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Gram-positive bacterial resistant strains of interest in animal and public health

Resistência bacteriana em gram positivos de interesse em saúde animal e pública

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Abstract

Among multiresistant Gram-positive microorganisms, stands out methicillin-resistant *Staphylococcus* (MRS), an opportunistic pathogen associated with hospital acquired and community infections reported in medicine and large increase in reports of veterinary medicine. In veterinary medicine, numerous reports regarding several species of animals have been described. MRS is intrinsically resistant to all β-lactam drugs. In veterinary medicine, numerous reports regarding several species of animals have been described, but *Staphylococcus aureus* with intermediate resistance and resistant to vancomycin (VISA/VRSA) has not yet been reported in veterinary medicine, still need further study. *Staphylococcus* spp. are also related to antimicrobial resistance of macrolides, lincosamides, and streptogramin B (MLSB) group, that has the same mechanism of action, although the drugs belong to different classes. In veterinary medicine, clindamycin (lincosamide class) is widely used for skin infections, wounds, bone infections, pneumonia, infections of the oral cavity, and infections caused by anaerobic bacteria, besides being used for treatments of MRS infections. *Enterococcus* is another resistant Gram-positive microorganism, from which vancomycin-resistant enterococci (VREs) are the most important strains. There are several reports of VREs in veterinary medicine due the use of a similar antimicrobial (avoparcin) in livestock; therefore this group of microorganisms has now acquired great prominence since vancomycin is considered as the last resort for the treatment of MRS and *Enterococcus* associated with nosocomial infections in humans. The biggest problem these microorganisms and their resistance mechanisms cause is related to its huge impact on public health due to the increasing close contact between animals and humans. The objective of this review was to identify the main Gram-positive microorganisms associated with animals, describing their mechanisms of action that lead to antimicrobial resistance, as well as their impact on public health through their zoonotic and anthropozoonotic potential.
Key words: MRS, VISA, VRSA, VRE, MLSb

Resumo

Dentre os micro-organismos gram positivos multirresistentes destacam-se, principalmente os *Staphylococcus* spp. meticilina resistente (MRS), patógenos considerados oportunistas e relacionados

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tanto a infecções hospitalares como infecções comunitárias, tendo inúmeros relatos na medicina e um grande aumento de relatos na medicina veterinária, em diversas espécies de animais. MRS são intrinsicamente resistentes a todas as drogas beta-lactâmicas. Os *Staphylococcus aureus* com resistência intermediária e os resistentes à vancomicina (VISA/VRSA) ainda não foram reportados em animais, porém são necessários estudos mais aprofundados. Os *Staphylococcus* spp. também estão relacionados com resistência aos antimicrobianos do grupo dos Macrolídeos, Lincosamidas e Streptogramineas B (MLSb), que apesar de serem de classes diferentes, possuem o mesmo mecanismo de ação. Na medicina veterinária, a clindamicina (antimicrobiano da classe da Lincosamida) é amplamente utilizada para tratamentos de infecções de pele, feridas, infecções ósseas, pneumonia, infecção da cavidade oral e infecções causadas por bactérias anaeróbicas, além de ser utilizada em infecções causadas por MRS. Outro gênero de micro-organismos gram positivos resistente é o *Enterococcus*, sendo os *Enterococcus* vancomicina resistente (VRE) os de maior importância. Após vários relatos de VRE na medicina veterinária, devido ao grande uso de um antimicrobiano análogo (avoparcina) na produção animal, esse grupo de micro-organismo passou a ter grande destaque, uma vez que a vancomicina é considerada o último recurso para o tratamento de MRS e de *Enterococcus* associados a infecções hospitalares em humanos, as quais já foram também isoladas cepas resistentes. O maior problema destes micro-organismos e seus mecanismos de resistência na medicina veterinária está relacionado ao seu impacto na saúde publica, devido ao contato cada vez mais próximo entre animais e o homem. Com isso, o objetivo dessa revisão foi apontar os principais micro-organismos gram positivos encontrados na medicina veterinária descrevendo seus mecanismos de ação que levam a resistência aos antimicrobianos, assim como o impacto na saúde publica através do seu potencial zoonótico e também antropozoonótico.
Palavras-chave: MRS, VISA, VRSA, VRE, MLSb

Introduction

Antimicrobial resistance is characterized by a set of conditions in which a microorganism can survive even when exposed to a drug having antimicrobial activity. According to the World Health Organization (WHO, 2009), antibiotic resistance refers to the resistance of a microorganism to an antimicrobial drug, to which it was originally sensitive. Wannmacher (2004) defined multiresistant strains as strains of microorganisms that are able to multiply even after the use of therapeutic doses or higher concentrations of antimicrobials.

The development of resistant strains is a natural phenomenon that occurs when microorganisms are exposed to antimicrobial drugs and is an intrinsic characteristic of the microorganism to ensure its survival in unfavorable environments. In 1941, after the introduction of penicillin in medicine, Abraham and Chain identified the first strains resistant to this drug that produced an enzyme capable of degrading penicillin called penicillinase (UMBER; BENDER, 2009). With the introduction of new antimicrobial drugs in clinical practice, the emergence of resistant strains was observed. Initially, the rate of development of new drugs by the pharmaceutical industry and antimicrobial use were extremely high, and new drugs were readily released upon detection of resistant strains. However, slowdown in the development of new drugs associated with the emergence of multidrug-resistant strains has brought the clinical microbiology to a critical level, where only few sensitive drugs are available. Slower development of new drugs and the emergence of multidrug resistant strains makes the control and treatment of various infections, especially hospital acquired infections, extremely difficult (SHEA, 2003; FERNANDES, 2006).

Epidemiological knowledge about the main Gram-positive pathogens are well understood. Since the last 2 decades, there has been no change in the concerned species, but the major problem has been the increased antimicrobial resistance developed by these pathogens (WOODFORD; LIVERMORE, 2009). In a hospital setting, the most common reported examples of Gram-positive bacteria are *Staphylococcus* (especially *S. aureus*) and *Enterococcus*, as described in Table 1, but other

bacterial genera are also implicated (ÁLVAREZ-LERMA et al., 2007). There is a wide variation in the pattern of susceptibility of these agents, and this resistance can be extended to multiple antimicrobials (MUÑOZ BELLIDO, 2008).

To control the spread of resistant bacteria some strategies must be implemented such as the following: education of health professionals (including veterinarians), isolation of infected patients, microbiological cultures for surveillance, use of personal protective equipment (PPE), hand hygiene, disinfecting surfaces, and restrictions on the use of antimicrobials (OLIVEIRA; SILVA, 2008).

Table 1. List of multidrug-resistant Gram-positive bacteria that are of importance in public health and antimicrobial resistance related to their identification.

Bacterial strain	Related antimicrobial resistance
MRS - Methicillin-resistant *Staphylococcus* spp. or **ORS** - Oxacillin-resistant *Staphylococcus* spp.	Oxacillin
VISA - *Staphylococcus aureus* with intermediate resistance to vancomycin, also called **GISA** (refers to the class of glycopeptides)	Vancomycin (intermediate resistance)
VRSA - Vancomycin-resistant *Staphylococcus aureus*, also called **GRSA**	Vancomycin
VRE - Vancomycin-resistant *Enterococcus*	Vancomycin
MLSB - Macrolides, lincosamides, and streptogramin B (MLSB) resistance in *Staphylococcus* spp.	Erythromycin, clindamycin, and streptogramin B

In recent times, the relationship between the owners and their pets (mainly dogs, cats, and horses) has changed dramatically. Today, the physical contact between humans and these animals is much closer than before as these pets have gained the status of family members in many homes (BLOUIN, 2008). Due to this close contact and the indiscriminate use of antimicrobials in both, veterinary medicine and medicine, pets might become a potential source for the diffusion of the resistance to human, and also this might lead to the interspecies transmission of multidrug-resistant bacteria (MOYAERT et al., 2006; UMBER; BENDER, 2009), as described in table 2.

Table 2. Prevalence of multiresistant Gram-positive bacteria in animals with significance in public health.

Study population	Microorganism	Prevalence	Country	Reference
Veterinarians	MRSP	5.3%	USA	Morris et al. (2010)
Healthy dogs	MRSP	0.8%	Germany	Ruscher et al. (2009)
Healthy cats	MRSP	0.1%	Germany	Ruscher et al. (2009)
Healthy horses	MRSP	0.1%	Germany	Ruscher et al. (2009)
Dogs with pyoderma	MRSP	66%	Japan	Kawakami et al. (2010)
Dogs with pyoderma	MRSP	66%	Japan	Kawakami et al. (2010)
People in contact with dogs and cats with MRSP infections	MRSP	33%	Netherlands	Van Duijkeren et al. (2011)
Healthy dogs	MRSP	2%	Italy	De Lucia et al. (2011)
Healthy dogs People in contact with dogs	MRSA MRSA MRSP	0.44% 1.44% 0.48%	Brazil	Pinto (2012)
Dogs with conjunctivitis	MRS	38.89%	Brazil	Sfaciotte (2014)
Wounds of pets	MRS	29.63%	Brazil	Bordin et al. (2015)

In most countries, national monitoring programs of antimicrobial resistance usually do not analyze the data for pets (dogs and cats) (RANTALA et al., 2004), but recently, interest in the study of antimicrobial resistance in animals has increased due to the emergence of multidrug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) in small animals, as shown by Bordin et al (2015), where 16 strains of MRS were found in wound samples of small animals.

Thus, this review aimed to discuss the main multiresistant Gram-positive microorganisms found in veterinary medicine, as well as their mechanisms of action and impact on public health.

Methicillin-resistant Staphylococcus (MRS)

In recent decades, the emergence of multidrug resistant microorganisms has been observed, among which MRS, including MRSA and MRSP, are prominent. These lineages though are not commonly reported in animals, except for few reports of MRSP. However, in recent years, there has been an increase in the number of reports of these infections in domestic animals.

Staphylococcal resistance to β-lactam drugs is mainly due to two distinct mechanisms. The first mechanism is the production of extracellular β-lactamase enzyme, encoded by *bla*Z gene usually plasmid may be chromosomal, characterizing constitutive resistance or regulated by the presence of the drug, using two adjacent genes, *bla*I, transcriptional repressor of *bla*Z and *bla*R1, anti-repressor (LOWY, 2003). The second mechanism is the production of PBP2a or PBP2' (additional penicillin binding protein), a low-affinity penicillin binding protein encoded by the *mec*A gene (CASTELLANO-GONZALEZ et al., 2009). The PBP2a acts as a transpeptidase resuming the functions of cell wall synthesis when the other PBPs are inhibited, ensuring the integrity of the bacterial cell in the presence of β-lactam agents (HIRAMATSU et al., 2002). Hiramatsu (2001) identified the *mec*R1 gene with repressor activity and the *mec*I gene with anti-repressor activity on the *mec*A gene. The expression of *mecA* gene is constitutive and is induced by β-lactam drugs such as oxacillin and cefoxitin (LOWY, 2003).

The *mec*A gene is inserted into the chromosome by a mobile genetic element, called staphylococcal cassette chromosome mec (SCC*mec*) (ENRIGHT, 2003). The SCC*mec* is composed of several essential genetic elements such as, the *mec* complex comprising the *IS431* pathogenicity island, *mec*A and their *mec*I and *mec*R1 regulatory genes, and *ccr* complex (*Cassete Chromossome Recombinases*), characterized by the presence of encoding recombinase genes. In all the types of SCC*mec*, the sequence of *mec*A gene is highly conserved in *Staphylococcus aureus* (currently represented by the group CoPS - *coagulase-positive staphylococci*) and *coagulase-negative staphylococcus* (CNS) (WELLER, 1999; MA et al., 2002). There are 13 types and some subtypes of SCC*mec* gene (DESCLOUX et al., 2008; BLACK et al., 2009; IWG-SCC, 2009). Analysis of the presence/ or absence of this gene serves as an indication, and thus helps in choosing the best antimicrobial therapy (FERREIRA et al., 2003).

Some methods are available for the detection of MRS; these include the traditional methods that are recommended by the Clinical Laboratory Standards Institute (CLSI, 2008) and European Committee and Antimicrobial Susceptibility Testing (EUCAST), such as: a) disk diffusion test with oxacillin and cefoxitin in Mueller Hinton agar (MH); b) Minimum Inhibitory Concentration (MIC), and c) the use of the oxacillin agar screen. A new method for detecting MRS, already accepted by the CLSI is the use of E-test strips, has an advantage of providing the value of MIC directly. Despite the traditional techniques, the most accepted method for detecting MRS is polymerase chain reaction (PCR), a rapid and sensitive method that is considered the "gold

standard" and is capable of detecting a single copy of the gene (OLIVEIRA; LENCASTRE, 2002; SCHISSLER et al., 2009).

MRSA is generally considered as hospital acquired pathogen (HA-MRSA); however, it was first observed in 1990s in healthy patients in the community (VANDENESCH et al., 2003). The first case of a community associated MRSA (CA-MRSA) was reported in 1993 in Australia in local indigenous populations (UDO et al., 1993). In 2002, CA-MRSA caught attention in the United States after the outbreaks of skin infections in the athletes of Los Angeles (CDC, 2003). In Brazil, the first cultures isolated in Porto Alegre city, identified as CA-MRSA, were similar to the clones reported in Australia (RIBEIRO et al., 2005). Subsequently, a study revealed the presence of similar clones isolated from Rio de Janeiro State, Southeast Brazil (RIBEIRO et al., 2007).

CA-MRSA strains are responsible for infection in children and young adults, promoting high mortality rates (RIBEIRO et al., 2005). The difference between community and hospital strains is based on the chromosome cassette. HA-MRSA strains carries SCCmec types I, II and III, while CA-MRSA preferably carry the type IV and V, these are smaller and are devoid of coupled gene of resistance to other antimicrobial drugs, giving susceptibility to CA-MRSA to most non-β-lactam drugs. CA-MRSA has the toxin Panton Valentine leukocidin (PVL), which destroys leukocytes and causes severe tissue damage (LOPES, 2005; VANDENESCH et al., 2003). In a study conducted in the United States, 98% of CA-MRSA isolates contained the genes encoding PVL (MORAN et al., 2006). The superior characteristics of CA-MRSA might give them selective advantages over HA-MRSA, since the former has higher growth rates than the latter (VANDENESCH et al., 2003).

Recent studies have shown MRS colonization usually occurs in pigs, and rarely in cattle and poultry, in several countries, mainly Europe. Molecular characterization revealed that the isolated clones are grouped in the complex 398 (CC398), called livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA). LA-MRSA has been shown with pathogenic to humans and can cause serious infections such as endocarditis and pneumonia (REISCHL et al., 2009; MONACO et al., 2013).

Since the first report of MRSA in animals by Devriese et al. (1972), in relation with bovine mastitis in Belgium, the number of infections by this agent has been increasing, especially in Europe, Canada, Australia, and the United States (WEESE, 2005).

In veterinary medicine, a new species of *Staphylococcus* was discovered in 2005, especially associated with dermatological diseases such as pyoderma, in postoperative wounds, and otitis (WEESE; VAN DUIJKEREN, 2010; GRIFFETH et al., 2008). This discovery was achieved through molecular analysis of cat, dog, horse, and parrot isolates, and since its phenotypic profile was similar to both *S. intermedius* and *S. delphini* (a species found in dolphin by Varaldo and employees in 1988), this species was named *Staphylococcus pseudintermedius* (DEVRIESE et al., 2005), and it is often identified as *S. aureus* or *S. intermedius* by similar biochemical characteristics, especially coagulase test (SASAKI et al., 2007). The importance of *S. pseudintermedius* as a zoonotic agent is less than *S. aureus* because the infection in human by this agent is highly unusual, even in the individuals having direct contact with animals (WEESE; VAN DUIJKEREN, 2010).

An international multicenter study was held in Europe and the United States, evaluating the resistance profiles of MRSP identifying multidrug-resistant strains tthat are resistant to all the oral antibiotics used for treatment at the clinic of small animals.The antimicrobials to which these samples were susceptible are not authorized for animal use in these countries (PERRETEN et al., 2010). The MRSP

strains that have been isolated contain *mec*A and various other resistance genes, such as those related to resistance to erythromycin (*erm*B), tetracycline (*tet*M and *tet*K), gentamicin (aac6'-Ie-aph2'-Ia), clindamycin (*erm*B e *Inu*A), trimethoprim (*dfr*G), streptomycin (ant6'-Ia), kanamycin (aph3'-III), and chloramphenicol (*catp*C221), besides the resistance gene for β-lactam drugs (PERRETEN et al., 2010).

Recently, several studies have identified the presence of the *mec*A gene in different species of *Staphylococcus* isolated from animals, including both CoPS and CNS species, as shown in Table 3.

Table 3. Detection of the *mec*A gene in different species of *Staphylococcus* present in animals.

Staphylococcal species	Animal species
coagulase-positive staphylococci and *Staphylococcus aureus*	Pigs, cattle, horses, poultry, sheep, dogs and cats
S. pseudintermedius	Dogs and cats
S. hyicus	Pigs
coagulase-negative staphylococci	
S. capitis, S. epidermidis, S. haemolyticus, S. lentus, S. saprophyticus, S. xylosus and *S. sciuri*	Cattle
S. epidermidis, S. lentus, S. saprophyticus and *S. sciuri*	Chickens
S. cohnii, S. fleurettii, S. haemolyticus, S. epidermidis, S. xylosus, S. equorum, S. lentus, S. pasteuri, S. saprophyticus and *S. sciuri*	Pigs
S. lentus, S. sciuri, S. vitulinus, S. auricularis, S. capitis, S. cohnii, S. epidermidis, S. haemolyticus, S. hominis, S. kloosii and *S. xylosus*	Horses
S. haemolyticus, S. sciuri, S. epidermidis and *S. warneri*	Dogs and cats

Source: Adapted from WENDLANDT et al. (2013).

In 2007, an epidemiological study was performed to study bovine mastitis by usingwith bovine mastitis, milk tank samples were colected in Southwest of England isolated a strain of *S. aureus* called LGA251, which was phenotypically identified as MRSA (GARCIA-ALVAREZ et al., 2011a). At the time, this fact was fully significant because it represented the first MRSA detection in dairy cattle from the UK, however, confirmatory tests for *mec*A gene and PBP2a/20 were repeatedly negative. Therefore, genome sequencing was performed, which revealed that the LGA251 strain carried a homologous *mec*A gene, with approximately 69% identity with the *mec*A gene at the DNA level and approximately 63% identity with the PBP2a/20 protein (GARCIA-ALVAREZ et al., 2011b). Initially, this gene was named *mec*ALGA251; it was located within an SCC*mec* element known as conventional *mec*A. It was submitted to the Working Group on the SCCmec rating and named as SCC*mec* type XI in 2009. In 2012, the *mec*ALGA251 was named *mec*C (ITO et al., 2012). Studies performed with stored samples of isolates from UK and Denmark have identified another 65 samples positive for *mec*C, not only from dairy cattle samples but also from human samples. Among those 65 samples, the oldest isolate was a sample of human blood from 1975. Although *mec*C has recently been discovered, it might have caused human infections since 35 years (GARCIA-ALVAREZ et al., 2011b).

Like the conventional MRSA strains, *mec*C MRSA carriers are also highly versatile pathogens and can cause a variety of infections including several veterinary diseases (CUNY et al., 2011; SABAT et al., 2012; HARRISON et al., 2013;

MEDHUS et al., 2013; PATERSON et al., 2012).

In a study involving 896 *S. aureus* isolates (*mec*A MRSA, *mec*C MRSA, and *mec*-negative MSSA) which were found to be 88.7% sensitive and 99.5% specific for the resistance profile (CARTWRIGHT et al., 2013), mecA MRSA was found to be resistant to oxacillin and cefoxitin, though most of the *mec*C MRSA stains are resistant to cefoxitin, but susceptible to oxacillin. PBP2a encoded by the *mec*C gene, unlike the homologous *mec*A-coded, has greater affinity for oxacillin than cefoxitin, leading to higher levels of resistance to cefoxitin than oxacillin (KIM et al., 2012).

These and other epidemiological data indicate a high rate of transfer of resistance among animal to human bacteria and otherwise, which shows hygienic precautions whenever colonization and infection in animals and veterinarians to limit the spread of this bacterium (BOND; LOEFFLER, 2012).

In veterinary medicine, multidrug-resistant strains of MRSP are a challenge for antimicrobial therapy due to fewer treatment options, leading to the use of modern drugs of human line by the veterinarians, which raises ethical issues (WEESE; DUIJKEREN, 2010). The use of drugs such as vancomycin and linezolid (only treatment for some MRS infections in humans) in animals is questionable, due to the fact that transfer of resistance genes can occur between different strains and species of staphylococci, infecting animals and humans respectively (PERRETEN et al., 2010).

Staphylococcus aureus with intermediate resistance and resistant to vancomycin (VISA/VRSA)

After the discovery of multidrug-resistant gram-positive bacteria, especially MRS, antimicrobial drugs including the glycopeptides, vancomycin and teicoplanin, has been the last alternative for the treatment of these microorganisms for several years (WHO, 2009). However, in the early 90s, strains of *S. aureus* resistant to teicoplanin *in vivo* (failed therapy) have been reported in USA and Europe. *In vitro* testing of these strains showed susceptibility to vancomycin by MIC (KAATZ et al., 1990; MANQUAT et al., 1992). In 1997, the first strains of *S. aureus* with reduced susceptibility to vancomycin (VISA) were isolated in Japan, resulting in significant concern about the future of therapy for staphylococcal infections (HIRAMATSU et al., 1997).

Other isolates of *S. aureus* showed heterogeneous resistance to vancomycin (hVISA), with MIC to vancomycin within the likely range. However, when detailed tests with higher inoculum or a prolonged incubation were tested, subpopulations with MIC higher with vancomycin-resistance were detected (HIRAMATSU, 2001). These findings aggravated concern regarding the vancomycin-resistance in staphylococci, leading to the isolation and characterization of VISA and hVISA in many countries around the world (HOWDEN et al., 2010). There were also made retrospective analysis of samples, detecting several strains of VISA and hVISA, isolated initially before the permission of use of vancomycin (ROBERT et al., 2006; RYBAK et al., 2005; YAMAKAWA et al., 2012).

Most of the hVISA and VISA strains are reported in HA-MRSA strains instead of CA-MRSA strains since greater selection pressure is present in the hospital environment. However, VISA has also been rarely reported, in specimens of methicillin-susceptible Staphylococcus aureus (MSSA) (PILLAI et al., 2009), and CA-MRSA (GARDETE et al., 2012).

According to Sousa (2006), strains of *Staphylococcus* that are resistant to vancomycin, are generally resistant to teicoplanin as well; however, the opposite is not true. Authors described some strains of *S. epidermidis* and *S. haemolyticus* resistant to teicoplanin, but susceptible to vancomycin.

In Michigan, USA, the first sample of *S. aureus* resistant to vancomycin, was isolated in a

dialysis patient (CHANG et al., 2003). This strain was the first to show the *van*A gene (gene that causes resistance to vancomycin and teicoplanin in *Enterococcus faecalis*) (SOUSA, 2006). The origin of this strain can be explained by the conjugal transfer of this gene from *Enterococcus* to *Staphylococcus* (WEESE, 2005). Melo-Cristino et al. (2013) reported the first case of human infection by VRSA in Portugal, Europe.

According to CLSI, the MIC or agar screen test described for VRE should be performed to detect VISA and VRSA strains. These strains are not detected by disk diffusion tests even with 24 hours of incubation.

For the multiplication of Gram-positive bacteria in an environment where the external osmotic pressure is less than bacterial cell, bacteria need to synthesize a strong extracellular structure to prevent their rupture. This structure, called peptidoglycan is synthesized inside the cell (murein monomer) and then gets transferred to the outside. As β-lactams, glycopeptides exert their function by inhibiting the synthesis of bacterial cell walls by binding to the terminal D-alanyl-D-alanine of precursor units of the cell wall with high affinity (HIRAMATSU, 2001). The thickening of cell wall is considered as a pre-requisite for resistance to vancomycin (CUI et al., 2003; HIRAMATSU, 2001), however, decrease of peptidoglycan and an increase of the free residues of D-alanyl-D-alanine, can cause an increased resistance to vancomycin (CUI et al., 2000; REIPERT et al., 2003). The *van*A-positive strains have the ability to produce a different D-alanyl-D-alanine ligase, which leads to the modification of the side chains of peptidoglycans, showing lower affinity for this group of antibiotics (FLUIT et al., 2001).

In veterinary medicine, studies about the glycopeptides-resistance have been limited due to their limited use, (MONCHIQUE, 2013). Haenni et al. (2010) could not identify any resistant isolate despite a specific search for vancomycin and teicoplanin-resistance strains in 60 isolates of *Staphylococcus* obtained from horses (59 *S. aureus* and 1 *S. pseudintermedius*). Thus, VRSA strains have not yet been reported in veterinary medicine (MONCHIQUE, 2013).

According to Kirst et al. (1998), avoparcin, an antimicrobial drug of the glycopeptide class, was widely used as a growth promoter in the livestock, thus making it a possible source for resistant organisms and disseminators of this class of antimicrobials, especially in farm animals.

Resistance to macrolides, lincosamides, and streptogramin B (MLSB) group in Staphylococcus spp.

Macrolides (streptomycin), lincosamides (clindamycin), and streptogramin B (quinupristin / dalfopristin) form the MLSB group of antibiotics because despite having different chemical formulas, they have the same mechanism of action, i.e., they inhibit protein synthesis by binding to the rRNA 23S receptor, part of 50S subunit of the bacterial ribosome (LECLERCQ, 2002; ROSSI; ANDREAZZI, 2005).

Resistance to MLSB group can occur in two ways: first by active efflux, encoded by the *msr*A gene and second through the methylation of the bacterial ribosome target site, encoded by *erm* genes (LECLERCQ, 2002). This second mechanism might be manifested in two ways: a constitutive form, when there is constant methylase production and the resistance phenotype is shown throughout the MLSB group; or an induced form, when the methylase is produced only in the presence of the inducer (STEWARD et al., 2005). In the induced form, resistance phenotype involves the *erm* A, B or C genes, which are carried by the Tn554 transposon (MCDOUGAL et al., 2003). Two other genes have been described in the individual animal's isolates, the *mph*C (macrolide C-phosphotransferase) from dogs and cats (LÜTHJE; SCHWARZ, 2007), and

*lnu*A (nucleotide lincosamide transferase) from the subclinical mastitis in cattle (LOEZA-LARA et al., 2004).

In veterinary medicine, clindamycin is widely used for the treatment of wide variety of infections Fiebelkorn et al. (2003) mentioned its use for the treatment of infections caused by Staphylococcus, especially MRSA. In South Korea, Kim et al. (2004) investigated the MLSB-resistance in *S. aureus*, noting that 97% of MRSA strains were resistant to at least one of the drugs of this group, but all isolates studied were susceptible to quinupristin/dalfopristin. Similar data were found by Bordin et al. (2015), where 94% of the MRS at the Veterinary Hospital, in Brazil, were found resistant to at least one of the drugs tested (erythromycin and clindamycin).

Epidemiologically, cross-resistance among these three classes of antimicrobial agents is very important (DIPERSIO; DIPERSIO, 2005), since the macrolides and lincosamides are widely used in veterinary medicine, leading to increased resistance in bacterial strains of animal origin (WANG et al., 2008; JAGLIC et al., 2012). Nawaz et al. (2000) and De Leener et al. (2004) reported the possible transmission of resistance genes of animals to humans, through the food chain.

The conventional disk diffusion test might give false results when detecting the induced resistance to MLSB, showing *in vitro* resistance to erythromycin, and false susceptibility to clindamycin (FIEBELKORN et al., 2003; WEISBLUM, 2005). The CLSI developed a phenotypic method for detection of induced resistance, named double disc diffusion test or D-Test where disks of clindamycin (2 mg) and erythromycin (15 µg) are arranged beside each other at a distance of 15-25 mm. Clindamycin resistance is detected by the appearance of an inhibition zone in the form of "D".

In MRSA isolates from humans and animals, clindamycin induced resistance is well documented and there has been some reports of this type of resistance in MRSP strains (RICH et al., 2005; FAIRES et al., 2009; PERRETEN et al., 2010; RUBIN et al., 2011). It is well known that the antimicrobial pressure leads to the selection of bacteria which are resistant to MLSB group, but the horizontal transfer of resistance genes is also well elucidated (MARTEL et al., 2003;. PATTERSON et al., 2007).

Vancomycin-Resistant Enterococcus spp. (VRE)

Enterococci were first described in 1899 by Thiercelin, and until the year 1984, they were grouped under the *Streptococcus* genus (SCHLEIFER; KILPPER, 1984). Today, 40 different species have been described, and the most common ones found in humans are *E. faecalis* and *E. faecium*, whereas in animals, in addition to these two species, *E. cecorum* and *E. hirae* are also highlighted (DEVRIESE et al., 1991; KLEIN, 2003). Enterococci colonize the gastrointestinal tract of both humans and animals (SHEPARD; GILMORE, 2002), and can survive for months in this environment, even under adverse conditions (KRAMER et al., 2006).

Currently, enterococci are considered as an important opportunistic pathogen, especially in hospital acquired infections, usually associated with wound infections, urinary tract infections, and endocarditis (FISHER; PHILLIPS, 2009), and is considered as the third most prevalent nosocomial pathogen, worldwide (ECDC, 2011). They are intrinsically resistant to commonly used antibiotics, including cephalosporins, and some aminoglycosides (SHEPARD; GILMORE, 2002). In addition to acquiring resistance to penicillin / ampicillin, high-level of aminoglycoside and glycopeptide, limiting the therapeutic practice (SOOD et al., 2008).

Vancomycin is an important antibiotic in the treatment of enterococcal infections, but the efficiency of this antibiotic has been limited by the appearance of VRE strains especially in the presence of vanA gene, thus becoming one of the most important bacteria, clinically resistant to several

antimicrobial agents present worldwide (EISNER et al., 2005; FUJITA et al., 1998). There are few therapeutic agents capable of treating enterococcal infections, including quinupristin/dalfopristin, linezolid, tigecycline, and daptomycin, and these are only used in certain situations, and yet resistant to these drugs have also been described (WERNER et al., 2002, 2008a; ARIAS et al., 2011).

The *van*A gene that confers resistance to vancomycin, was first detected in Europe in the strains of *E. faecium* and *E. faecalis*, in 1986 (LECLERCQ et al., 1988; UTTLEY et al., 1989). Subsequently it was also detected in the strains of *E. durans, E. hirae, E. gallinarum, E. casseliflavus, E. raffinosus, E. avium, E. mundtii* (WERNER et al., 2008a), and *E. cecorum* in samples from birds (HARADA et al., 2012). So far, nine different variants have been described for vancomycin-resistance in enterococci, consisting of *van* A, B, C, D, E, G, L, M, and N genes (COURVALIN, 2006; BOYD et al., 2008; XU et al., 2010; LEBRETON et al., 2011), where *van* A, B, and C types are the most common types (WERNER et al., 2008b; FISHER; PHILLIPS, 2009). Another variant (*van*F) with high similarity in the amino acid sequence to *van*A has been described, but only in *Pàenibacillus popilliae*, and it has been suggested as a possible source of resistance to vancomycin in enterococci (PATEL et al., 2000).

Before 1975 avoparcin, an analogue of vancomycin, was used as a growth promoter and a prophylactic agent in the feed of farmed animals (KLARE et al., 1999; JUNG et al., 2007), mainly chickens, and pigs, and also used in turkeys, calves and, other animals to a lesser extent, in Europe, Asia, and Oceania (HAMMERUM et al., 2010). Avoparcin was used to such an extent that, in 1994 in Denmark, 24 kg of vancomycin was used in human medicine, whereas around 24.000 kg of avoparcin was used in the treatment of animal infections (WEGENER, 1998). A similar incident occurred in Australia, where less than 600 kg of vancomycin was used whereas more than 62.000 kg avoparcin was imported (WITTE, 1998). In the United States and Canada, avoparcin has never been approved for use in animals (MCDONALD et al., 1997).

Thus, the use of avoparcin started being associated with the appearance of VRE in livestock, since avoparcin confers cross-resistance to vancomycin (BAGER et al., 1997; BORGEN et al., 2000; CHAN et al., 2008). *E. faecium* vanA gene carriers became common in the intestinal microbiota of farm animals across Europe in the 1990s (KLARE et al., 1995), but this did not happen in the United States and Canada, owing to the possible ban on avoparcin. The first VRE isolate obtained from farm animals in USA was only obtained in 2008 (DONABEDIAN et al., 2010), pointing to other media selection, introduction and spread of *van*A-VRE in this site (GORDONCILLO et al., 2013).

Once the connection between avoparcin and VRE was established, the use of antimicrobial was banned in Denmark, in 1995, and in Germany and throughout Europe by 1997, with the institution of Directive 97/6/EC (ANONYMOUS, 1997; KIRST et al., 1998; AARESTRUP et al., 2000). Even after the ban on the use of avoparcin, thus reducing the selective pressure exerted by this growth promoter, resistant enterococci strains continued to be found (JOHNSEN et al., 2009), a fact corroborated by the study of Harada et al. (2010), who isolated strains of *van*A-VRE in 8 samples of birds, out of 171 (4.7%), in Japan, even after 11 years of the ban on avoparcin.

Although rare, there is evidence of VRE from animal sources causing infections in humans (LARSEN et al., 2010, 2011), a fact proven by Gelsomino et al. (2003), who isolated strains identical to *E. faecalis* and *E. casseliflavus* in milk, cheese, and human stool samples, suggesting a route for cross-resistance. Freitas et al. (2011) confirmed the relation between the hospital strains and VRE

associated with pigs.

Whenever enterococci derived from animals colonize the human intestinal microbiota even for a short period of time, without causing any changes, it might be sufficient for the transmission of resistance genes to develop adapted strains (LESTER et al., 2006), and it might also spread among humans, thus showing a great zoonotic potential of certain resistance genes, such as *van*A gene of VRE, where the livestock can be considered as a potential reservoir of resistance (WITTE, 2000).

The vanA gene is often transferred by a transposon, a genetic element that can be incorporated into both, a bacterial plasmid or chromosomal DNA and the main transposon involved is the Tn1546 (COURVALIN, 2006). This transfer can occur from animal bacterial to human bacteria, as described by Jensen (1988), that shown specific embodiments of Tn1546 in broilers and pigs and also in healthy humans.

In the US, a report conducted by the CDC's National Healthcare Safety Network (2006-07) showed that *Enterococcus* is the second, most common pathogen in North American hospitals (HIDRON et al., 2008) due to the widespread use of vancomycin, and extended-spectrum cephalosporins without control, over the past 20 years (KIRST et al., 1998). In 1996, the first human isolate was found in Curitiba (Brazil), when a *van*D-VRE strain was initially identified and, a year later, similar strain (*van*A-VRE) was isolated in São Paulo (DALLA et al., 1998; ZANELLA et al., 2003). Later, such strains were detected in hospitals in several cities around the country, such as Marilia, Campinas, Rio de Janeiro, Uberlândia, and Porto Alegre (D'AZEVEDO et al., 2000; CAMARGO et al., 2006; PALAZZO et al., 2011).

Transmission of the vancomycin-resistance gene from animals bacteria to humans bacteria and the ease with which organisms from the *Enterococcus* genus acquire resistance and spread it among bacteria of the same genus, and even to other bacterial species (as seen for the *van*A gene found in MRSA strains), have already been well elucidated. Therefore, VRE need to be monitored constantly in order to prevent nosocomial infections and risk to public health.

Conclusion

With the indiscriminate use of antimicrobial drugs in veterinary medicine, the number of multiresistant isolates is increasing. The emergence of multidrug-resistant strains is a reality and must not be ignored by health professionals, including veterinarians, as these resistance genes can be transmitted between bacteria from animal species to the microbiota of humans, posing a huge problem for public health.

The bacterial resistance profile has varied over the years and in the different regions, thus its monitoring should be constant, and should not be ignored by both clinical veterinary professionals like surgeons. The prudent choice of an adopted antimicrobial therapy can reduce the indiscriminate use of antibiotics and consequently the development of bacterial resistance, especially in hospital settings.

Despite these variations of the resistance profile, multidrug-resistant microorganisms are the main Gram-positive bacteria, especially MRSA, which was initially considered as a hospital pathogen, but now is spread in the community as well. If the use of antimicrobials will not be controlled, this resistance will only increase and spread. The ease with which these microorganisms acquire resistance is so high, that as new drugs are being produced, strains resistant to them are already being observed. Therefore, not only the medical and veterinary doctors, but also all the health professionals, and even the community should be made aware of this problem, because these "superbugs" are no longer only a hospital problem, but rather a public health problem.

References

AARESTRUP, F. M.; KRUSE, H.; TAST, E.; HAMMERUM, A. M.; JENSEN, L. B. Associations between the use of antimicrobial agents for growth promotion and the occurrence of resistance among *Enterococcus faecium* from broilers and pigs in Denmark, Finland, and Norway. *Microbial Drug Resistance*, Larchmont, v. 6, n. 1, p. 63-70, 2000.

ÁLVAREZ-LERMA, F.; PALOMAR, M.; OLAECHEA, P.; OTAL, J. J.; INSAUSTI, J.; CERDA, E. Evolutive report of the years 2003-2005. *Medicina Intensiva,* Madrid, v. 31, n. 1, p. 6-17, 2007.

ANONYMOUS. Commission directive 97/6/EC. Off J Eur Commun 1997. L35 5. 2. 97:11-3.

ARIAS, C. A.; PANESSO, D.; MCGRATH, D. M.; QIN, X.; MOJICA, M. F.; MILLER, C.; DIAZ, L.; TRAN,T. T.; RINCON, S.; BARBU, E. M.; REYES, J.; ROH, J. H.; LOBOS, E.; SODERGREN, E.; PASQUALINI, R.; ARAP, W.; QUINN, J. P.; SHAMOO, Y.; MURRAY, B. E.; WEINSTOCK, G. M. Genetic basis for in vivo daptomycin resistance in enterococci. *New England Journal of Medicine*, Boston, v. 365, p. 892-900, 2011.

BAGER, F.; MADSEN, M.; CHRISTENSEN, J.; AARESTRUP, F. M. Avoparcin used as a growth promoter is associated with the occurrence of vancomycin-resistant *Enterococcus faecium* on Danish poultry and pig farms. *Preventive Veterinary Medicine*, Amsterdan, v. 31, n. 1-2, p. 95-112, 1997.

BLACK, C. C.; SOLYMAN, S. M.; EBERLEIN, L. C.; BEMIS, D. A.; WORON, A. M.; KANIA, S. A. Identification of a predominant multilocus sequence type, pulsed-field gel electrophoresis cluster, and novel staphylococcal chromosomal cassette in clinical isolates of mecA-containing, methicillin resistant *Staphylococcus pseudintermedius*. *Veterinary Microbiology*, Amsterdan, v. 139, n. 3-4, p. 333-338, 2009.

BLOUIN, D. D. *All in the family? Understanding the meaning of dogs and cats in the lives of american pet owners*. 2008. Thesis (Doctor in Philosophy) - Department of Sociology, Indiana University, Bloomington.

BOND, R.; LOEFFLER, A. What's happened to Staphylococcus intermedius? Taxonomic revision and emergence of multi-drug resistance. *Journal of Small Animal Practice*, Oxford, v. 53, n. 3, p. 147-154, 2012.

BORDIN, J. T.; SFACIOTTE, R. A. P.; CORONEL, L. G.; MENDES, L. M.; VIGNOTO, V. K. C.; CONTI, J. B. de; WOSIACKI, S. R. Identification of bacterial multidrug resistance in wounds of pets. *Revista de Ciência Veterinária e Saúde Pública*, Maringá, v. 2, n. 1, 2015.

BORGEN, K.; SIMONSEN, G. S.; SUNDSFJORD, A.; WASTESON, Y.; OLSVIK, Ø.; KRUSE, H. Continuing high prevalence of VanA-type vancomycin-resistant enterococci on Norwegian poultry farms three years after avoparcin was banned. *Journal of Applied Microbiology,* Oxford, v. 89, n. 3, p. 478-485, 2000.

BOYD, D. A.; WILLEY, B. M.; FAWCETT, D.; GILLANI, N.; MULVEY, M. R. Molecular characterization of *Enterococcus faecalis* N06-0364 with low-level vancomycin resistance harboring a novel D-Ala-D-Ser gene cluster, vanL. *Antimicrobial Agents and Chemotherapy*, Washington, v. 52, n. 7, p. 2667-2672, 2008.

CAMARGO, I. L. B. C.; GILMORE, M. S.; DARINI, A. L. C. Multilocus sequence typing and analysis of putative virulence factors in vancomycin-resistant and vancomycin-sensitive *Enterococcus faecium* isolates from Brazil. *Clinical Microbiology and Infection*, Paris, v. 12, n. 11, p. 1123-1130, 2006,

CARTWRIGHT, E. J. P.; PATERSON, G. K.; RAVEN, K. E.; HARRISON, E. M.; GOULIOURIS, T.; KEARNS, A.; PICHON, B.; EDWARDS, G.; SKOV, R. L.; LARSEN, A. R.; HOLMES, M. A.; PARKHILL, J.; PEACOCK, S. J.; TOROK, M. E. Use of Vitek 2 antimicrobial susceptibility profile to identify mecC in methicillin-resistant *Staphylococcus aureus*. *Journal of Clinical Microbiology*, Washington, v. 51, n. 8, p. 2732-2734, 2013.

CASTELLANO-GONZALEZ, M. J.; PEROZO-MENA, A. J.; VIVAS-VEJA, R. L.; GINESTRE-PEREZ, M. M.; RINCON-VILLALOBOS, G. C. Molecular and phenotypical typification of methicillin resistant *Staphylococcus aureus* (MRSA) strains in a university hospital. *Revista Chilena de Infectología*, Santiago, v. 26, n. 1, p. 39-48, 2009.

CENTERS FOR DISEASE CONTROL AND PREVENTION - CDC. Public health dispatch: outbreaks of community-associated methicillin-resistant *staphylococcus aureus* skin intections - Los Angeles County, California, 2002-2003. *MMWR*, Atlanta, v. 52, n. 5, p. 88, 2003.

CHAN, Y. Y.; NASIR, M. H. B. A.; YAHAYA, M. A. B.; SALLEH, N. M. A. B.; DAN, A. D. B. M.; MUSA, A. M. B.; RAVICHANDRAN, M. Low prevalence of vancomycin and bifunctional aminoglycoside-resistant enterococci isolated from poultry farms in Malaysia. *International Journal of Food Microbiology,* Amsterdan, v. 122, n. 1-2, p. 221-226, 2008.

CHANG, S.; SIEVERT, D. M.; HAGEMAN, J. C.; BOULTON, M. L.; TENOVER, F. C.; DOWNES, F. P.; SHAH,S.; RUDRIK, J. T.; PUPP, J. R.; BROWN,

W. J.; CARDO, D.; FRIDKIN, S. K. Infection with vancomycin-resistant *Staphylococcus aureus* containing the vanA resistance gene. *New England Journal of Medicine,* Boston, v. 348, n. 14, p. 1342-1347, 2003.

CLINICAL AND LABORATORY STANDARDS INSTITUTE - CLSI. Performance standards for antimicrobial disk and dilution susceptibility test for bacteria isolated from animals; approved standard. 3th ed. M31-A3. Wayne: Clinical and Laboratory Standards Institute, 2008. v. 28, n. 8, 103 p.

COURVALIN, P. Vancomycin resistance in gram-positive cocci. *Clinical Infectious Diseases*, Chicago, v. 42, suppl. 1, p. S25-34, 2006.

CUI, L.; MA, X.; SATO, K.; OKUMA, K.; TENOVER, F. C.; MAMIZUKA, E. M.; GEMMELL, C. G.; KIM, M. N.; PLOY, M. C.; ELSOLH, N.; FERRAZ, V.; HIRAMATSU, K. Cell wall thickening is a common feature of vancomycin resistance in *Staphylococcus aureus*. *Journal of Clinical Microbiology,* Washington, v. 41, n. 1, p. 5-14, 2003.

CUI, L.; MURAKAMI, H.; KUWAHARA-ARAI, K.; HANAKI, H.; HIRAMATSU, K. Contribution of a thickened cell wall and its gultamine nonamidated component to the vancomycin resistance expressed by *Staphylococcus aureus* Mu50. *Antimicrobial Agents and Chemotherapy*, Wahington, v. 44, n. 9, p. 2276-2285, 2000.

CUNY, C.; LAYER, F.; STROMMENGER, B.; WITTE, W. Rare occurrence of methicillin-resistant *Staphylococcus aureus* CC130 with a novel mecA homologue in humans in Germany. *PLoS ONE*, San Francisco, v. 6, n. 9, p. e24360, 2011.

DALLA COSTA, L. M.; SOUZA, D. C.; MARTINS, L. T.; ZANELLA, R. C.; BRANDILONE, M. C.; BOKERMANN, S.; SADER, H. S.; SOUZA, H. A. Vancomycin-Resistant *Enterococcus faecium*: First Case in Brazil. *Brazilian Journal of Infectious Diseases*, Salvador, v. 2, n. 3, p. 160-163, 1998.

D'AZEVEDO, P. A.; KACMAN, S. B.; SCHMALFUSS, T.; SILVA, A.; RODRIGUES, L. F. Primeiro caso de *Enterococcus* resistente a vancomicina isolado em Porto Alegre, RS. *Jornal Brasileiro de Patologia*, Rio de Janeiro, v. 36, n. 3, p. 258, 2000.

DE LEENER, E.; MARTEL, A.; DECOSTERE, A.; HAESEBROUCK, F. Distribution of the *erm*(B) gene, tetracycline resistance genes, and Tn1545-like transposons in macrolide- and lincosamide-resistant enterococci from pigs and humans. *Microbial Drug Resistance*, Larchmont, v. 10, n. 4, p. 341-345, 2004.

DE LUCIA, M.; MOODLEY, A.; LATRONICO, F.; GIORDANO, A.; CALDIN, M.; FONDATI, A.; GUARDABASSI, L. Prevalence of canine methicillin resistant *Staphylococcus pseudintermedius* in a veterinary diagnostic laboratory in Italy. *Research in Veterinary Science,* Oxford, v. 91, n. 3, p. 346-348, 2011.

DESCLOUX, S.; ROSSANO, A.; PERRETEN, V. Characterization of new staphylococcal cassette chromosome mec (SCCmec) and topoisomerase genes in fluoroquinolone- and methicillin resistant *Staphylococcus pseudintermedius*. *Journal of Clinical Microbiology*, Washington, v. 46, n. 5, p. 1818-1823, 2008.

DEVRIESE, L. A.; HOMMEZ, J.; WIJFELS, R.; HAESEBROUCK, F. Composition of the enterococcal and streptococcal intestinal flora of poultry. *Journal of Applied Microbiology,* Oxford, v. 71, n. 1, p. 46-50, 1991.

DEVRIESE, L. A.; VAN DAMME, L. R.; FAMEREE, L. Methicillin-(cloxacillin)-resistant *Staphylococcus aureus* strains isolated from bovine mastitis cases. *Zentralbl. Veterinarmed. B,* Berlin, v. 19, n. 7, p. 598-605, 1972.

DEVRIESE, L. A.; VANCANNEYT, M.; BAELE, M.; VANEECHOUTTE, M.; GRAEF, E.; SNAUWAERT, C.; CLEENWERCK, I.; DAWYNDT, P.; SWINGS, J.; DECOSTERE, A.; HAESEBROUCK, F. *Staphylococcus pseudintermedius* sp. nov., a coagulase-positive species from animals. *International Journal of Systematic and Evolutionary Microbiology*, Reading, v. 55, n. 4, p. 1569-1573, 2005.

DIPERSIO, J. R.; DIPERSIO, L. P. Update on the prevalence and spread of macrolide and lincosamide-resistant staphylococcal and streptococcal species. *Reviews in Medical Microbiology,* Edinburgh, v. 16, n. 3, p. 117-123, 2005.

DONABEDIAN, S. M.; PERRI, M. B.; ABDUJAMILOVA, N.; GORDONCILLO, M. J.; NAQVI, A.; REYES, K. C.; ZERVOS, M. J.; BARLETT, P. Characterization of vancomycin resistant *Enterococcus faecium* isolated from swine in three Michigan counties. *Journal of Clinical Microbiology,* Washington, v. 48, n. 11, p. 4156-4160, 2010.

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL - ECDC. Annual epidemiological report Reporting on lligence data. Annual Epidemiological Report on Communicable Diseases in Europe. Stockholm: ECDC, 2011. 227 p.

EISNER, A.; FEIERL, G.; GORKIEWICZ, G.; DIEBER, F.; KESSLER, H. H.; MARTH, E.; KÖFER, J. High prevalence of VanA-type vancomycin-resistant enterococci in Austrian poultry. *Applied and Environmental Microbiology*, Washington D.C, v. 71, n. 10, p. 6407-6409, 2005.

ENRIGHT, M. C. The evolution of a resistant pathogen--the case of MRSA. *Current Opinion in Pharmacology,* Oxford, v. 3, n. 5, p. 474-479, 2003.

FAIRES, M.; GARD, S.; AUCOIN. D.; WEESE, J. S. Inducible clindamycin-resistance in methicillin-resistant *Staphylococcus aureus* and methicillin-resistant Staphylococcus pseudintermedius isolates from dogs and cats [letter to the editor]. *Veterinary Microbiology,* Amsterdam, v. 139, n. 3-4, p. 419-420, 2009.

FERNANDES, P. Antibacterial discovery and development-the failure of success? *Nature Biotechnology,* New York, v. 24, n. 12, p. 1497-1503, 2006.

FERREIRA, R. B. R.; LORIO, N. L. P.; MALVAR, K. L.; NUNES, A. P. F.; FONSECA, L. S.; BASTOS, C. C. R.; SANTOS, K. R. N. Coagulase-negative staphylococci: comparison of phenotypic and genotypic oxacillin susceptibility tests and evaluation of the Agar screen test by using different concentrations of oxacillin. *Journal of Clinical Microbiology*, Washington, v. 41, n. 8, p. 3609-3614, 2003.

FIEBELKORN, K. R.; CRAWFORD, S. A.; MCELMEEL, M. L.; JORGENSEN, J. H. Practical disk diffusion method for detection of inducible clindamycin resistance in *Staphylococcus aureus* and coagulase-negative staphylococci. *Journal of Clinical Microbiology,* Washington, v. 41, n. 10, p. 4740-4744, 2003.

FISHER, K.; PHILLIPS, C. The ecology, epidemiology and virulence of *Enterococcus*. *Microbiology,* Washington, v. 155, n. 6, p. 1749-1757, 2009.

FLUIT, A. C.; WIELDERS, C. L.; VERHOEF, J.; SCHMITZ, F. J. Epidemiology and susceptibility of 3,051 *Staphylococcus aureus* isolates from 25 university hospitals participating in the European SENTRY Study. *Journal of Clinical Microbiology*, Washington, v. 39, n. 10, p. 3727-3732, 2001.

FREITAS, A. R.; COQUE, T. M.; NOVAIS, C.; HAMMERUM, A. M.; LESTER, C. H.; ZERVOS, M. J.; DON-ABEDIAN, S.; JENSEN, L. B.; FRANCIA, M. V.; BAQUERO, F.; PEIXE, L. Human and swine hosts share vancomycin-resistant *Enterococcus faecium* CC17 and CC5 and *Enterococcus faecalis* CC2 clonal clusters harboring Tn1546 on indistinguishable plasmids. *Journal of Clinical Microbiology,* Washington, v. 49, n. 3, p. 925-931, 2011.

FUJITA, N.; YOSHIMURA, M.; KOMORI, T.; TANIMOTO, K.; IKE, Y. First report of the isolation of high-level vancomycin-resistant Enterococcus faecium from a patient in Japan. *Antimicrobial Agents and Chemotherapy*, Washington, v. 42, n. 8, p. 2150, 1998.

GARCIA-ALVAREZ, L.; HOLDEN, M. T. G.; LINDSAY, H.; WEBB, C. R.; BROWN, D. F. J.; CURRAN, M. D.; WALPOLE, E.; BROOKS, K.; PICKARD, D. J.; TEALE, C.; PARKHILL, J.; BENTLEY, S.; EDWARDAS, G. F.; GIRVAN, E. K.; KEARNS, E. M.; PICHON, B.; HILL, R. L. R.; LARSEN, A. R.; SKOV, R. L.; PEACOCK, S. J.; MASKELL, D. J.; HOLMES, M. A. Meticillin-resistant *Staphylococcus aureus* with a novel mecA homologue in human and bovine populations in the UK and Denmark: a descriptive study. *The Lancet Infectious Diseases*, New York, v. 11, n. 8, p. 595-603, 2011b.

GARCIA-ALVAREZ, L.; WEBB, C. R.; HOLMES, M. A. A novel field-based approach to validate the use of network models for disease spread between dairy herds. *Epidemiology and Infection,* Cambridge, v. 139, n. 12, p. 1863-1874, 2011a.

GARDETE, S.; KIM, C.; HARTMANN, B. M.; MWANGI, M.; ROUX, C. M.; DUNMAN, P. M.; CHAMBERS, H. F.; TOMASZ, A. Genetic pathway in acquisition and loss of vancomycin resistance in a methicillin resistant *Staphylococcus aureus* (MRSA) strain of clonal type USA300. *PLOS Pathogens,* San Francisco, v. 8, n. 2, p. e1002505, 2012.

GELSOMINO, R.; VANCANNEYT, M.; COGAN, T. M.; SWINGS, J. Effect of raw-milkcheese consumption on the enterococcal flora of human feces. *Applied and Environmental Microbiology,* Washington, v. 69, n. 1, p. 312-319, 2003.

GORDONCILLO, M. J.; DONABEDIAN, S.; BARTLETT, P. C.; PERRI, M.; ZERVOS, M.; KIRKWOOD, R.; FEBVAY, C. Isolation and molecular characterization of vancomycin-resistant *Enterococcus faecium* from Swine in Michigan, USA. *Zoonoses Public Health,* Berlin, v. 60, n. 5, p. 319-326, 2013

GRIFFETH, G. C.; MORRIS, D. O.; ABRAHAM, J. L.; SHOFER,F. S.; RANKIN,S. C. Screening for skin carriage of methicillin-resistant coagulase-positive staphylococci and *Staphylococcus schleiferi* in dogs with healthy and inflamed skin. *Veterinary Dermatology,* Oxford, New York, v. 19, n. 3, p. 142-149, 2008.

HAENNI, M.; TARGANT, H.; FOREST, K.; SÉVIN, C.; TAPPREST, J.; LAUGIER, C.; MADEC, J. Y. Retrospective study of necropsy-associated coagulase-positive staphylococci in horses**.** *Journal of Veterinary Diagnostic Investigation,* Thousand Oaks, v. 22, n. 6, p. 953-956, 2010.

HAMMERUM, A. M.; LESTER, C. H.; HEUER, O. E. Antimicrobial resistant enterococci in animals and meat: a human health hazard? *Foodborne Pathogens Diseases,* Larchmont, N.Y., v. 7, n. 10, p. 1137-1146, 2010.

HARADA, T.; KANKI, M.; KAWAI, T.; TAGUCHI, M.; ASAO, T.; KUMEDA, Y. Isolation of VanA-type vancomycin-resistant *Enterococcus* strains from domestic poultry products with enrichment by incubation in buffered peptone water at 42 °C. *Applied and Environmental Microbiology,* Washington, v. 76, n. 15, p. 5317-5320, 2010.

HARADA, T.; KAWAHARA, R.; KANKI, M.; TAGUCHI, M.; KUMEDA, Y. Isolation and characterization of *van*A genotype vancomycin-resistant *Enterococcus cecorum* from retail poultry in Japan. *International Journal of Food Microbiology,* Amsterdan, v. 153, n. 3, p. 372-377, 2012.

HARRISON, E. M.; PATERSON, G. K.; HOLDEN, M. T. G.; LARSEN, J.; STEGGER, M.; LARSEN, A. R.; PETERSEN, A.; SKOV, R. L.; CHRISTENSEN, J. M.; BAK ZEUTHEN, A.; HELTBERG, O.; HARRIS, S. R.; ZADOKS, R. N.; PARKHILL, J.; PEACOCK, S. J.; HOLMES, M. A. Whole genome sequencing identifies zoonotic transmission of MRSA isolates with the novel mecA homologue mecC. *EMBO Molecular Medicine,* Chichester, v. 5, n. 4, p. 509-515, 2013.

HIDRON, A. I.; EDWARDS, J. R.; PATEL, J.; HORAN, T. C.; SIEVERT, D. M.; POLLOCK, D. A.; FRIDKIN, S. K. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. *Infection Control and Hospital Epidemiology*, Thorofare, v. 29, n. 11, p. 996-1011, 2008.

HIRAMATSU, K. Vancomycin-resistant *Staphylococcus aureus*: a new model of antibiotic resistance. *The Lancet Infectious Diseases,* New York, v. 1, n. 3, p. 147-155, 2001.

HIRAMATSU, K.; HANAKI, H.; INO, T.; YABUTA, K.; OGURI, T.; TENOVER, F. C. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. *Journal of Antimicrobial Chemotherapy,* London, v. 40, n. 1, p. 135-136, 1997.

HIRAMATSU, K.; KATAYAMA, Y.; YUZAWA, H.; ITO, T. Molecular genetics of methicillin-resistant *Staphylococcus aureus*. *International Journal of Medical Microbiology,* Jena, v. 292, n. 2, p. 67-74, 2002.

HOWDEN, B. P.; DAVIES, J. K.; JOHNSON, P. D.; STINEAR, T. P.; GRAYSON, M. L. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. *Clinical Microbiology Reviews,* Washington, v. 23, n. 1, p. 99-139, 2010.

INTERNATIONAL WORKING GROUP ON THE CLASSIFICATION OF STAPHYLOCOCCAL CASSETTE CHROMOSOME ELEMENTS - IWG-SCC. Classification of staphylococcal cassette chromosome mec (SCCmec): guidelines for reporting novel SCCmec elements. *Antimicrobial Agents and Chemotherapy*, Washington, v. 53, n. 12, p. 4961-4967, 2009.

ITO, T.; HIRAMATSU, K.; TOMASZ, A.; DE LENCASTRE, H.; PERRETEN, V.; HOLDEN, M. T. G.; COLEMAN, D. C.; GOERING, R.; GIFFARD, P. M.; SKOV, R. L.; ZHANG, K.; WESTH, H.; O'BRIEN, F.; TENOVER, F. C.; OLIVEIRA, D. C.; BOYLE-VAVRA, S.; LAURENT, F.; KEARNS, A. M.; KREISWIRTH, B.; KO, K. S.; GRUNDMANN, H.; SOLLID, J. E.; JOHN, J. F.; DAUM, R.; SODERQUIST, B.; BUIST, G. Guidelines for reporting novel mecA gene homologues. *Antimicrobial Agents and Chemotherapy***,** Washington, v. 56, n. 10, p. 4997-4999, 2012.

JAGLIC, Z; VLKOVA, H.; BARDON, J.; MICHU, E.; CERVINKOVA, D.; BABAK, V. Distribution, characterization and genetic bases of erythromycin resistance in staphylococci and enterococci originating from livestock. *Zoonoses Public Health,* Berlin, v. 59, n. 3, p. 202-211, 2012.

JENSEN, L. B. Differences in the occurrence of two base pair variants of Tn1546 from vancomycin-resistant enterococci from humans, pigs, and poultry. *Antimicrobial Agents and Chemotherapy***,** Washington, v. 42, n. 9, p. 2463-2464, 1998.

JOHNSEN, P. J.; TOWNSEND, J. P.; BOHN, T.; SIMONSEN, G. S.; SUNDSFJORD, A.; NIELSEN, K. M. Factors affecting the reversal of antimicrobial-drug resistance. *The Lancet Infectious Diseases,* New York, v. 9, n. 6, p. 357-364, 2009.

JUNG, W. K.; LIM, J. Y.; KWON, N. H.; KIM, J. M.; HONG, S. K.; KOO, H. C.; KIM, S. H.; PARK, Y. H. Vancomycin-resistant enterococci from animal sources in Korea. *International Journal of Food Microbiology,* Amsterdan, v. 113, n. 1, p. 102-107, 2007.

KAATZ, G. W.; SEO, S. M.; DORMAN, N. J.; LERNER, S. A. Emergence of teicoplanina resistance during therapy of *Staphylococcus aureus* endocarditis. *Journal of Infectious Diseases,* Oxford, v. 162, n. 1, p. 103-108, 1990.

KAWAKAMI, T.; SHIBATA, S.; MURAYAMA, N.; NAGATA, M.; NISHIFUJI, K.; IWASAKI, T.; FUKATA, T. Antimicrobial susceptibility and methicillin resistance in *Staphylococcus pseudintermedius* and *Staphylococcus schleiferi* subsp. coagulans isolated from dogs with pyoderma in Japan. *Journal of Veterinary Medicine Science,* Tokyo, v. 72, n. 12, p. 1615-1619, 2010.

KIM, C.; MILHEIRIÇO, C.; GARDETE, S.; HOLMES, M. A.; HOLDEN, M. T. G.; LENCASTRE, H.; TOMASZ, A. Properties of a novel PBP2A protein homolog from *Staphylococcus aureus* strain LGA251 and its contribution to the betalactam-resistant phenotype. *Journal of Chemical Biology,* Baltimore, v. 287, n. 44, p. 36854-36863, 2012.

KIM, H. B.; LEE, B.; JANG, H. C.; KIM, S. H.; KANG, C. I.; CHOI, Y. J.; PARK, S. W.; KIM, B. S.; KIM, E. C.; OH, M. D.; CHOE, K. W. A high frequency of macrolide-lincosamide-streptogramin resistance determinants in *Staphylococcus aureus* isolated in South Korea. *Microbial Drug Resistance,* Larchmont, v. 10, n. 3, p. 248-254, 2004.

KIRST, H. A.; THOMPSON, D. G.; NICAS, T. I. Historical yearly usage of vancomycin. *Antimicrobial Agents and Chemotherapy,* Washington, v. 42, n. 5, p. 1303-1304, 1998.

KLARE, I.; BADSTÜBNER, D.; KONSTABEL, C.; BÖHME, G.; CLAUS, H.; WITTE, W. Decreased ncidence of VanA-type vancomycin-resistant enterococci isolated from poultry meat and from fecal samples of humans in the community after discontinuation of avoparcin usage in animal husbandry. *Microbial Drug Resistance*, Larchmont, v. 5, n. 1, p. 45-52, 1999.

KLARE, I.; HEIER, H.; CLAUS, H.; REISSBRODT, R.; WITTE, W. vanA-mediated high-level glycopeptide resistance in *Enterococcus faecium* from animal husbandry. *FEMS Microbiology Letters,* Amsterdan, v. 125, n. 2-3, p. 165-171, 1995.

KLEIN, G. Taxonomy, ecology and antibiotic resistance of enterococci from food and the gastro-intestinal tract. *International Journal of Food Microbiology,* Amsterdan, v. 88, n. 2-3, p. 123-131, 2003.

KRAMER, A.; SCHWEBKE, I.; KAMPF, G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC Infectious Diseases,* Boston, v. 6, n. 130, p. 1-8, 2006.

LARSEN, J.; SCHONHEYDER, H. C.; LESTER, C. H.; OLSEN, S. S.; PORSBO, L. J.; GARCIA-MIGURA, L.; JENSEN, L. B.; BISGAARD, M.; HAMMERUM, A. M. Porcine-origin gentamicin-resistant *Enterococcus faecalis* in Humans, Denmark. *Emerging Infectious Diseases,* Atlanta, v. 16, n. 4, p. 682-684, 2010.

LARSEN, J.; SCHONHEYDER, H. C.; SINGH, K. V.; LESTER, C. H.; OLSEN, S. S.; PORSBO, L. J.; GARCIA-MIGURA, L.; JENSEN, L. B.; BISGAARD, M.; MURRAY, B. E.; HAMMERUM, A. M. Porcine and human community reservoirs of *Enterococcus faecalis*, Denmark. *Emerging Infectious Diseases,* Atlanta, v. 17, n. 12, p. 2395-2397, 2011.

LEBRETON, F.; DEPARDIEU, F.; BOURDON, N.; FINES-GUYON, M.; BERGER, P.; CAMIADE, S.; LECLERCQ, R.; COURVALIN, P.; CATTOIR, V. D-Ala-d-Ser VanN-type transferable vancomycin resistance in *Enterococcus faecium*. *Antimicrobial Agents and Chemotherapy,* Washington, v. 55, n. 10, p. 4606-4612, 2011.

LECLERCQ, R. Mechanisms of resistance of macrolides and lincosamides: nature of the resistance elements and their clinical implications. *Clinical Infectious Diseases*, Chicago, v. 34, n. 4, p. 482-492, 2002.

LECLERCQ, R.; DERLOT, E.; DUVAL, J.; COURVALIN, P. Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. *The New England Journal of Medicine,* Boston, v. 319, n. 3, p. 157-161, 1988.

LESTER, C. H.; FRIMODT-MOLLER, N.; SORENSEN, T. L.; MONNET, D. L.; HAMMERUM, A. M. In vivo transfer of the *van*A resistance gene from an *Enterococcus faecium* isolate of animal origin to an *E. faecium* isolate of human origin in the intestines of human volunteers. *Antimicrobial Agents and Chemotherapy,* Washington, v. 50, n. 2, p. 596-599, 2006.

LOEZA-LARA, P. D.; SOTO-HUIPE, M.; BAIZABAL-AGUIRRE, V. M.; OCHOA-ZARZOSA, A.; VALDEZ-ALARCON, J. J.; CANO-CAMACHO, H.; LOPEZ-MEZA, J. E. pBMSa1, a plasmid from a dairy cow isolate of Staphylococcus aureus, encodes a lincomycin resistance determinant and replicates by the rolling-circle mechanism. *Plasmid,* New York, v. 52, n. 1, p. 48-56, 2004.

LOPES, H. V. CA-MRSA: um novo problema para o infectologista. *Revista Panamericana de Infectologia,* São Paulo, v. 7, n. 3, p. 34-36, 2005.

LOWY, F. D. Antimicrobial resistance: the example of *Staphylococcus aureus*. *Journal of Clinical Investigation*, New Haven, v. 111, n. 9, p. 1265-1273, 2003.

LÜTHJE, P.; SCHWARZ, S. Molecular basis of resistance to macrolides and lincosamides among staphylococci and streptococci from various animal sources collected in the resistance monitoring program BfT-GermVet. *International Journal of Antimicrobial Agents*, Amsterdam, v. 29, n. 5, p. 528-35, 2007.

MA, X. X.; ITO T.; TIENSASITORN, C.; JAMKLANG, M.; CHONGTRAKOOL, P.; BOYLE-VAVRA, S.; DAUM, R. S.; HIRAMATSU, K. Novel type of staphylococcal cassette chromosome *mec* identified in community-acquired methicillin resistant*Staphylococcus aureus* strans. *Antimicrobial Agents and Chemotherapy,* Washington, v. 46, n. 4, p. 1147-1152, 2002.

MANQUAT, G.; CROIZE, J.; STAHL, J. P.; MEYRAN, M.; HIRTZ, P.; MICOUD, M. Failure of teicoplanin treatment associated with an increase in MIC during therapy of *Staphylococcus aureus* septicaemia. *Journal of Antimicrobial Chemotherapy,* London, v. 29, n. 6, p. 731-732, 1992.

MARTEL, A.; MEULENAERE, V.; DEVRIESE, L. A.; DECOSTERE, A.; HAESEBROUCK, F. Macrolide and lincosamide resistance in the gram-positive nasal and tonsillar flora of pigs. *Microbial Drug Resistance,* Larchmont, v. 9, n. 3, p. 293-297, 2003.

MCDONALD, L. C.; KUEHNERT, M. J.; TENOVER, F. C.; JARVIS, W. R. Vancomycin-resistant enterococci outside the health-care setting: prevalence, sources, and public health implications. *Emerging Infectious Diseases,* Atlanta, v. 3, n. 3, p. 311-317, 1997.

McDOUGAL, L. K.; STEWARD, C. D.; KILGORE, G. E.; CHAITRAM, J. M.; McALLISTER, S. K.; TENOVER, F. C. Pulsed-field gel electrophoresis typing of oxacillin-resistant *Staphylococcus aureus* isolates from the United States: establishing a national database. *Journal of Clinical Microbiology,* Washington, v. 41, n. 11, p. 5113-5120, 2003.

MEDHUS, A.; SLETTEMEAS, J. S.; MARSTEIN, L.; LARSSEN, K. W.; SUNDE, M. Methicillin-resistant *Staphylococcus aureus* with the novel mecC gene variant isolated from a cat suffering from chronic conjunctivitis. *Journal of Antimicrobial Chemotherapy,* London, v. 68, n. 4, p. 968-969, 2013.

MELO-CRISTINO, J.; RESINA, C.; MANUEL, V.; LITO, L.; RAMIREZ, M. First case of infection with vancomicyn-resistant *Staphylococcus aureus* in Europe. *Lancet,* London, v. 382, n. 9888, p. 205, 2013.

MONACO, M.; PEDRONI, P.; SANCHINI, A.; BONOMINI, A.; INDELICATO, A.; 'PANTOSTI, A. Livestock associated MRSA responsible for human colonization and infection in an area of Italy with hight density or pig farming. *BMC Infectious Diseases*, Boston, v. 13, p. 258, 2013.

MONCHIQUE, C. R. O. *Evolução da resistência aos antibióticos em staphylococcus spp. -1999 a 2006.* 2013. Dissertação (Mestrado Integrado em Medicina Veterinária) - Faculdade de Medicina Veterinária da Universidade de Lisboa, Lisboa.

MORAN, G. J.; KRISHNADASAN, A.; GORWITZ, R. J.; FOSHEIM, G. E.; MCDOUGAL, L. K.; CAREY, R. B. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *The New England Journal of Medicine,* Boston, v. 355, n. 7, p. 666-674, 2006.

MORRIS, D. O.; BOSTON, K. R.; SHEA, C. O.; RANKIN. S. C. The prevalence of carriage of methicillin-resistant Staphylococci by veterinary dermatology practice staff and their respective pets. *Veterinary Dermatology,* Oxford, New York, v. 21, n. 4, p. 400-407, 2010.

MOYAERT, H.; DE GRAEF, E. M.; HAESEBROUCK, F.; DECOSTERE, A. Acquired antimicrobial resistance in the intestinal microbiota of diverse cat populations. *Research in Veterinary Science,* Oxford, v. 81, n. 1, p. 1-7, 2006.

MUÑOZ BELLIDO, J. L. Problematic bacteria. *Revista Española de Quimioterapia,* Barcelona, v. 21, n. 1, p. 2-6, 2008.

NAWAZ, M. S.; KHAN, S. A.; KHAN, A. A.; KHAMBATY, F. M.; CERNIGLIA, C. E. Comparative molecular analysis of erythromycin-resistance determinants in staphylococcal isolates of poultry and human origin. *Molecular and Cellular Probes,* London, New York, v. 14, n. 5, p. 311-319, 2000.

OLIVEIRA, A. C.; SILVA, R. S. Desafios do cuidar em saúde frente á resistência bacteriana: uma revisão. *Revista Eletrônica de Enfermagem,* Goiânia, v. 10, n. 1, p. 189-197, 2008.

OLIVEIRA, D. C.; DE LENCASTRE, H. Multiplex PCR strategy for rapid identification of structural types and variants of the mec element in methicillin-resistant *Staphylococcus aureus*. *Journal of Antimicrobial Chemotherapy,* London, v. 46, n. 7, p. 2155-2161, 2002.

PALAZZO, I. C. V.; PITONDO-SILVA, A.; LEVY, C. E.; DARINI, A. L. C. Changes in vancomycin-resistant *Enterococcus faecium* causing outbreaks in Brazil. *Journal of Hospital Infection,* London, v. 79, n. 1, p. 70-74, 2011.

PATEL, R.; PIPER, K.; COCKERILL, F. R. III.; STECKELBERG, J. M.; YOUSTEN, A. A. The biopesticide Paenibacillus popilliae has a vancomycin resistance gene cluster homologous to the enterococcal *van*A vancomycin resistance gene cluster. *Antimicrobial Agents and Chemotherapy,* Washington, v. 44, n. 3, p. 705-709, 2000.

PATERSON, G. K.; LARSEN, A. R.; ROBB, A.; EDWARDS, G. E.; PENNYCOTT, T. W.; FOSTER, G.; MOT, D.; HERMANS, K.; BAERT, K.; PEACOCK, S, J.; PARKHILL, J.; ZADOKS, R. N.; HOLMES, M. A. The newly described *mec*A homologue, *mec*A(LGA251), is present in methicillin-resistant *Staphylococcus aureus* isolates from a diverse range of host species. *Journal of Antimicrobial Chemotherapy,* London, v. 67, n. 12, p. 2809-2813, 2012.

PATTERSON, A. J.; COLANGELI, R.; SPIGAGLIA, P.; SCOTT, K. P. Distribution of specific tetracycline and erythromycin resistance genes in environmental amples assessed by macroarray detection. *Environmental Microbiology,* Oxford, v. 9, n. 3, p. 703-715, 2007.

PERRETEN, V.; KADLEC, K.; SCHWARZ, S.; GRÖNLUND ANDERSSON, U.; FINN, M.; GREKO, C.; MOODLEY, A.; KANIA, S. A.; FRANK, L. A.; BEMIS, D. A.; FRANCO, A.; IURESCIA, M.; BATTISTI, A.; DUIM, B.; WAGENAAR, J. A.; VAN DUIJKEREN, E.; WEESE, J. S.; FITZGERALD, J. R.; ROSSANO, A.; GUARDABASSI, L. Clonal spread of methicillin-resistant *Staphylococcus pseudintermedius* in Europe and North America: an international multicenter study. *Journal of Antimicrobial Chemotherapy,* London, v. 65, n. 6, p. 1145-1154, 2010.

PILLAI, S. K.; WENNERSTEN, C.; VENKATARAMAN, L.; ELIOPOULOS, G. M.; MOELLERING, R. C.; KARCHMER, A. W. Development of reduced vancomycin susceptibility in methicillin-susceptible *Staphylococcus aureus*. *Clinical Infectious Diseases,* Chicago, v. 49, n. 8, p. 1169-1174, 2009.

PINTO, N. B. *Avaliação da sensibilidade e caracterização molecular de estafilococos coagulase positiva isolados das narinas de humanos e cães de clínicas veterinárias, Maringá-Pr.* 2012. Dissertação (Mestrado em Biociências aplicadas à Farmácia) - Universidade Estadual de Maringá, Maringá.

RANTALA, M.; LAHTI, E.; KUHALAMPI, J.; PESONEN, S.; JARVINEN, A. K.; SAIJONMAA-KOULUMIES, L.; HONKANEN-BUZALSKI, T. Antimicrobial resistance in *Staphylococcus* spp., *Escherichia coli* and *Enterococcus* spp. in dogs given antibiotics for chronic dermatological disorders, compared with non-treated control dogs. *Acta Veterinaria Scandinavica,* London, v. 45, n. 1-2, p. 37-45, 2004.

REIPERT, A.; EHLERT, K.; KAST, T.; BIERBAUM, G. Morphological and genetic differences in two isogenic *Staphylococcus aureus* strains with decreased susceptibilities to vancomycin. *Antimicrobial Agents and Chemotherapy,* Washington, v. 47, n. 2, p. 568-576, 2003.

REISCHL, U.; FRICK, J.; HOERMANSDORFER, S.; MELZL, H.; BOLLWEIN, M.; LINDE, H. J.; BECKER, K.; KÖCK, R.; TUSCHAK, C.; BUSCH, U.; SING, A. Single-nucleotide polymorphism in the SCCmec-orfX junction distinguishes between livestock-associated MRSA CC 398 and human epidemic MRSA strains. *Eurosurveillance*, Stockholm, v. 14, n. 49, p. 19436, 2009.

RIBEIRO, A.; CORONADO, A. Z.; SILVA-CARVALHO, M. C.; FERREIRA-CARVALHO, B. T.; DIAS, C.; ROZENBAUM, R.; DEL PELOSO, P. F.; LEITE, C. C. F.; TEIXEIRA, L. A.; FIGUEIREIDO, A. M. S. Detection and characterization of international community-acquired infections by methicillin-resistant *Staphylococcus aureus* clones in Rio de Janeiro and Porto Alegre cities causing both community-and hospital-associated diseases. *Diagnostic Microbiology and Infectious Disease,* New York, v. 59, n. 3, p. 339-345, 2007.

RIBEIRO, A.; DIAS, C.; SILVA-CARVALHO, M. C.; BERQUÓ, L.; FERREIRA, F. A.; SANTOS, R. N. S.; FERREIRA-CARVALHO, B. T.; FIGUEIREDO, A. M. First report of infection with Community- Acquired Methicillin-Resistant *Staphylococcus aureus* in South America. *Journal of Clinical Microbiology,* Washington, v. 43, n. 4, p. 1985-1988, 2005.

RICH, M.; DEIGHTON, L.; ROBERTS, L. Clindamycin-resistance in methicillin-resistant *Staphylococcus aureus* isolated from animals. *Veterinary Microbiology,* Amsterdan, v. 111, n. 3-4, p. 237-240, 2005.

ROBERT, J.; BISMUTH, R.; JARLIER, V. Decreased susceptibility to glycopeptides in methicillin-resistant *Staphylococcus aureus*: a 20 year study in a large French teaching hospital, 1983-2002. *Journal of Antimicrobial Chemotherapy,* London, v. 57, n. 3, p. 506-510, 2006.

ROSSI, F.; ANDREAZZI, D. B. *Resistência bacteriana: interpretando o antibiograma*. São Paulo: Atheneu; 2005. 118 p.

RUBIN, J. E.; BALL, K. R.; CHIRINO-TREJO, M. Antimicrobial susceptibility of *Staphylococcus aureus* and *Staphylococcus pseudintermedius* isolated from various animals. *Canadian Veterinary Journal,* Ottawa, v. 52, n. 3, p. 153-157, 2011.

RUSCHER, C.; LUBKE-BECKER, A.; WLEKLINSKI, C. G.; SOBA, A.; WIELER, L. H.; WALTHER, B. Prevalence of methicillin-resistant *Staphylococcus pseudintermedius* isolated from clinical samples of companion animals and equidaes. *Veterinary Microbiology,* Amsterdan, v. 136, n. 1-2, p. 197-201, 2009.

RYBAK, M. J.; CHA, R.; CHEUNG, C. M.; MEKA, V. G.; KAATZ, G. W. Clinical isolates of *Staphylococcus aureus* from 1987 and 1989 demonstrating heterogeneous resistance to vancomycin and teicoplanin. *Diagnostic Microbiology and Infectious Disease***,** New York, v. 51, n. 2, p. 119-125, 2005.

SABAT, A. J.; KOKSAL, M.; AKKERBOOM, V.; MONECKE, S.; KRIEGESKORTE, A.; HENDRIX, R.; EHRICHT, R.; KOCK, R.; BECKER, K.; FRIEDRICH, A. W. Detection of new methicillin-resistant *Staphylococcus aureus* strains that carry a novel genetic homologue and important virulence determinants. *Journal of Clinical Microbiology,* Washington, v. 50, n. 10, p. 3374-3377, 2012.

SASAKI, T.; KIKUCHI, K.; TANAKA, Y.; TAKAHASHI, N.; KAMATA, S.; HIRAMATSU, K. Reclassification of phenotypically identified *Staphylococcus intermedius* strains. *Journal of Clinical Microbiology,* Washington, v. 45, n. 9, p. 2770-2778, 2007.

SCHISSLER, J. R.; HILLIER, A.; DANIELS, J. B.; COLE, L. K.; GEBREYES, W. A. Evaluation of clinical laboratory standards institute interpretative criteria for methicillin-resistant *Staphylococcus pseudintermedius* isolated from dogs. *Journal of Veterinary Diagnostic Investigation,* Columbia, v. 21, n. 5, p. 684-688, 2009.

SCHLEIFER, K. H.; KILPPER, B. R. Transfer of *Streptococcus faecalis* and *Streptococcus faecium* to the genus *Enterococcus* nom. rev. as *Enterococcus faecalis* comb. nov. and *Enterococcus faecium* comb. nov. *International Journal of Systematic Bacteriology,* Reading, v. 34, n. 2, p. 31-34, 1984.

SFACIOTTE, R. A. P. *Perfil fenotípico e genotípico de resistência a antimicrobianos em patógenos bacterianos em animais de companhia.* 2014. Dissertação (Mestrado em Ciência Animal) - Universidade Federal do Paraná, Palotina.

SHEA, K. Antibiotic resistance: what is the impact of agricultural uses of antibiotics on children's health? *Pediatrics,* Springfield, v. 112, n. 1 pt. 2, p. 253-258, 2003.

SHEPARD, B. D.; GILMORE, M. S. Antibiotic-resistant enterococci: the mechanisms and dynamics of drug introduction and resistance. *Microbes and Infection,* Paris, v. 4, n. 2, p. 215-224, 2002.

SOOD, S.; MALHOTRA, M.; DAS, B. K.; KAPIL, A. Enterococcal infections and antimicrobial resistance. *Indian Journal of Medical Research,* New Delhi, v. 128, n. 2, p. 111-121, 2008.

SOUSA, J. C. *Manual de antibióticos antibacterianos.* 2. ed. Porto: Edições Universidade Fernando Pessoa, 2006. 686 p.

STEWARD, C. D.; RANEY, P. M.; MORRELL, A. K.; WILLIAMS, P. P.; McDOUGAL, L. K.; JEVITT, L.; McGOWAN JUNIOR, J. E.; TENOVER, F. C. Testing for induction of clindamycin resistance in erythromycin-resistant of *Staphylococcus aureus*. *Journal of Clinical Microbiology*, Washington, v. 43, n. 4, p. 1716-1721, 2005.

UDO, E. E.; PEARMAN, J. W.; GRUBB, W. B. Genetic analysis of community isolates of methicillin-resistant *Staphylococcus aureus* in Western Australia. *Journal of Hospital Infection*, London, v. 25, n. 2, p. 97-108, 1993.

UMBER, J. K.; BENDER, J. B. Pets and antimicrobial resistance. *Veterinary Clinics North America: Small Animal Practice,* Philadelphia, v. 39, n. 2, p. 279-292, 2009.

UTTLEY, A. H. C.; GEORGE, R. C.; NAIDOO, J.; WOODFORD, N.; JOHNSON, A. P.; COLLINS, C. H.; MORRISON, D.; GILFILLAN, A. J.; FITCH, L. E.; HEPTONSTALL, J. High-level vancomycin-resistant enterococci causing hospital infections. *Epidemiology and Infection*, Cambridge, v. 103, n. 1, p. 173-181, 1989.

VAN DUIJKEREN, E.; KAMPHUIS, M.; VAN der MIJE, I. C.; LAARHOVEN, L. M.; DUIM, B.; WAGENAAR, J. A.; HOUWERS, D. J. Transmission of methicillin-resistant *Staphylococcus pseudintermedius* between infected dogs and cats and contact pets, humans and the environment in households and veterinary clinics. *Veterinary Microbiology,* Amsterdan, v. 150, n. 3-4, p. 338-343, 2011.

VANDENESCH, F.; NAIMI, T.; ENRIGHT, M. C.; LINA, G.; NIMMO, G. R.; HEFFERNAN, H.; LIASSINE, N.; BES, M.; GREENLAND, T.; REVERDY, M. E.; ETIENNE, J. Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Carrying *Panton-Valentine Leukocidin* Genes: Worldwide Emergence. *Emerging Infectious Diseases,* Atlanta, v. 9, n. 8, p. 978-984, 2003.

WANG, Y.; WU, C. M.; LU, L. M.; REN, G. W.; CAO, X. Y.; SHEN, J. Z. Macrolide-licosamide-resistant phenotypes and genotypes of Staphylococcus aureus isolated from bovine clinical mastitis. *Veterinary Microbiology*, Amsterdan, v. 130, n. 1-2, p. 118-125, 2008.

WANNMACHER, L. Uso indiscriminado de antibióticos e resistência microbiana: uma guerra perdida? *Uso Racional de Medicamentos: Temas Selecionados*, Brasília, v. 1, n. 4, p. 1-6, 2004.

WEESE, J. S. Methicillin resistant *Staphylococcus aureus*: an emerging pathogen in small animals. *Journal of the American Animal Hospital Association,* Lakewood, v. 41, n. 3, p. 150-157, 2005.

WEESE, J. S.; VAN DUIJKEREN, E. Methicillin-resistant *Staphylococcus aureus* and *Staphylococcus pseudintermedius* in veterinary medicine. *Veterinary Microbiology,* Amsterdan, v. 140, n. 3-4, p. 418-429, 2010.

WEGENER, H. C. Historical yearly usage of glycopeptides for animals and humans: the American-European paradox revisited. *Antimicrobial Agents and Chemotherapy,* Washington, v. 42, n. 11, p. 3049, 1998.

WEISBLUM, B. Erythromycin resistance by ribosome modification. *Antimicrobial Agents and Chemotherapy*, Washington, v. 39, n. 3, p. 577-585, 1995.

WELLER, T. M. The distribuition of *mecA*, *mecRI* and *mecI* ande sequence analysis of *mecI* and the mec promoter region in staphylococci expressing resistance to methicillin. *Journal of Antimicrobial Chemotherapy,* London, v. 43, n. 1, p. 15-22, 1999.

WENDLANDT, S.; FEBLER, A. T.; MONECKE, S.; EHRICHT, R.; SCHARWS, S.; KADLEC, K. The diversity of antimicrobial resistance genes among staphylococci of animal origin. *International Journal of Medical Microbiology*, Jena, v. 303, n. 7, p. 338-349, 2013

WERNER, G.; COQUE, T. M.; HAMMERUM, A. M.; HOPE, R.; HRYNIEWICZ, W.; JOHNSON, A.; KLARE, I.; KRISTINSSON, K. G.; LECLERCQ, R.; LESTER, C. H.; LILLIE, M.; NOVAIS, C.; PEIXE, L. V.; SADOWY, E.; SIMONSEN, G. S.; TOP, J.; WILLEMS, R. J.; WITTE, W.; WOODFORD, N. Emergence and spread of vancomycin resistance among enterococci in Europe. *EuroSurveill,* Stockholm, v. 13, n. 47, p. 19043, 2008b.

WERNER, G.; GFRÖRER, S.; FLEIGE, C.; WITTE, W.; KLARE, I. Tigecycline-resistant *Enterococcus faecalis* strain isolated from a German ICU patient. *Journal of Antimicrobial Chemotherapy,* London, v. 61, n.5, p. 1182-1183, 2008a.

WERNER, G.; KLARE, I.; WITTE, W. Molecular analysis of streptogramin resistance in enterococci. *International Journal of Medical Microbiology*, Jena, v. 292, n. 2, p. 81-94, 2002.

WORLD HEALTH ORGANIZATION - WHO. WHO list of critically important antimicrobials for human medicine. Geneva: World Health Organisation, 2009. 18 p.

WITTE, W. Medical consequences of antibiotic use in agriculture. *Science*, New York, v. 279, n. 5353, p. 996-997, 1998.

_____. Selective pressure by antibiotic use in livestock. *International Journal of Antimicrobial Agents*, Amsterdan, v. 16, suppl. 1, p. S19-24, 2000.

WOODFORD, N.; LIVERMORE, D. M. Infections caused by gram-positive bacteria: a review of the global challenge. *Journal of Infection*, London, v. 59, suppl. 1, p. S4-S16, 2009.

XU, X.; LIN, D.; YAN, G.; YE, X.; WU, S.; GUO, Y.; ZHU, D.; HU, F.; ZHANG, Y.; WANG, F.; JACOBY, G. A.; WANG, M. *van*M, a new glycopeptide resistance gene cluster found in *Enterococcus faecium*. *Antimicrobial Agents and Chemotherapy*, Washington, v. 54, n. 11, p. 4643-4647, 2010.

YAMAKAWA, J.; AMINAKA, M.; OKUZUMI, K.; KOBAYASHI, H.; KATAYAMA, Y.; KONDO, S.; NAKAMURA, A.; OGURI, T.; HORI, S.; CUI, L.; ITO, T.; JIN, J.; KUROSAWA, H.; KANEKO, K.; HIRAMATSU, K. Heterogeneously vancomycin-intermediate *Staphylococcus* a retrospective study. *Journal of Infection and Chemotherapy***,** Tokyo, v. 18, n. 3, p. 406-409, 2012.

ZANELLA, R. C.; BRANDILEONE, M. C. C.; BOKERMANN, S.; ALMEIDA, S. C. G.; VALDETARO, F.; VITÓRIO, F.; MOREIRA, M. F. A.; VILLINS, M.; SALOMÃO, R.; PIGNATARI, A. C. C. Phenotypic and genotypic characterization of *van*A *Enterococcus* isolated during the first nosocomial outbreak in Brazil. *Microbial Drug Resistance*, Larchmont, v. 9, n. 3, p. 283-291, 2003.