr*-1-harboring *E. coli* from broilers and free-range layer hens in several poultry farms in Rio de Janeiro, southeastern Brazil. Most *E. coli* strains carried IncI2, FIB, and B/O plasmids. In November 2016, the MAPA banned the use of colistin as a feed additive for animal growth promotion purposes (regulatory instruction no. 45 [http://www.agricultura.gov.br/]), following the international recommendations of the World Health Organization. Despite this government action, in 2019, our group detected a high prevalence of the *mcr*-1 gene as the only resistance gene in *E. coli* strains isolated from broilers in several poultry farms in Rio de Janeiro (unpublished data). Data suggest that poultry is still an important reservoir to colistin resistance gene *mcr*-1. As poultry meat is an inexpensive source of protein, its impact on transferring resistance cannot be neglected. The overuse of antibiotics will promote the unrestricted expansion and circulation of drug-resistant strains among the human-animal environment. Therefore, continuous surveillance must be of great concern, improving prevalence data in both human and veterinary settings.

2.1.3 Colistin resistance genes in soils

Colistin, also known as polymyxin E, is produced by some strains of *Paenibacillus polymyxa*, a bacterium commonly found in soils associated with plant roots [40]. In some places around the world, the use of poultry litter is an ordinary measure to improve the physical, chemical, and biological properties of soils in

agricultural production. However, animal manure, such as poultry litter, a mixture of organic materials including feces, feed, and bedding, is a valuable nutrient-rich soil fertilizer also has been considered an important reservoir of antibiotic residues, antibiotic-resistant bacteria, and antibiotic resistance genes [41, 42]. The enhancement of the concentration and diversity of antibiotic resistance determinants in soils treated with this organic fertilizer is of concern, even considering that untreated soil environments harbor a natural source of both antibiotics and antibiotic resistance genes [43–46]. The colistin resistance *mcr*-1 gene was detected in all soil samples from intensive vegetable production that received poultry litter as organic fertilizer but also in native vegetation areas that comprise a legal reserve at a mountain region of Rio de Janeiro, Brazil, confirming the previous statement that even natural soil environments act as a reservoir of resistance determinant [47].

2.2 Animal production environmental impact on genetic markers mutations: a study of *mec*A gene of *Staphylococcus aureus* isolated from dairy system

Methicillin-resistant *Staphylococcus* (MRS) spp. are important human pathogens that are also a concern in veterinary medicine and animal agriculture. *Staphylococcus* species are present in a wide range of animal species, including dogs, cats, rabbits, horses, cattle, pigs, poultry, and exotic species, both in healthy carriers and as a cause of infection [48–50]. Besides the broad host range distribution and pathogenicity, its significant antimicrobial resistance levels are of great concern [51]. The high antimicrobial resistance level to beta-lactams favors treatment failures and its persistence in the environment. Bacterial resistance mechanisms to this antimicrobial class include a low-affinity penicillin-binding protein 2a (PBP2a) determined by the expression of *the mec*A gene [52]. The phenotypic methicillin-resistant expression does not depend only on the *mec*A gene. This expression is under a more complex control and is only beginning to be better understood since it is expressed in a peculiar and heterogeneous way [53]. Because of this phenotypic heterogeneity, detection of the *mec*A gene is considered the gold standard method for the confirmation of methicillin-resistant isolates by the Clinical Laboratory Institute [54, 55]. However, for samples of animal origin, this proposition is not reliable, since variants of the *mec* gene impair this detection [56, 50].

2.2.1 The mecC *homolog*

In 2011, the report of MRSA strains presenting unusual features in bovine milk samples from the United Kingdom led to the discovery of a novel *mec*A gene named *mec*ALGA251 [57]. This gene presented just 70% similarity at the nucleotide level to the classical *mec*A gene and could not be detected by routine PCR assays targeting the latter [57]. Shortly after its description, the *mec*ALGA251 was isolated from human clinical infections in the United Kingdom, Denmark, and Ireland [58]. It was renamed as *mec*C gene and has been reported from 13 European countries and have been isolated from 14 different host species [59]. Recently, Loncaric et al. [60] reported its occurrence in coagulase-negative staphylococci (CoNS) from various wild and domestic animals. The discovery of the *mecC* gene reinforced the idea of the circulation of gene variants in the animal production environment and the consequent emergence of new methicillin-resistant strains [61]. Until now, the detection of *the mec*C gene is a challenge, and even though there are several reports of *the mec*C gene in *Staphylococcus* species from humans and animals, the puzzling question is that they are all restricted to European countries. In Brazil, the presence of *mec*ALGA251 in the bovine isolates tested negative for *mec*A was investigated, but all isolates also tested negative for *the mec*ALGA251 [50].

2.2.2 A universal primer design experiment

Previous studies [62, 63] reported several phenotypic methicillin-resistant *Staphylococcus* spp. isolates not correlated with the presence of the *mec*A gene. Otherwise, Melo et al. [56] reported the discovery of a *mec*A gene variant from bovine samples containing mutations in the annealing region that does not allow detection of the gene with the already described primers. It was detected that the primer F's annealing site based on the human *S. aureus* mecA gene specified by Murakami et al. [64] presented punctual nucleotide differences that possibly impaired the annealing and amplification of *mec*A gene from the bovine strains. A two-set study was conducted to confirm this hypothesis. Firstly, original primers were synthesized based on the nucleotide sequences of the *mec*A gene of *Staphylococcus aureus* (HE681097). Those primers failed in amplifying the whole *mec*A gene segment in bovine strains. Instead, they did it successfully for human and equine *Staphylococcus* strains. Next, a second-step primer set was based on a sequence of *S. sciuri mec*A gene (AY820253) and only yielded *mec*A gene segments for bovine strains. The multiple alignments of *mec*A gene sequences from bovine, human, and equine origins revealed that bovine ones presented punctual but significant differences leading to the observed impairment of *mec*A gene detection in bovine strains. This divergence of *mec*A gene sequences is a specificity of bovine samples, probably due to some selective pressure in the dairy environment [56].

To validate the newly designed primers, a set of 107 strains was tested for the presence of the *mec*A gene and its bovine variant in *Staphylococcus* spp. isolates from dairy farms in Brazil and Turkey. Seventeen isolates tested positive for the *mec*A variant, nine from Turkey, and eight from Brazil [65]. Recently, a universal PCR primer set was developed and validated to ensure adequate detection of the *mec* genes (classical and variant) [50]. A set of 563 *Staphylococcus* spp. of different animal origins, from the United States of America, and 248 isolates from Brazil, was tested, and 220 (39.1%) were confirmed as MRS by amplification using a classical, variant, and universal primers. The classical *mec*A gene was detected in 201 isolates, being 177 *S. aureus*, whereas the variant *mec*A was detected in 14 isolates, being 2 *S. aureus* and 12 CoNS isolates. These results reinforce that the variant *mec*A is widespread in the animal environment. Surprisingly, a single strain of *S. xylosus* isolated from a porcine nasal swab carried both *mec* genes (classical and variant). The developed universal primer set successfully amplified *mec* genes in 205 isolates, even four isolates that did not amplify any classical or variant *mec*A using conventional primers. It presented sensitivity, specificity, positive predictive, and negative predictive values higher than 90%, comparing to the classical *mec* gene detection. Also, it presented a higher discriminatory power once four isolates just amplified *mec* genes using this primer set. This report is of high relevance once the development of tools to improve MRS diagnosis is crucial for its accurate and rapid identification. The dairy environment represents a considerable challenge in the emergence of new variants of beta-lactam resistance genes due to the frequent use of this antimicrobials class to prevent subclinical mastitis.

2.3 Companion animals environmental impact on antimicrobial resistance

Companion animals are part of human societies around the world [65]. In veterinary medicine clinical practice, diseases such as pyodermitis, external otitis, urinary tract, and respiratory infections are the most frequent causes for the implementation of antibiotic therapy in dogs and cats. Wide-spectrum antimicrobials also prescribed in human medicine are commonly used in these treatments, such as aminopenicillins with beta-lactamase inhibitors, cephalosporins, fluoroquinolones,

macrolides, aminoglycosides, and potentiated sulfonamides [66]. As a result, the extensive and indiscriminate use of such antimicrobials in companion animals, coupled with their proximity to humans, gives canine and feline species importance as sources of antimicrobial resistance spread [67]. In the last decade, the escalation of infectious conditions in the veterinary clinic of pet animals related to hitherto unknown or low prevalence agents such as *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex (Acb complex). Parallel to this, the advances in molecular biology applied to bacteriological diagnosis allowed the reclassification of pathogens, and to identify the sharing pathways to virulence and resistance genes between closely related species, as occurs with *Staphylococcus pseudintermedius*, a species reclassified from molecular studies, with some significant gene sharing with *Staphylococcus aureus*, the most recognized species of this genus, of significant importance in human medicine.

2.3.1 Acinetobacter calcoaceticus-Acinetobacter baumannii *complex (Acb complex): an emerging challenge in companion animal environment*

The *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex (Acb complex) is formed by highly genetically related Gram-negative bacteria, which makes species identification difficult through routine laboratory phenotypic methods [68]. The Acb complex comprises *Acinetobacter baumannii* and its close relatives, *A. calcoaceticus*, *A. dijkshoorniae*, *A. lactucae*, *A. nosocomialis*, *A. pittii*, and *A. seifertii* [69]. The clinically relevant species include *A. baumannii*, *A. pittii*, and *A. nosocomialis* [70]. Members of this complex have emerged as opportunistic pathogens causing infections in human and animal health facilities [71]. Infections include pneumonia, especially in ventilated patients; urinary tract infections, especially in patients with urinary catheters; and other infections associated with the use of intravascular catheters [72]. Infections caused by Acb complex agents are difficult to treat since these pathogens have intrinsic resistance to different classes of antimicrobials and also have the ability to acquire additional resistance genes [73]. Infections caused by representatives of the Acb complex has become a growing challenge in clinical routine, both human and animal, especially considering the multiresistant character of these pathogens. Further, there are currently few studies in the field of veterinary medicine that report the occurrence of the other species of this complex, besides *A. baumannii*, as well as the resistance profile.

The analyses developed by our research group have identified all three species of clinical relevance of Acb complex, with the prevalence of *A. pittii*, in samples of animal infectious processes, which has also presented multiresistant profiles. The identified multidrug-resistant isolates were mainly involved in urinary tract infections of dogs and cats, which confirm the real challenge in the veterinary clinical routine. These findings reinforce the need for proper investigation of these agents in the veterinary environment for the adoption of appropriate control and treatment measures. Carbapenemic antimicrobials constitute an excellent alternative for the treatment of infections caused by these pathogens. However, carbapenemases production is one of the biggest challenges in the healthcare system [74]. Agents of Acb complex have become resistant to carbapenems through different mechanisms, including the presence of metallo-beta-lactamases (class B) and the presence or overexpression of OXA (class D) carbapenemases, especially $bla_{\text{OXA-23}}$, $bla_{\text{OXA-24}}$, $bla_{\text{OXA-58}}$, and $bla_{\text{OXA-51}}$. Considering the species *A. baumannii*, the gene $bla_{\text{OXA-51}}$ codes for the intrinsic carbapenemase [73]. This additional resistance conferred by OXA-type carbapenemases is commonly grouped into resistance islands located in a region that favors insertion or deletion within the bacterial chromosome [75]. The ISAba1 insertion sequence located in the upstream region of the OXA genes, such as

bla$_{\text{OXA-23}}$, results in increased expression of this gene, observed by an increase in the minimal inhibitory concentration for carbapenems [76]. In addition to antimicrobial resistance, another factor that has favored the emergence of infections caused by species of the Acb complex is related to the biofilm formation capacity of these pathogens, which contributes to their survival in environmental conditions, favoring their persistence in hospital devices, and on different abiotic and biotic surfaces [77]. Biofilm-associated infections require higher doses of antibiotics, resulting in antimicrobial resistance, increased death, prolonged hospital stays, considerable economic loss, and loss of protection for patients [78].

2.3.2 Staphylococcus pseudintermedius*: an underestimated risk for animal and men*

Staphylococcus pseudintermedius was first described as *S. intermedius* [79] based on bacterial isolates from pigeons, dogs, minks, and horses. For decades, *S. intermedius* was considered the leading species of staphylococci associated with skin and soft tissue infections in dogs until it was demonstrated that *S. intermedius* was actually a heterogeneous group of bacteria [80]. Devriese et al. [80] described the *S. pseudintermedius* species through DNA hybridization and 16S rRNA gene sequencing. Subsequent studies evaluated the phenotypic and genotypic diversity in *S. intermedius* and differentiated it into four distinct species: *S. intermedius*, *S. pseudintermedius*, *S. delphini*, and *S. cornubiensis* which are together referred to as the *Staphylococcus intermedius* group (SIG) [81–83]. Since then, *S. pseudintermedius* has been recognized as the common cause of skin infections in dogs, and it has been proposed that all canine isolates should be termed *S. pseudintermedius* unless genotypic typing methods reveal otherwise [84]. This coagulase-positive staphylococci (CoPS) is commensal to the skin and mucosa of healthy dogs, including hair follicles, conjunctival sacs, nares, oral cavity, and perianal region [85]. It is an opportunistic pathogen, capable of causing disease when the natural resistance of the host is suppressed or when the skin barrier is changed [81]. Atopic dermatitis, medical or surgical procedures, and immunosuppressive diseases are examples of predisposing factors to infection [81]. This pathogen is the leading cause of skin and ear infections but may also cause infection in other tissues and cavities and may be transmitted in the community or hospital setting [48, 81, 85]. Besides being the leading cause of canine pyoderma, *S. pseudintermedius* is also frequently isolated from samples of urinary tract infections and may be a complicating factor in immunomodulatory-responsive lymphocytic-plasmacytic pododermatitis [81].

Although dogs are the natural hosts, *S. pseudintermedius* can colonize and infect other animal species, mainly cats [86, 87]. *Staphylococcus pseudintermedius* and *S. aureus* are the species of CoPS that may be composed of the commensal skin microbiota in cats, but there is no consensus in the veterinary literature as to which is dominant and geographic factors should be considered [88]. In these animals, *S. pseudintermedius* can cause tissue infections, rhinitis, nephritis, pneumonia, urinary tract infections, and septicemia [87, 89, 90]. Since the first report of human infection by *S. pseudintermedius* [86], infections have been reported occasionally and are often directly related to close contact with a dog [81]. Pet owners with *S. pseudintermedius* infections and veterinarians are more likely to be nasally colonized by this agent than other individuals [91–93]. *S. pseudintermedius* infections associated with dog bite wounds and post-mastoidectomy, onycholysis, otitis externa, sinusitis, bacteremia, hospital acquired pneumonia, and brain abscess procedures have been described in humans [94–102].

2.3.2.1 Is methicillin-resistant Staphylococcus pseudintermedius *(MRSP) the novel MRSA?*

Two cases of methicillin-resistant *S. pseudintermedius* (MRSP) infection have been described in patients with sinusitis, and in one case, at first, *S. pseudintermedius* was misidentified as MRSA [102, 103], suggesting that there may be an underreporting of cases due to the misidentification of the agent. Twenty-four cases of human infections caused by *S. pseudintermedius* were reported in Canada, most of them associated with skin and soft tissue infections, and in three of them, the strain involved was multidrug-resistant [104]. Human MRSP infections in patients without any contact with dogs suggest that humans may eventually be colonized by MRSP [104, 105] and that human-to-human transmission may occur [81]. These reports highlight the importance of *S. pseudintermedius* as a potential emerging pathogen of zoonotic origin and the need for further studies to understand the transmission to humans and to recognize this epidemiological phenomenon.

The relevance of *S. pseudintermedius* as a pathogen is also related to its antimicrobial resistance potential [48]. The inappropriate prescription and use of the same drugs in humans and animals provide a selection of multidrug-resistant (MDR) isolates and consequently compromise the treatment efficacy [106]. Beta-lactam antibiotics are often the first choice of treatment for *Staphylococcus*-associated infections [107], and methicillin-resistant staphylococci (MRS) are an increasing concern. The emergence of MRSP worldwide has become a major problem for small animal veterinary medicine [108] and the infections caused by this agent, a challenge. This resistance is mainly due to two distinct mechanisms: the production of the beta-lactamase enzyme, encoded by the *bla*Z gene, and the production of the additional low-affinity penicillin-binding protein (PBP2a), which is encoded by the *mec*A gene and regulated by *mec*I and *mec*RI genes. PBP2a determines oxacillin/methicillin resistance due to its reduced affinity for beta-lactams and can carry out transpeptidation reactions when normal PBPs are blocked by the drug, allowing peptidoglycan synthesis and conferring resistance to all antimicrobials of the beta-lactam class [109].

The *mec*A gene is located in a mobile genetic element called staphylococcal cassette chromosome (SCC*mec*) chromosomal cassette, which can be transferred via plasmid, transposons, or mobile genetic elements and integrate into the bacterial genome [110, 111]. The *mec* cassette is made up of two main components: the *mec* complex, composed of the IS43 pathogenicity island, the *mec*A gene, and its *mec*I and *mec*RI regulators, and by the *ccr* complex that encodes the chromosome cassette recombinases, which are responsible for the correct excision and consequent integration of this element into the staphylococcal chromosome [112].

The *mec* cassette may carry other genetic elements such as Tn554, pUB110, and pT181, which encode resistance to other classes of antimicrobials. For example, the erm genes, which are responsible for constitutively expressed or induced cross-resistance to macrolides, lincosamides, and streptogramin B (MLSB), are located in Tn554, present in SCC*mec* types II and III [113, 114]. Horizontal transfer of the *mec*A gene into staphylococci and the genetic elements inserted into the SCC*mec* thus resulted in the worldwide spread of oxacillin/methicillin and MDR clones, making it an additional difficulty to control infections caused by these agents [113]. MDR is often observed in MRSP strains [115–117], which also constitute a reservoir of resistance genes for other staphylococci [108] and represents a major problem as the distribution and prevalence of these organisms in animal clinical specimens are relatively unknown, as well as the presence and circulation of genes such as *mec*A and its potential for propagation in companion animals.

2.3.2.2 Staphylococcus pseudintermedius*: genetic diversity and clonal distribution*

In addition to the challenges of identifying *S. pseudintermedius*, there is a need for standardized typing methods that support an epidemiological investigation and monitoring of MRSP [81]. Different techniques have been employed to characterize and determine the genetic diversity among MRSP strains. Pulsed field gel electrophoresis (PFGE), *spa* gene typing, multilocus sequence typing (MLST), and SCC*mec* cassette typing are commonly used. Despite a considerable number of studies seek to understand the population dynamics of *S. pseudintermedius* worldwide, little is known about the clonal distribution patterns of MRSP strains from Africa and South America [118].

In Brazil, the prevalence of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) as a cause of infectious diseases in companion animals remains unknown. A recent study, developed by Motta [119] provides an overview of the prevalence and characterization of multidrug-resistant MRSP strains from canine and feline clinical samples in Rio de Janeiro. A significative occurrence of multidrug resistance (MDR) in MRSP strains from Brazilian canine and feline clinical was revealed: all MRSP strains analyzed were resistant to seven different antimicrobial classes: fluoroquinolones, phenicols, macrolides, aminoglycosides, aminoglycosides, lincosamides, and tetracyclines. Among these strains, four closely related *spa* types were detected, with predominance of t02. Two clones were identified by the PFGE technique and four closely related strains (groups III and X). MLST typing revealed the presence of three STs/CCs (ST/CC71, ST265/CC258 and ST282/CC45) never reported previously in MRSP strains derived from canine and feline clinical samples from Brazil, with predominance of the worldwide disseminated ST/CC71-*spa*t02-SCC*mec*II-III strain. Comparative analysis of the typing methods used revealed the importance of combining techniques for a broader understanding of the genetic diversity of MRSP. The report highlights the need for further studies to determine the prevalence and characteristics of MRSP from Brazil, supporting preventive and control measures to overcome the antimicrobial resistance.

2.4 β-Lactamase-producing Gram-negative bacteria in a one health approach

Most Enterobacteria pathogens associated with human enteric illness originate from animals and can be transmitted directly to humans or indirectly through animal origin food, contaminated water, or a common reservoir [120]. Currently, β-lactamase-producing strains have been recovered from urban environments, companion/production animals, and animal source foods, which indicate a possible route of dissemination in different ecosystems.

To better understand these links and to identify control measures to reduce the bacterial resistant infections in humans and animals, a One Health approach is needed [121, 122]. The application of a global concept of cross-linking data will improve the prevention, prediction, and control of zoonotic diseases [123, 124].

Undoubtedly, the mobilization of resistance genes through plasmids, transposons, and integrons is intimately linked with widespread of β-lactamases, facilitating the exchange of genetic elements among various bacteria species that can later colonize different hosts and ecosystems and can be spread by different routes [125].

The detection of ESBLs in bacterial isolates of animal origin, such as *Acinetobacter baumannii*, has raised concern regarding the transmission of ESBL genes between human and animal [126]. Also, *E. coli* strains carrying AmpC-β-lactamases have already been reported in healthy and sick animals and food-producing animals [127, 128]. AmpC-hyperproducing *E. coli* was detected in dairy

herds in Brazil in 2019. Since there was no previous report of these AMR bacteria in dairy cattle, it was not possible to compare the mutation positions. Nevertheless, many of the positions observed in *E. coli* from beef cattle, broiler, and meat had already been described for human samples. These findings demonstrate a possible transmission route for these bacteria in the food chain and its dissemination through the environment [129].

ESBL or plasmidial AmpC-β-lactamase producers are also frequently resistant to aminoglycosides and fluoroquinolones. The rate of resistance to these antibiotics among *E. coli* isolates of animal origin has been increasingly reported, and the impact of animal-derived broad-spectrum-β-lactamase-producing Gram-negative bacteria on public health has drawing considerable attention worldwide [127].

2.4.1 β-Lactamases resistance in Gram-negative bacteria

The most common mechanism of resistance to beta-lactam antibiotics in Gram-negative bacteria is the production of hydrolytic enzymes of antimicrobial agents, including extended-spectrum beta-lactamases (ESBLs) [130]. Two systems of classifying this array of enzymes are in use: the Bush-Jacoby-Medeiros activity-based system [131] and the Ambler system [132] based on nucleotide and amino acid sequence information [133]. The resistance to beta-lactamase inhibitors characterizes the group I (Ambler class C) beta-lactamases (also known as AmpC enzymes). AmpC is mostly found on chromosomes, and its production is inducible. Group 2 (Ambler Class A) beta-lactamases could easily be transmitted into different bacterial cells once plasmids carry them. This group comprises the largest number of characterized enzymes divided into subgroup 2b hydrolyzing penicillins and cephalosporins and its variation 2be (known as "ESBL"). ESBL present a broad spectrum of various antimicrobials as ceftazidime, cefotaxime, and aztreonam. Clavulanic acid exerts potent inhibition towards them. Group 3 (Ambler Class B) enzymes are metalloenzymes capable of destroying carbapenems. Finally, group 4 beta-lactamases contain those unusual penicillinases not inhibited by clavulanic acid, and four of these enzymes exhibit high rates of hydrolysis with carbenicillin or cloxacillin [134].

The spread of extended-spectrum β-lactamase-producing Gram-negative bacteria has dramatically increased worldwide regarding as one of the most important public health threats. Therefore, their appropriate classification and epidemiological data on the main enzymes disseminated in humans, animals, and the environment are of utmost importance.

2.4.2 An historical approach

The first plasmid-mediated beta-lactamase in Gram-negative bacteria was reported in Greece in the 1960s. At the end of the 1970s, most *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) strains contained ampicillin hydrolyzing β-lactamases mediated by plasmid (TEM-1, TEM-2, and SHV-1). They could be eliminated using third-generation cephalosporins [135]. The emergence of *K. pneumoniae* strains to harbor a gene encoding β-lactamase that hydrolyzes the extended-spectrum cephalosporins was firstly reported by a study from Germany in 1983. Further, in 1986, *K. pneumoniae* strains resistant to the third-generation cephalosporins were detected in France [136, 137]. This resistance was attributed to a new β-lactamase gene, closely related to TEM-1 and TEM-2, and these newly detected enzymes capable of hydrolyzing extended-spectrum beta-lactam antibiotics were named extended-spectrum β-lactamases (ESBLs) [138]. In 1989, a new ESBL family member not belonging to either the TEM or SHV types was reported:

CTX-M type. Its origin has been confirmed to be completely different from that of TEM or SHV ESBL [139]. Nowadays, more than 600 ESBL has been described, the majority belonging to the CTX-M families and TEM-1/2, SHV-1 β-lactamases mutants [140].

2.4.3 The CTX-M-type β-lactamase resistance dissemination

The CTX-M-type β-lactamases can be further differentiated into at least six sub-lineages or groups, namely, CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, CTX-M-25, and KLUC [141]. The impressive worldwide spread of CTX-M-producing Gram-negative bacteria turned them to be considered the primary ESBL producers associated with community-acquired infections. The CTX-M family is described as predominant in South America, as well as in Spain and Eastern Europe [142]. Therefore, according to the increasing number of reports describing these enzymes in Brazil, it appears that CTX-M variants are also prevalent in the country compared to TEM and SHV enzymes, prevalent in North America and Western Europe, respectively [143]. In Brazil, CTX-M has been reported in several states; CTX-M-2, CTX-M-8, and CTX-M-9 subtypes are the most prevalent in human samples. In animal production species such as poultry, swine, cattle, and horses, the prevalent enzymes are CTX-M-2, CTX-M-8, and CTX-M-15 [144]. Unfortunately, there are no nationwide surveillance programs on bacterial resistance and its mechanisms, making it difficult to estimate the proportion of ESBL producers [141].

2.4.4 The AmpC-type β-lactamases

Another enzyme group of the β-lactamases type is AmpC. They are relevant enzymes produced constitutively or induced by chromosomal or plasmidial genes expressed by members of Enterobacterales and other Gram-negative bacteria. This class of β-lactamases belongs to the functional groups 1 and C of the Bush and Ambler's classification, respectively [129]. They are often overlooked because they are not within groups 2b or 2b, as CTX-M, TEM, and SHV. AmpC producers hydrolyze almost all β-lactam antibiotics, including cephalosporins, cephamycins, and penicillins, solely or associated with B -lactamase inhibitors, limiting therapeutic options to treat infections caused by these resistant bacteria.

Of major concern is the hyperproduction of this enzyme in *E. coli*. This phenomenon is caused by spontaneous mutations that produce deregulation of *ampC* and is responsible for resistance to first-, second-, and third-generation cephalosporins and to extended-spectrum beta-lactamase inhibitors [145]. Also, some mutations can induce the appearance of an extended-spectrum AmpC (ESAC) that can hydrolyze fourth-generation cephalosporins and carbapenems. Once carbapenems are the choice therapy for Enterobacteria-producing extended-spectrum beta-lactamase infections, the detection of *ampC* production and its control represent an even big challenge.

2.4.5 The carbapenemases

The carbapenem resistance is related to the production of β-lactamases with versatile hydrolytic capacities. Currently, the most important type of class A carbapenemases are KPC enzymes, whereas VIM, IMP, and (particularly) NDM in class B and OXA-48 (and related) in class D are the more relevant enzymes. Most carbapenemases are plasmid-mediated (with genes frequently located in integrons), favoring its dissemination [146]. Since carbapenemase-producing Gram-negative bacteria generally also contain gene coding for other beta-lactam

resistance mechanisms, it is not uncommon for organisms to exhibit complex beta-lactam resistance phenotypes. Besides, these organisms often contain other genes that confer resistance to quinolones, aminoglycosides, tetracyclines, sulfonamides, and other families of antimicrobial agents that cause multidrug resistance (AMR) or even pan-resistance. The emergence of new variants and the prevalence of β-lactamases in isolates of community, environmental, and animal origin has demonstrated the complexity of establishing the origin of resistance.

2.4.6 Challenges in detecting the prevalence of β-lactamases

The incidence of large-scale beta-lactamase-producing organisms' spectrum is difficult to determine. There are significant differences between the detection and interpretation methods used by countries and health institutions throughout the study [147]. Considerable phenotypic confirmatory tests for ESBL (2be and 2b) producers have been described in the literature, and all methods utilize the characteristics of ESBL production inhibition by clavulanic acid.

The Clinical and Laboratory Standard Institute (CLSI) recommended test consists of an initial screening by disk diffusion or by the broth dilution method with ceftazidime, ceftriaxone, cefotaxime, cefpodoxime, and aztreonam followed by a phenotypic confirmatory test with cefotaxime and ceftazidime in the presence and absence of clavulanate [54]. The European Antimicrobial Susceptibility Testing Committee (EUCAST) [148] also recommends these tests, but both documents preconize different disk concentrations, and there are also differences in susceptibility zone sizes for consideration of resistance patterns. These factors lead to difficult interlaboratory standardization and consequently to the correct definition of local, regional, and national epidemiological data.

Specifically, regarding AmpC, the Clinical and Laboratory Standards Institute (CLSI) offers no standard test to detect AmpC producer isolates. There are few antimicrobial agents safely effective against these isolates, and many of them are not available or even not approved for animal use. Although different detection methods are available, the lack of international standardization limits the reporting of AmpC by clinical laboratories, which may underestimate this important mechanism of antimicrobial resistance [149].

3. Conclusions

Different environments related to animal production and clinical care can act as a source of the emergence of resistance genes. Studies developed over two decades show that there are relevant peculiarities that must be considered in the detection and understanding of emerging resistance in animal environments to achieve a systemic and practical approach to control antimicrobial resistance worldwide. This chapter discussed some current challenges, the importance of the poultry production environment in the significant emergence of colistin resistance, the development of a universal primer that made it possible to detect a variant of the *mec*A gene in *Staphylococcus aureus* from the dairy environment, and the emergence of *Acinetobacter baumannii-Acinetobacter calcoaceticus* complex and methicillin-resistant *Staphylococcus pseudintermedius* considering companion animals. Finally, the significant dissemination of the resistance mechanism is determined by the production of different classes of beta-lactamases in Gram-negative bacteria in human and animals environments. These concepts allow considering antimicrobial resistance in a One Health approach, which provides a global strategy for expanding collaboration and interdisciplinary communication.

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