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Review

Antimicrobial resistance of *Staphylococcus* spp. in swine farming: a challenge for one health

Resistência antimicrobiana de *Staphylococcus* spp. na suinocultura: desafio para a saúde única

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A B S T R A C T

The inadequate and excessive use of antimicrobial agents in pig farming has contributed to the emergence and increase of resistance to antibiotics in both bacteria related to infectious processes in these animals as those that constitute their own microbiota. This conduct also causes the dissemination of these microorganisms throughout the pig production chain, causing damages to health of consumers of their meat and processed-meat products. The effect of excess use of these medicines can even reach and compromise other ecosystems. Methicillin-resistant *Staphylococcus* (MRS) stands out among bacterium species of interest to the public health. They emerged as important zoonotic pathogens, whose evolution generated different virulence and mechanisms of resistance to antimicrobial agents and has been associated to high use of these medicines in pig farming. The development of resistance to antibiotics in *Staphylococcus* spp., especially the expression of the gene *mec*A, and their interrelation with pig farming are aspects considered in this work. The emergence and global presence of MRS in pig farming denote the important epidemiological involvement of these animal species in the dissemination of these microorganisms, and the occurrence of infections in humans and animals in the whole world. This is a scenario that requires attention by public health agencies and should not be overlooked.

Palavras-chave:
*mec*A
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Suínos

R E S U M O

O uso inadequado e excessivo de agentes antimicrobianos na suinocultura tem contribuído para o surgimento e aumento da resistência a antibióticos, seja para as bactérias relacionadas aos processos infecciosos nesses animais, como para as que compõem a sua própria microbiota. Essa conduta também causa a disseminação desses microrganismos por toda a cadeia produtiva de suínos, causando danos à saúde dos consumidores de suas carnes e derivados. O efeito do uso excessivo desses medicamentos pode até atingir e comprometer outros ecossistemas. O *Staphylococcus* resistente à meticilina (MRS) se destaca entre as espécies de bactérias de interesse para a saúde pública. Surgiram como importantes patógenos zoonóticos, cuja evolução gerou diferentes virulências e mecanismos de resistência a agentes antimicrobianos e tem sido associada ao alto uso desses medicamentos na suinocultura. O desenvolvimento de resistência a antibióticos em *Staphylococcus* spp., principalmente a expressão do gene *mec*A, e sua inter-relação com a suinocultura são aspectos considerados neste trabalho. O surgimento e a presença global da MRS na suinocultura denotam o importante envolvimento epidemiológico dessa espécie animal na disseminação desses microrganismos e a ocorrência de infecções em humanos e animais em todo o mundo. Este é um cenário que requer atenção das agências de saúde pública e não deve ser esquecido.

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INTRODUCTION

Changes in animal-origin food production have required high use of antimicrobial agents to maintain the health of animals or increase their yield. However, this excessive use has favored the increase of global Antimicrobial Resistance (AMR), which is a great threat to human and animal health, denoting dangers to modern human and veterinary medicines, and hinders the food and environmental safety (MOREL, 2019; REGITANO; LEAL, 2010).

Pig farming stands out among the food production chains that use antimicrobial agents inadequately or abusively (AGUILAR *et al.*, 2015; BARCELLOS *et al.*, 2009; SANTOS *et al.*, 2009).

The excess use of these medicines can be exemplified by the case of *Staphylococcus* spp., whose evolution generated different mechanisms of resistance to antibiotics has enabling the emergence of multiresistant strains. This fact has been related to their colonization in pigs and the increasing use of antibiotics in these animals (BUTAYE; ARGUDÍN; SMITH, 2016).

The present work discusses the use of antimicrobial agents in pig farming and the emergence of the *mec* determinant as the main resistance mechanism of *Staphylococcus* spp. and its transmissibility between these animals and humans.

PIG FARMING AND USE OF ANTIBIOTICS

Pig farming is changing from extensive systems to more intensive managements of production because of the need for increasing yield (SEAB, 2013; USDA, 2015). As a consequence, there is a higher contact between animals in this production system, which contributes to an increase in occurrence and dissemination of infectious diseases and also increases the stress level of the animals, affecting negatively the defense mechanisms of their immune system (BARCELLOS *et al.*, 2009).

Several strategies have been used to minimize the risks of the intensive production systems, including: medication programs and rigorous norms for cleaning, disinfection, and sanitary void between the lots, and the use of antimicrobial agents (AGUILAR *et al.*, 2015; BARCELLOS *et al.*, 2009; SANTOS *et al.*, 2009).

Most pig farms use antimicrobial agents throughout the development of the animal until the slaughter, which is not limited only to the infection therapeutics in these animals. The prophylactic use to control diseases and promote the growth of animals increases the use of these medicines, which are also been adopted to the detriment of basic hygiene norms and conducts (COMPASSION IN WORLD FARMING, 2011; FDA, 2018; FERREIRA, 2014).

Global data estimated that the consumption of antimicrobial agents for animal production in 2013 was above 131,000 Mg, with an increase of 50% for 2030 (VAN BOECKEL *et al.*, 2017). These data show the high use of these medicines, which became essential for intensive production systems. This use can reach 60% to 80 % of the total antimicrobial agents used in the United Kingdom (UK), some countries of the European Union (EU), and in the United States (USA) (AGUILAR *et al.*, 2015; BARCELLOS *et al.*, 2009; SANTOS *et al.*, 2009).

The high use of these medicines in pig farming generates a high selection pressure, favoring the emergence and increase of resistance to antibiotics in microorganisms involved with infectious diseases in these animals and also in their own microbiota (BARTLETT; GILBERT; SPELLBERG, 2013; DARWISH *et al.*, 2013; MARSHALL; LEVY, 2011; VAN BOECKEL *et al.*, 2015).

The inadequate use of these medicines also has consequences to the environment, since 90.0% of antimicrobial agents administered to animals are eliminated by urine and feces, and the dispersion of these products can compromise some ecosystems (MOREL, 2019; REGITANO; LEAL, 2010).

Another consequence of the inadequate use of antimicrobial agents in swine farming is their effects on the health of humans that consume the meat or processed-meat products from this animal species. These effects can be due to: a) possible presence of antibiotic residues that can trigger allergic reactions or other diseases, which can even cause death; and b) presence of resistant bacteria in the food (DARWISH *et al.*, 2013; RAKOTOHARINOME *et al.*, 2014; REGITANO; LEAL, 2010; SERI, 2013).

Restrictions in the use of these medicines started to be considered in England, a pioneer country that developed regulations in the 1960's to avoid the consequences of inadequate or excessive application of antimicrobial agents in livestock. According to the Swann Report, the English government recommended that antibiotics used for both human and veterinary therapeutics should no longer be used as growth promoters (KIRCHHELLE, 2018a).

This directive was followed by other countries until January 2008, when the EU made the prohibition of this additive official by the regulation CE Nº 1831/2003 (HUYGHEBAERT; DUCATELLE; IMMERSEEL, 2011; NÉVOA *et al.*, 2013; NOSCHANG *et al.*, 2017). Since then, consumer and producing countries have been advancing and moving back on regulations for the use of antimicrobial agents in animal production (KIRCHHELLE, 2018b).

In addition to some individual initiatives, the increasing reports of resistance to antibiotics in the world made the World Health Organization (WHO) to implement a global task force in 2015, involving the Food and Agriculture Organization (FAO), World Organization for Animal Health (OIE), and United Nations (UN), to gather data on

the consumption and the impact of use of antimicrobial agents, and to define and assist the execution of strategies to contain the advance of resistance to antibiotics in the whole world (FAO, 2016; OIE, 2019; WHO, 2015; WHO, 2017).

The use of antimicrobial agents as prophylactics and growth promoter in Brazil is not prohibited. However, the Brazilian Ministry of Agriculture and Livestock and Supply (MAPA), considering the history of international concerns (OMS, FAO, Codex Alimentarius) about the increasing resistance to antimicrobial agents, vetoed the use of several of these substances as additive for performance improvement in animals used for food production (BRASIL, 2018; CARDOSO, 2019).

Table 1 presents the main Brazilian regulations related to the prohibition of use of antimicrobial agents in animal production.

Table 1. Regulations of the Brazilian Ministry of Agriculture and Livestock and Supply (MAPA) that regulate the use of antimicrobial agents in animals.

Year	Regulation	Antimicrobial	Prohibition of use
1998	OC 047/1998	Avoparcin	Feed additive
2003	IN 09/2003	Chloramphenicol and Nitrofurans	Veterinary Use
2004	IN 11/2004	Olaquindox	Growth Promoter
2005	IN 35/2005	Carbadox	Feed additive
2007	IN 34/2007	Gentian Violet	Feed additive
2009	IN 26/2009	Amphenols, tetracyclines, β-lactams (penicillins and cephalosporins), quinolones and systemic sulfonamides	Growth Promoter and Food preservative
2012	IN 14/2012	Spiramycin and erythromycin	Growth Promoter
2016	IN 45/2016	Colistin	Growth Promoter
2018	Ordinance 171/2018	Tylosin, lincomycin, virginiamycin, bacitracin and tiamulin	Growth Promoter

Source: adapted from Cardoso (2019).

The main antibiotics used in the therapeutics of food animals, including pig, are: tetracycline, penicillin, fluoroquinolone, streptomycin, erythromycin, nystatin, tyrosine, virginiamycin, and sulfonamides; some of which are also used for treatments of infections in humans. Therefore, the presence of multiresistant bacteria can hinder the efficacy of therapeutics of infectious diseases either in humans or in animals (COMPASSION IN WORLD FARMING, 2011; FDA, 2018) .

There are reports of dissemination of several resistant microorganisms throughout the pig meat production cycle. Among these microorganisms, some stand out by their high morbidity, multiresistance, and involvement in outbreaks, including *Staphylococcus aureus*, *Enterococcus* spp., *Escherichia coli*, and *Salmonella* spp., which cause infections in humans and in animals (HAMMERUM *et al.*, 2014; OLIVEIRA *et al.*, 2011; SFACIOTTE *et al.*, 2015).

Staphylococcus spp.

The genus *Staphylococcus* has 54 species and 28 subspecies described as Gram-positive coccus, non-mobile, with diameters of 0.5 the 1.5 μm, and producers of the catalase enzyme, which tend to form clusters similar to grape bunches (PARTE, 2018; SCHLEIFER; BELL, 2015).

These ubiquitous microorganisms are predominantly isolated from the skin, glands of skin, and mucous membranes of mammals and birds, in their mouth, mammary glands, and intestinal, genitourinary, and respiratory tracts (LINHARES *et al.*, 2015; PROCOP *et al.*, 2017; SANTOS *et al.*, 2007; SCHLEIFER; BELL, 2015).

The capacity or lack of capacity of producing the coagulase enzyme divides species of this genus, respectively, into *Staphylococcus* coagulase positive (SCP) and *Staphylococcus* coagulase negative (SCN) (HENNEKINNE *et al.*, 2010; PROCOP *et al.*, 2017).

The multiplicity of diseases that SCP and SCN can cause goes from simple superficial skin infections to deep and serious invasive infections, such as pneumonia, osteomyelitis, meningitis, septicemia, and endocarditis in humans; and dermatitis, external otitis, urinary infections, and mastitis in animals (BARTLETT; HULTEN, 2010; FONTANA; FAVARO, 2018; MARSILIO; DI FRANCESCO; DI MARTINO, 2018).

Among SCP species, *Staphylococcus aureus* is the most important and prevalent in several human and animal infections; its pathogenicity is related to several virulence factors produced by it, which are constituted by different proteins of cellular link, enzymes, toxins, and mechanisms of escape from the immune response of the host (AL-MEBAIRIK *et al.*, 2016; BARTLETT; HULTEN, 2010; COSTA *et al.*, 2013; FOSTER; GEOGHEGAN, 2015; PROCOP *et al.*, 2017; SANTOS *et al.*, 2007).

The *S. aureus* has a high epidemiologic importance; in the last years, SCN species has drawn the attention of public health agents by presenting high resistance to antibiotics. The SCN are important reservoirs of

resistance genes that can be transferred and integrated to the *S. aureus* genome and can cause serious infections in humans (BECKER; HEILMANN; PETERS, 2014; TULINSKI *et al.*, 2012; VANDERHAEGHEN *et al.*, 2012).

In addition to the several virulence factors that *S. aureus* can express, it shows a high versatility for emergence of different determinants of resistance to antibiotics. This capacity has challenging the empirical treatment and control of *Staphylococcus* infections (FOSTER, 2017; MARQUES *et al.*, 2008; RATTI; SOUSA, 2009).

Methicillin-resistant *Staphylococcus* spp.

The emergence of successive mechanisms of resistance in *Staphylococcus* spp. to different classes of antimicrobial agents have been seen in genetic changes due to mutations or horizontal transference of genes contained in mobile accessory genetic elements, such as plasmids, transposons, and pathogenicity genomic islands (JENSEN; LYON, 2009; MUNITA; ARIAS, 2016; PARTRIDGE *et al.*, 2018).

The antibiotic resistance developed by *Staphylococcus* spp. to several antimicrobial agents used in therapeutics is expressed by different biochemical mechanisms and involves several genes that can codify a phenotype of resistance to a specific medicine. This diversity has been found in strains of *Staphylococcus* spp. of animal and human origin. In addition, some genes of resistance can be shared between animals and humans (ARGUDIN *et al.*, 2017; KADLEC *et al.*, 2012; REYGAERT, 2013; WENDLANDT *et al.*, 2013).

The different biochemical resistance mechanisms of these microorganisms to antibiotics and the profile of some related genes are presented in Table 2.

Table 2. Main mechanisms of acquired resistance to antimicrobials observed in *Staphylococcus* spp. strains.

Mechanism	Affected Antimicrobial Class (examples of genes involved)
Enzymatic Inactivation	Beta-lactams (*bla*Z), Aminoglycosides (*aac*A-*aph*D) and Phenicols (*cat*); Lincosamides (*Inu*A; *Inu*B)
Active Efflux of Antibiotics	Macrolides (*msrA*), Tetracyclines (*tet*K; *tet*L), Lincosamides (*Isa*B), Phenicols (*fex*A), Quinolones (*nor*A)
Antibiotic Binding Site Change (Target)	Beta-lactams (*mec*A; *mec*C), Glycopeptides (*van*A), Macrolides (*erm*A, *ermB*, *erm*C), Quinolones (*gyr*A; *grl*A); Phenicols (*cfr*)

Source: adapted from Blair *et al.* (2019); Munita; Arias (2016); Reygaert *et al.* (2013).

Staphylococcus spp. strains have overcoming even the most promising antibiotics by using one of these mechanisms or their combination, regardless of the chemical class of the antibiotic (DWEBA; ZISHIRI; EL ZOWALATY, 2019; FOSTER, 2017; REYGAERT, 2013).

The evolution of *Staphylococcus* spp. for resistance to antibiotics emerged with the use of sulfonamides in the late 1930's and, currently, adapted strains are maintaining resistant to new different antibiotics used in therapeutics for infections caused by these microorganisms (ADALETI *et al.*, 2010; RINCÓN *et al.*, 2014; SANTOS *et al.*, 2007; VELÁZQUEZ-GUADARRAMA *et al.*, 2010).

Resistance to beta-lactam antibiotics is among the mechanisms of antimicrobial resistance that species of this genus can have, and became the most studied (HAMILTON *et al.*, 2017; LAKHUNDI; ZHANG; 2018; PEACOCK; PATERSON, 2015).

The beta-lactam antibiotics are bactericidal antimicrobial agents, represented by penicillin, penicillin combined with inhibitors of beta-lactamase enzymes, semisynthetic penicillin, and cephalosporins (PLATA; ROSATO; WEGRZYN, 2009). These compounds bind to proteins present in the bacterial cell membrane known as penicillin-binding proteins (PBPs), which have enzymatic functions involved with the establishment of cross-links between the peptidoglycan molecules, resulting in the synthesis of the bacterium wall. Thus, these medicines prevent these bindings and activate the function of autolysins enzymes, breaking the cell wall and leading to the death of the bacterium (FOSTER, 2017; PLATA; ROSATO; WEGRZYN, 2009; RATTI; SOUSA, 2009).

Resistance to penicillin G by *S. aureus* strains emerged in 1944 because of the production of penicillinases or beta-lactamases enzymes, which hydrolyze the beta-lactam ring of this medicine inactivating the penicillin (COHEN, 1986). In the late 1950's, the percentage of resistant *S. aureus* strains to this antimicrobial that were isolated in the hospital environments reached 80% (LYON; SKURRAY, 1987).

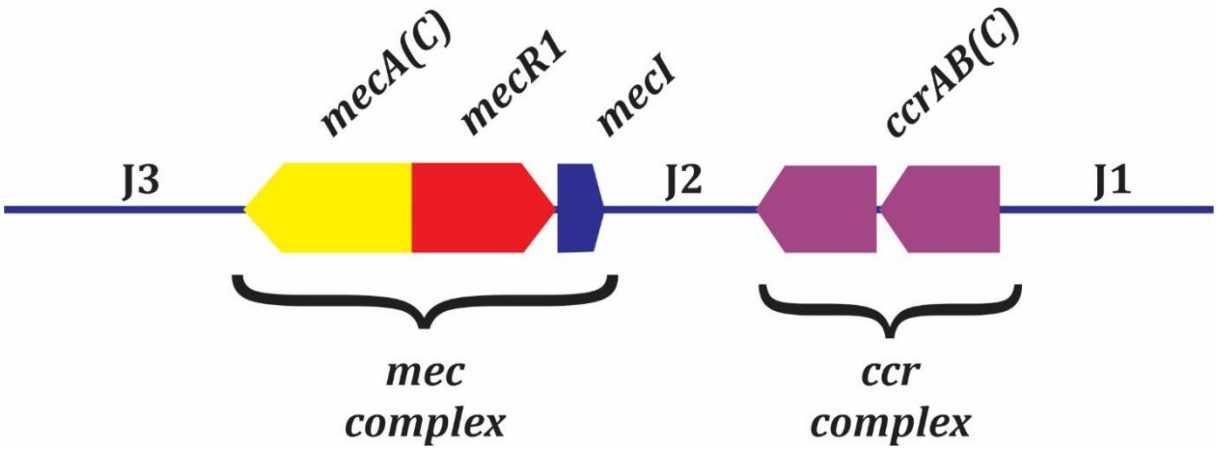
Penicillins resistant to beta-lactamases were produced in the 1960's to solve this problem; this was a new group of beta-lactam semisynthetic antibiotics that include oxacillin and the methicillin (FRENCH, 2010). However, the first resistant *S. aureus* strains to methicillin emerged after only one year of using these antimicrobials; they were termed methicillin-resistant *Staphylococcus aureus* (MRSA) (JEVONS, 1961; LAKHUNDI; ZHANG; 2018).

The resistance to oxacillin is determined by a mobile genetic element termed Staphylococcal cassette chromosome *mec* (SCC*mec*), which has the *mec*A gene—responsible for the resistance to beta-lactam antibiotics (HIRAMATSU *et al.*, 2013).

This phenotype of resistance is found in *Staphylococcus* spp. by the codification of a new target protein termed PBP2a or PBP2', which presents low affinity for most penicillins and cephalosporins (GELATTI *et al.*, 2009; HARTMAN; TOMASZ, 1984; UBUKATA; YAMASHITA; KONNO, 1985). This mechanism compromises the use of different beta-lactam antibiotics in therapeutics for infections, including fifth generation cephalosporins (ceftobiprole and ceftaroline) in vivo and in vitro (CHAMBERS; DELEO, 2010; CHAN *et al.*, 2015; GELATTI *et al.,* 2009; HAMILTON *et al.,* 2017; HODILLE *et al.,* 2017; MORONI *et al.,* 2018; PLATA; ROSATO; WEGRZYN, 2009).

The insertion of SCC*mec* in the chromosome of methicillin-sensitive *Staphylococcus aureus* (MSSA) strains is the key event for the emergence of MRSA. SCC*mec is* a mobile genetic element that is highly diverse in its structural organization and genetic content; three regions are used for its classification: a) *mec* complex, which includes the *mec*A gene and can include the regulatory genes *mec*I and *mec*R1, which are involved with the expression of *mec*A gene; and can include the sequence IS*431*; b) *ccr* complex, which can include the *ccr*AB *or ccr*C genes, which codify recombinase enzymes that control integration and excision in the genome that will host the SCC*mec*; thus, they are responsible for the mobility of the *mec* determinant; c) J regions (J1, J2, and J3), which consist of non-essential elements to SCC*mec*, but, in some cases, they have carried additional determinants of resistance to antibiotics. SCC*mec* is integrated to a specific site (*attBscc*) located near the origin of replication of *S. aureus* (EL-HAMID, 2016; HIRAMATSU *et al.,* 2013; TURLEJ; HRYNIEWICZ; EMPEL, 2011). Figure 1 shows the basic structure of SCC*mec*.

Figure 1. Overall structure of Staphylococcal cassette chromosome *mec* (SCC*mec*). SCC*mec* has three main regions: 1 = *mec* complex (including *mec*A or *mec*C gene, and the regulatory genes *mec*R1 and *mec*I involved with the expression of resistance to semisynthetic beta-lactam antibiotics); 2 = *ccr* complex (including genes involved with the excision and integration of SCC*mec* in the genome of *Staphylococcus* spp.); 3 = J regions (sites that can contain additional genetic determinants of resistance).



Source: adapted from Hiramatsu *et al.* (2014).

SCC*mec* is widely distributed in methicillin-resistant non-*S.aureus* staphylococci (MRNAS). This group includes other SCP and SCN species. In short, SCN species that have SCC*mec* are termed methicillin-resistant coagulase negative staphylococci (MRCoNS) (BOURGUIGNON *et al.,* 2016; SABER *et al.,* 2017; SAPUTRA *et al*., 2017; VELÁZQUEZ-GUADARRAMA *et al.,* 2017).

Genetic and molecular studies have shown that the origin of SCC*mec* and the transference of this determinant of resistance to the genome of *S. aureus* strains are related to SCN species. The presence and homology of nucleotide sequences of the *mec*A gene and homologs genes (*mec*A1, *mec*A2) in genomes of *Staphylococcus fleurettii, Staphylococcus sciuri*, *and Staphylococcus vitulinus* support these evidences and indicate that these species are related to the SCC*mec* evolution (BECKER; HEILMANN; PETERS, 2014; ROLO *et al.,* 2017; SABER *et al.,* 2017;).

The structural and genic differences of SCC*mec* have been analyzed in MRSA and MRCoNS strains, showing diverse nucleotide sequences and the identification of more than 80 SCC*mec* determinants (EL-HAMID, 2016; MARTÍNEZ-MELÉNDEZ *et al.*, 2015; SABER *et al.*, 2017; VANDERHAEGHEN *et al.*, 2012). The variations found have been used for the classification of the *mec* determinant into types and subtypes; currently, 13 types have been described (BAIG *et al.*, 2018; CARRETTO; VISIELLO; NARDINI, 2018; LAKHUNDI; ZHANGA, 2018; WU *et al.*, 2015).

Some SCC*mec* types (I - V) are present worldwide, and others appear to be only in strains occurring in their original location (BECKER; HEILMANN; PETERS, 2014;

BUTAYE; ARGUDÍN; SMITH, 2016; EL-HAMID, 2016; SABER *et al.*, 2017).

SCC*mec* types I, II, and III are frequently described in MRSA strains associated to hospital infections—hospital-associated methicillin resistant *Staphylococcus aureus* (HA-MRSA).

They present a *mec* determinant of relatively large size (34.3 to 66.9 Kb) and carry several markers of resistance to antibiotics. MRSA containing SCC*mec* types IV and V are characteristic of strains that emerged in the community and are termed community-associated methicillin resistant *Staphylococcus aureus* (CA-MRSA); these strains have a *mec* determinant of smaller size (20.9 to 28 Kb) and commonly do not have genes that codify resistance to other non-beta-lactam antimicrobial agents; thus, these MRSA are sensitive to most antimicrobial agents belonging to other classes (DEURENBERG *et al.*, 2007; LAKHUNDI; ZHANG, 2018).

HA-MRSA strains emerged in hospitals in the 1960's, and the CA-MRSA strains started to be described in the 1980's. These MRSA were spread in hospital environments and in communities around the world. The coexistence of these microorganisms in these ecosystems and their overcoming of ecological barriers have been reported, with infections or colonization in pets and production animals (BARBER, 1961; CHAMBERS, 1988; EVANGELISTA; OLIVEIRA, 2015; FIGUEIREDO; FERREIRA, 2014; KAYSER; MAK, 1972; KLEIN *et al.*, 2013).

The first report of MRSA strains causing infections in animals was described in cases of bovine mastitis in Belgium (DEVRIESE; VAN DAMME; FAMEREE, 1972). Since then, sporadic reports and outbreaks affecting pets and production animals, such as horses, birds, pigs, dogs, and cats, have been reported around the world (CUNY *et al.*, 2010; FITZGERALD, 2012; PRICE *et al.*, 2012). The presence of HA-MRSA or CA-MRSA in raw or processed meat foods has also been reported, denoting the dissemination potential of these microorganisms (AIRES-DE-SOUSA, 2017; COSTA *et al.*, 2015).

MRSA strains from animals but capable of colonize humans are termed livestock-associated methicillin resistant *Staphylococcus aureus* (LA-MRSA); they have drawn attention since 2005 due to concerns regarding public health, especially the MRSA strains termed LA-MRSA ST398 (FITZGERALD, 2012; PEETERS *et al.*, 2015; PETON; LE LOIR, 2014). This MRSA clone emerged in pigs and has been described colonizing or causing infections in humans, production animals (bovine, birds, and equines), pets (dogs and cats), and wild species in different countries, denoting its high-dissemination potential (BUTAYE; ARGUDÍN; SMITH, 2016; LAKHUNDI; ZHANG, 2018; LIMA *et al.*, 2017; PEETERS *et al.*, 2015; SMITH, 2015).

García-Álvarez *et al.* (2011) found MRSA strains in bovine milk, in which the presence of the *mec*A gene was not confirmed by polymerase chain reaction (PCR), which is commonly used for identification of MRSA of different origins; or by agglutination tests for PBP2a. After further analysis, García-Álvarez *et al.* (2011) found differences in nucleotide sequences of the *mec*A gene in the strains and characterized a new *mec*A gene homologous to that widely known, which they termed *mec*A_{LGA251} and lately was termed *mec*C. The diversity found in the SCC*mec* determinant of this microorganisms allowed its classification as SCC*mec* type XI by Ito *et al.* (2012), who described the presence of the genetic determinant *mec*C in *S. aureus* strains isolated from human specimens.

The identification of MRSA strains that have the *mec*C gene is a challenge, since they can be mistakenly classified as sensitive or borderline depending on the technic used for their identification, and can present resistant to cefoxitin while being sensitive to oxacillin (PATERSON; HARRISON; HOLMES, 2014).

Strains that have the *mec*C gene has similar high dissemination potential to strains with *mec*A gene and have also been described for isolates obtained from humans, production and wild animals, wastewaters, waters of sewage treatment stations. The *mec*C gene can also be present in MRCoNS strains (BECKER; HEILMANN; PETERS, 2014; PETERSEN *et al.*, 2013; PORRERO *et al.*, 2014).

Staphylococcus epidermidis and *Staphylococcus haemolyticus* are the most common MRCoNS species isolated from humans in clinical cases; however, the diversity of species reported is higher when their sources are animals or food (AGOSTINIS; MELLO; MARTINS, 2012; BECKER; HEILMANN; PETERS, 2014; FONTANA; FAVARO, 2018; NUNES *et al.*, 2016).

Pigs have been reported as significant reservoirs of MRSA and MRNAS strains, which have drawn attention of researchers that seek a better understanding of epidemiological aspects involving their transmissibility to humans and animals and development of resistance to antibiotics in these microorganisms (BUTAYE; ARGUDÍN; SMITH, 2016; NORMANNO *et al.*, 2015; SMITH *et al.*, 2013; SOUZA *et al.*, 2012; VERKADE; KLUYTMANS, 2014).

Staphylococcus spp. IN PIG FARMING

The *Staphylococcus* species that are most frequently isolated from pigs at all ages are *S. aureus*, *S. hyicus*, *S. epidermidis*, *S. chromogenes*, *S. sciuri*, *S. warneri*, and *Staphylococcus xylosus* (FRANA, 2012; PROCOP *et al.*, 2017; SANTOS *et al.*, 2007; SCHLEIFER; BELL, 2015).

The involvement of *S. aureus* in diseases that affect these animals is not common; however, the presence of these microorganisms have been described for the following diseases: abscesses, arthritis, enteritis, mastitis, metritis, neonatal septicemia, vaginitis, osteomyelitis, and endocarditis (FRANA *et al.*, 2013; HERMANS *et al.*, 2010;

LINHARES *et al.*, 2015; PROCOP *et al.*, 2017; SANTOS *et al.*, 2007; SCHLEIFER; BELL, 2015).

Staphylococcus spp. are present in all pig production processes until the slaughter and the final consumer. Microbiological analysis from nasal mucus, skin, tonsils, feces, and internal organs of apparently healthy pigs at slaughter showed presence of *S. aureus*, denoting the importance of this animal species as a reservoir of these microorganisms (FRANA *et al.*, 2013; HERMANS *et al.*, 2010; O'SULLIVAN *et al.*, 2011; SCHLEIFER; BELL, 2015; TENHAGEN *et al.*, 2009).

The presence of *Staphylococcus* spp. in pigs has not been limited to the colonization of these animals. Changes in production systems from open pastures and low animal density to a more dense and intensive system made the animal environment also a reservoir of *Staphylococcus* spp. The animals in a production system can have contact with the same surfaces; thus, water drinkers, feeders, and the air and dust deposited in their environment become sources of contagion for all animals and handlers. The formation of bioaerosols causes risks of secondary exposition, which can lead to contaminations outside the production site (BARCELLOS *et al.*, 2009; DAVIS *et al.*, 2018; FELD *et al.*, 2018).

The direct contact of handlers with animals that carry *Staphylococcus* spp. is also an important form of transmission of these microorganisms from pigs to humans, exposing them to the colonization of microorganisms and possible infections. These handlers are in a high-risk class, with frequency of contamination of 15% to 37.8%, which is higher than that for workers of slaughterhouses, who have less contact with the animals and are trained for good hygiene practices while handling food (CUI *et al.*, 2009; MASSON; FERREIRA; CARVALHO, 2012; PARISI *et al.*, 2019; SCHMIDT; KOCK; EHLERS, 2015; SMITH *et al.*, 2013).

However, the origin of *S. aureus* is not associated exclusively with pigs or to their environments of growth and slaughter, or to handlers of these animals, but also to handlers that assist in the production and processing of meat products. Persistent or intermittent nasal colonization by *S. aureus* have been found in 30% to 50% of healthy individuals (SERGELIDIS; ANGELIDIS, 2017; CASTRO *et al.*, 2016; SEZER *et al.*, 2015; COSTA *et al.*, 2015; FERREIRA *et al.*, 2014; KLUYTMANS, 2010).

The presence of *S. aureus* in raw or processed pig meat and the contamination of these bacteria between food handlers and these foods have been described in the literature (BUYUKCANGAZ *et al.*, 2013; CASTRO *et al.*, 2016; CHON; SUNG; KHAN, 2017; COSTA *et al.*, 2015; FALL *et al.*, 2012; SEZER *et al.*, 2015).

The importance of investigating *S. aureus* strains in animal production, including pigs, denotes the hygienic-sanitary quality of production systems and the potential of these strains to of staphylococcal enterotoxins. These superantigens are involved with staphylococcal food intoxication, which is one of the diseases transmitted by food that presents high occurrence worldwide. The production of staphylococcal enterotoxins increases the pathogenic potential of these bacteria (DIEDRICH *et al.*, 2013; FERREIRA *et al.*, 2014; HENNEKINNE *et al.*, 2010; KLUYTMANS, 2010; SERGELIDIS; ANGELIDIS, 2017)

Therefore, considering the production chain of pig meat and the involved animals, environments, handlers, workers, and equipment and utensils, there are several different sources of contamination and transmission of *Staphylococcus* spp., which denotes the importance of this animal production for public health (DWEBA; ZISHIRI; EL ZOWALATY, 2019; FERGUSON *et al.*, 2016; MASSON; FERREIRA; CARVALHO, 2012; VAN CLEEF *et al,.* 2010).

Before the recognition of pigs and other production animals as reservoirs of MRSA strains, little interest was perceived for researches about *S. aureus* in these animals (LINHARES *et al.*, 2015; PANTOSTI, 2012). This is evidenced by the many works that researched only the presence of MRSA strains in these animals (LASSOK; TENHAGEN, 2013; PANTOSTI, 2012; SUN *et al.*, 2015).

Pigs have been described as the most important reservoir and ecosystem for the development of resistance *S. aureus* strains to antimicrobial agents (BUTAYE; ARGUDÍN; SMITH, 2016). Price *et al.* (2012) showed that the LA-MRSA ST398 developed from a clone of human MSSA that colonized pigs and acquired the genetic determinant SCC*mec*. The origin and transmissibility of SCC*mec* for *S. aureus* involve the MRCoNS, whose presence in pigs is also widely reported (BECKER; HEILMANN; PETERS, 2014; TULINSKI *et al.*, 2012).

The presence of the clone LA-MRSA ST 398 in Brazil was first reported in cows with mastitis (SILVA *et al.*, 2014). Its occurrence in pigs was first described in a case of exudative epidermitis in the state of Rio Grande do Sul, and the strain already presented an intermediate resistance to the glycopeptide vancomycin (MORENO *et al.*, 2016).

The first description of this microorganism in humans involved a patient with cystic fibrosis, whose infection probably occurred after a visit to a rural propriety, where the patient had recreational contact with animals of that environment (LIMA *et al.*, 2017). However, André Neto *et al.* (2017) described nasal colonization by strains of the clone MRSA ST398 in six children, which presented no apparent risk factor—did not live in rural environments or had contact with animals. This result denotes the potential of this MRSA, which emerged in pigs, to disseminate and overcome ecological barriers.

Currently, the frequency of MRSA strains that belong to the clone LA-MRSA ST398 in Brazil appears to be low, and no reports of strains containing the *mec*C gene are found. However, a recent study on the use of antimicrobial agents in 25 pig production systems and

on detection of MRSA strains showed the presence of these microorganisms in 80% of the systems evaluated, with 68.0% of pigs hosting LA-MRSA ST398 strains (DUTRA, 2017).

Therefore, the evident high capacity of dissemination and genomic plasticity for the development of different mechanisms of resistance to antibiotics make essential the oversight of multiresistant strains of *Staphylococcus* spp.; and these researches should involve pets and wild and production animals, and the whole food production chain for human consumption, with especial attention to pig farming.

CONCLUSIONS

The emergence and wide dispersion of methicillin-resistant *Staphylococcus aureus* and methicillin-resistant non *aureus Staphylococci* because of inadequate use of antimicrobial agents in pig farming denote the epidemiological involvement of this animal species with the transmission of these microorganisms and occurrence of infections in humans and animals all around the world.

The risk of dissemination of these microorganisms is particularly high in countries where legislation, regulatory oversight, and monitoring systems for the use of antimicrobial agents and prevention and control of antimicrobial resistance are weak or inadequate. Brazil fits this profile; thus, the public health policies involving actions that generate a careful and responsible use of antibiotics are essential for the preservation of the efficacy of these medicines and to support the One Health approach.

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