Molecular Diversity of Methicillin-Resistant and -Susceptible *Staphylococcus aureus* Detected in Animals: A Focus on Aquatic Animals

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Abstract: *Staphylococcus aureus* (*S. aureus*) are one of the best-known opportunistic pathogens capable of causing different types of infections in animals. Furthermore, it has the ability to acquire resistance to various antibiotics very easily. Methicillin-resistant *S. aureus* (MRSA) are currently of great concern as they are the leading cause of infections in humans and animals, with a major impact on health and the economy. Several studies already demonstrate that the spread of MRSA is constantly increasing due to its ability to form reservoirs in humans, animals and the environment. In fact, several works have already identified the presence of these bacteria in animals, including domestic animals, farm animals and even wild animals. Furthermore, the incidence of various *S. aureus* strains in aquatic animals has also been reported by different authors, although it is still a rarely discussed topic. Some of these strains have previously been associated with humans and other animals. Strain 398 is the strain that manages to infect a wider spectrum of hosts, having been identified in several different species. Aside from this strain, many others have yet to be identified. In addition, many of these strains have virulence factors and antibiotic resistance genes that worsen the situation. The present work is a review of studies that intend to investigate the epidemiology of this agent in samples of aquatic animals from different origins, in order to better understand its distribution, prevalence and the molecular lineages associated with these species.

Keywords: *S. aureus*; MRSA; wildlife; aquatic animals

1. Introduction

The rapid emergence of multiresistant bacteria is one of the greatest threats to public health worldwide. According to the European Center for Disease Prevention and Control, in Europe alone, antibiotic resistance has an economic impact of around EUR 1.5 billion and is estimated to be responsible for approximately 33,000 deaths each year [1]. This problematic situation is, in large part, related to the incorrect prescription of these drugs, their overuse, and the lack of development of new drugs due to the low economic investment in the pharmaceutical industries [2]. Epidemiological studies have already shown that there is a direct relationship between the overuse of antibiotics and the emergence of resistant bacterial strains. However, despite warnings about the consequences of their overuse, these drugs continue to be highly prescribed worldwide [3], especially penicillins, which currently account for 85% of beta-lactams used [4]. The penicillinase enzyme was first detected in *Staphylococcus aureus* (*S. aureus*) shortly after penicillin began to be used, which shows that the consumption of an antibiotic will eventually favor the selection of resistant strains [5]. Furthermore, in some countries, antibiotics can be easily purchased without the need for a medical prescription and at a low cost, which can cause their consumption to be uncontrolled [6]. The incorrect prescription of antibiotics in the hospital sector also contributes to the emergence of resistance. According to some studies, the choice of antibiotic, as well as the duration of treatment, is incorrect in 30–50% of cases [7]. The incorrect prescription of these drugs has questionable therapeutic benefits and can bring potential complications for the patient [8]. The use of these drugs in the agricultural sector has also been identified as a risk factor for the emergence of resistance and has received special attention in recent years. Although the administration of antibiotics in farm animals has already been banned in Europe, in many countries, antibiotics continue to be used indiscriminately to promote the growth of these animals [9]. The indiscriminate use of antibiotics, whether in human or veterinary medicine, creates a natural selective pressure in which resistant bacteria survive and reproduce, even in the presence of the antibiotic [10]. When used in sub-inhibitory concentrations, an antibiotic is able to promote genetic alterations, such as alterations in gene expression, horizontal gene transfer and mutagenesis [11]. Antibiotic-induced changes in gene expression can increase the virulence of the bacterial strain in question, while mutagenesis and horizontal gene transfer processes promote antibiotic resistance and its spread, respectively [11]. Although this issue has emerged in clinical practice, antimicrobial resistance is found in several other sectors such as animal production facilities, agriculture, effluents and water systems, making it a problem that involves not only humans and animals, but also the entire environment [12–16]. In addition, the microorganisms found in the environment converge with human and animal pathogens, and there may be exchanges and transfers of resistance genes between different bacterial strains, which further aggravates this problem [5]. Due to this situation, it has already been estimated that most antibiotics currently used to fight bacterial infections will become completely useless within five to ten years, taking us back to the pre-antibiotic era [10].

2. *Staphylococcus* spp.

The *Staphylococcus* genus belongs to the Staphylococcaceae family and features cocci-shaped microorganisms that are capable of causing various infections. This family includes more than 45 species and 24 subspecies, presenting typically respiratory and fermentative metabolisms, most of them aerobic or facultative anaerobic [17]. These bacteria were first described by surgeon Sir Alexander Ogston in the 1980s and their name comes from the Greek staphylos (grape) and kokkos (berry). They are typically characterized as being Gram-positive and catalase-positive, although some strains have been identified as catalase-negative. Furthermore, these bacteria are capable of producing a huge variety of virulence factors responsible for their level of pathogenicity [18].

S. aureus are one of the species of the Staphylococcaceae family, classified as coagulase-positive (SCoP), oxidase-negative and salt-tolerant (they are able to grow in a medium

containing 10% NaCl) [17]. These bacteria are generally commensal residents of the human flora, residing in the skin and mucosa of about 30% of individuals. However, commensal staphylococci are recognized as opportunistic pathogens capable of causing a wide variety of infections [19]. In the case of *S. aureus* these infections can range from skin and soft tissue infections to more severe infections such as necrotic pneumonia, endocarditis and osteomyelitis [20]. This bacterium has the ability to infect almost every organ system in the human body, often with fatal consequences. This remarkable adaptability is largely due to the wide range of virulence factors they produce, many of which are encoded in plasmids, transposons, prophages, and pathogenicity islands [5]. The acquisition of resistance genes to a variety of antibiotics has made *S. aureus* one of the most important pathogens today. Methicillin-resistant *S. aureus* (MRSA) are currently a serious problem in hospitals around the world. These bacteria are estimated to be responsible for around 171,200 infections in Europe each year [21]. These bacteria were first described in 1961 in England, shortly after methicillin was introduced into clinical practice [22]. However, the genome sequencing of some isolates suggests that these bacteria may have emerged in the 1940s, due to the excessive use of penicillin [22]. In fact, just 2 years after the introduction of penicillin, around 80% of *S. aureus* isolates were resistant to this antibiotic [23]. Methicillin resistance occurred through two distinct mechanisms: firstly, by producing enzymes that hydrolyze and destroy beta lactams, called beta lactamases, which were encoded by the *bla*Z gene [24]; then, by producing a modified penicillin binding protein (PBP2a) that participated in the synthesis of peptidoglycan, a natural component of the bacterial cell wall. However, this modified protein had an inaccessible active site, preventing antibiotic binding and thus, cell wall synthesis was not affected, allowing the bacteria to survive [23]. The PBP2a protein was encoded by the *mec* genes (*mec*A/*mec*C). These genes were embedded within the staphylococcal *mec* cassette (SCC*mec*), a highly transmissible mobile genetic element between bacteria, which could be classified into at least 14 different types (I-XIV) [25].

Initially, MRSA was restricted only to the hospital environment, causing different types of nosocomial infections and, for this reason, they were called HA-MRSA (Hospital-acquired MRSA) [26]. Years later, MRSA began to be identified in individuals with no prior contact with the hospital environment and thus came to be called CA-MRSA (Community-acquired MRSA) [27]. More recently, a third type of MRSA strain associated with farm animals (LA-MRSA) has been reported. Genotypically CA-MRSA strains were newer and more virulent and usually contained SCC*mec* type IV or V [26]. Despite being susceptible to non-beta lactam antibiotics, these strains generally carried the gene for Panton-Valentine leukocidin, a protein associated with greater virulence [28]. On the contrary, HA-MRSA strains were associated with SCC*mec* types I, II, and III, and were resistant to non-beta lactam antibiotics, especially aminoglycosides, macrolides, lincosamides and fluoroquinolones [26].

CA-MRSA strains have been extensively studied in recent years and have been reported in several animals including domestic pets, cattle, pigs and horses, as well as in wild animals. Conversely, MRSA strains associated with farm animals (LA-MRSA) have emerged in the human population, which highlights the idea that there is a traffic of these microorganisms between different species.

3. MRSA in Animals

The first reported case of MRSA infection in animals was the case of a bovine mastitis that occurred in Belgium in the early 1970s. After this case many others followed in both companion and farm animals. Molecular typing studies demonstrated that some MRSA strains have host specificity, while others were capable of colonizing or infecting a wide variety of animals [29]. Typing studies were of high clinical and epidemiological importance as they allowed for the determination of causes of infection, modes of transmission and relationships with other bacteria, as well as accessing the specific characteristics of a particular genetic lineage [5]. Thus, MRSA were generally characterized by Multilocus

Sequence Typing (MLST), *spa*-typing or SCC*mec* typing. Table 1 describes the main MRSA genetic lines associated with companion and farm animals.

Table 1. Major MRSA strains associated with companion animals and farm animals.

	ST	*spa*-**Types**
Companion animals	ST5, ST22, ST398	t032, t432, t747, t4726
Horses	ST1, ST8, ST22, ST254, ST398	t11, t036, t127
Pigs	ST1, ST9, ST97. ST398	t011
Cattle	ST8, ST130, ST398	t011, t034
Birds	ST5, ST398	t011, t567

ST: sequence type.

In farm animals, the first case of MRSA colonization was reported in 2005 in the Netherlands [30]. This new MRSA clone with ST398 was identified in pigs and clustered within the clonal complex (CC) 398 [9]. In another European study that analyzed the presence of MRSA associated with pigs, it was found that the most frequent strain was ST398, but other strains such as ST1, ST9 and ST97 were also reported [31]. In fact, it is scientifically well-known that the CC398 strain asymptomatically colonizes about half of these animals in swine farms. Although ST398 is mostly associated with swine, this lineage has also been reported in other farm animals [32,33]. This strain has a broad host spectrum and is commonly found in 77–86% of people with occupational activities who have direct contact with pigs, causing the same type of infections in humans as other strains of *S. aureus* or MRSA in general [34]. Additionally, the strain CC130 appears to have a low host specificity. In a very large study by Monecke et al., 2016, this strain was identified in a huge variety of animals such as the rat, hedgehog, red fox, common hare and deer [35]. Some MRSA strains appear to be specific to bovines, namely CC130, ST425 and CC1943 [29]. In fact, *S. aureus* is currently the leading cause of infection in cows, with a huge economic impact on the dairy industry [29]. A study by Tenhagen et al. concluded that most MRSA isolates obtained from these animals, regardless of their origin, belonged to the types t011 and t034, both associated with the CC398 clonal complex [36].

Regarding birds, the CC5 clonal complex seems to be the predominant complex, being widely distributed in several continents [37]. In the study by Monecke et al. this clonal complex was identified in gray partridge [35]. Although CC5 seems predominant, CC398 isolates associated with chickens and turkeys with *spa* types t011 and t567 have been identified in Europe [38].

In the case of companion animals such as dogs and cats, a correlation between the clonal types found in these animals and the clonal types that infect humans in the same geographic region has already been verified [29]. Apparently, contact between pets and their owners favors the transmission of these bacteria. Therefore, the clonal types most frequently found in companion animals correspond to the clonal types dominant at that location. For example, in the UK, MRSA isolates from dogs correspond to the dominant HA-MRSA strain at that site, ST22 [39]. The same results are obtained in Portugal, where four different *spa* types were identified (t032, t432, t747 and t4726), with t032 being the most frequent [40].

In horses, the most frequently found MRSA strains are, as with companion animals, strains associated with humans. The strain, CC8 (ST8 and ST254), is associated with the most cases of colonization and infection in horses in Canada, while in Europe the most frequently reported strains are ST1, ST22, ST254 [41]. In the same study, the *spa* types reported were t036, t011 and t127, with t036 being the most frequent.

Regarding wild animals, a study by Porrero et al., 2014, analyzed the genetic diversity and predominant genotypes in different animal species in Spain [42]. Samples were collected from the skin and nostrils of animals and the isolates were characterized by *spa*-typing and MLST. Sixty-three different *spa*-types were identified, of which the most common was t528 (Iberian ibex), followed by t548 and t11212 (red deer) and t3750 (wild boar). Regarding the sequence types (ST), through the MLST technique, it was possible

to identify 27 different STs. The most frequent STs were ST581 (Iberian ibex), ST425 (red deer) and ST2328 (wild boar). More recently, the presence of an CC398-MRSA isolate was identified with a new variant, SCC*mec* type IV J3, in wild boar [43]. Monecke et al. analyzed fecal samples from 2,855 wild animals. In total, 155 *S. aureus* were isolated, of which 124 were further genetically characterized. From a genetic point of view, 29 different clonal complexes (CC) were identified as associated with different animal species, namely: CC1, CC5, CC6, CC7, CC8, CC9, CC12, CC15, CC22, CC25, CC30, CC49, CC59, CC88, CC97, CC130, CC398, CC599, CC692, CC707, CC1956, and CC2767 [35].

Silva et al. have also identified the presence of MRSA in wild rodent samples. In this study, six MRSA were identified, three of which contained the *mec*C gene, while the other three contained the *mec*A gene [44]. All *mec*C-MRSA isolates belonged to ST1945 (which belonged to CC130) and spa-type t1535, while *mec*A-MRSA isolates belonged to ST22 and ST36 with spa-types t747 and t018. Furthermore, this was the first study to report MRSA *mec*C in Portugal. Different results were obtained by Mrochen et al. who obtained MRSA isolates from different strains, the most common being CC49, followed by CC1946 and ST890 [45]. In this work, similarly to the previous one, one *mec*C-MRSA isolate was also identified, showing that rodents function as reservoirs or vectors of *S. aureus*.

4. MRSA in Aquatic Animals

In general, it is possible to verify that there is a huge genetic variety of *S. aureus* associated with different animal species in several continents. Wildlife can serve as a reservoir for *S. aureus*, and later on there may be a transmission to domestic animals, farm animals and, directly or indirectly, to humans. These natural *S. aureus* reservoirs contribute to the exchange of resistance and virulence genes between bacteria, enhancing the appearance of new strains [46]. Table 2 shows the genetic diversity of MRSA and methicillin-susceptible *S. aureus* strains (MSSA) strains isolated from aquatic animals.

Table 2. Animal species: location of isolation and genetic lineages of MSSA and MRSA isolated from aquatic animals.

Animal Species	Location	MRSA/MSSA (Number of Isolates)	Clonal Lineages		Virulence	Reference
			spa-Type	ST/CC		
Canada geese (*Branta canadensis*)	Northeast Ohio, USA	**MRSA (7)** MSSA (6)	**t008, t2595, t127**, t1149, t002, t008, t1451, t15031, t688	**ST8**, ST291, ST5, ST8, ST398, ST211	**PVL+, PVL−,** PVL−	[47]
Green mussels (*Perna canaliculus*)	Malasya	**MRSA (4)**	n.d.	n.d.	n.d.	[48]
Blood cockles (*Anadara granosa*)		**MRSA (3)**				
Risso's dolphin (*Grampus griseus*)	Italy	**MRSA (2)**	**t008**	**ST8**	n.d.	[49]
Bottlenose dolphin (*Tursiops truncatus*)						
Mud crab (*Scylla serrata*), Snake head fish (*Channa striatus*), Milk fish (*Chanos chanos*), Mackerel (*Rastrelliger kanagurta*), Indian anchovy (*Stolephorus indicus*), Indian prawn (*Penaeus indicus*), Scampi (*Macrobrachium rosenbergii*), Deep sea crab Mullet (*Mugil cephalus*), Black clam meat (*Villorita cyprinoides*)	India	**MRSA (8)**	**t15669, t311**	n.d.	n.d.	[50]

Table 2. *Cont.*

Animal Species	Location	MRSA/MSSA (Number of Isolates)	Clonal Lineages		Virulence	Reference
			spa-Type	ST/CC		
Mud crab (*Scylla serrata*), Pearl spot (*Etroplus suratensis*), Tilapia (*Tilapia mosambica*), Mullet (*Mugil cephalus*), Indian anchovy (*Stolephorus indicus*), black clam meat (*Villorita cyprinoides*)	India	**MRSA(6)**	**t186, t121, t311, t15669**	n.d.	n.d.	[50]
Shellfish (*Corbiculid heterodont*)	Nigeria	**MRSA(35)** MSSA(10)	n.d.	n.d.	n.d	[51]
Sea Bass (*Dicentrarchus labrax*)	Korea	**MRSA (1)**	n.d.	**ST72**	**PVL−**	[52]
Rockfish (*Sebastes*)	Korea	**MRSA (1)**	n.d.	**ST1**	**PVL−**	[52]
Short-Finned Pilot Whales (*Globicephala macrorhynchus*)	USA	**MRSA (6)**	**t008, t126**	**ST8, ST72**	n.d.	[53]
Mute swan, (*Cygnus olor*)	Sweden	MSSA(1)	n.d.	CC133	n.d.	[35]
Moose (*Alces alces*)	Sweden	MSSA(18)	n.d.	ST2691 CC15, CC97	n.d.	[35]
Harbour porpoise, (*Phocoena phocoena*)	Sweden	MSSA(1)	n.d.	CC12	n.d.	[35]

Abbreviations. ST: sequence type; CC: clonal complex; PVL: Panton-Valentine leucocidin; n.d.: not determined. Note: *spa*-types and CC/ST in bold correspond to MRSA isolates.

A study on the characterization of *S. aureus* in fecal samples of Canadian geese identified the presence of both MSSA and MRSA in these samples. In this study, 182 samples were analyzed. Of these, 13 were contaminated by *S. aureus* (7.1%, 13/182). Of the 13 positive *S. aureus* isolates, seven were MRS's (3.8%) and six MSSAs (3.3%). The authors performed the characterization of the isolates using MLST, *spa* typing and PCR to detect the presence of the Panton-Valentine, *mec*A and *scn* protein genes. The results of the molecular characterization showed that a total of eight different *spa* types were identified among the 13 isolates obtained, of which t008 was the most common (46.2%, 6/13). A total of five different STs were also identified, ST8 being the most common, followed by ST5. The *mec*A gene was identified in 53.8% (7/13) of the isolates, while the *scn* gene was found in all isolates. As for the PVL gene, only one isolate (7.7%, 1/13) was considered positive. The isolates also showed resistance to several antibiotics such as penicillin, erythromycin, clindamycin and oxacillin [47]. The presence of *scn* and tetracycline susceptibility indicated that the ST398 isolates were likely human-adapted isolates of the CC398 lineages [54,55]. In this study it was not clear how the geese acquired *S. aureus*, or whether it is spread among animals. However, the environmental contamination through freshwater beaches is one possibility. In turn, geese, as well as other birds carrying *S. aureus* may have spread the bacteria into human areas via their feces [56,57]. Although this is the first study to document MRSA in goose feces, the authors recommend additional research to determine whether animal species including migratory birds are colonized with MRSA or whether they are persistent reservoirs for drug-resistant organisms.

Another study carried out in Italy linked the death of two dolphins to an infection caused by a strain of MRSA. In this study, the two animals of different origins were submitted to a detailed necropsy through microbiological examinations, among others. Confirmation of MRSA was done through genetic analyses such as spa-typing, PFGE and MLST. In both animals, the MRSA strain found belonged to ST8 and spa-type t008. Through the PFGE analysis it was possible to conclude that the analyzed strains were 100%

identical. It was also possible to identify the presence of the *nuc* gene, as well as other genes responsible for antibiotic resistance such as the *mec*A gene and other penicillinase genes (*bla*Z, *bla*I, *bla*R). This is the first work to identify the ST8 *t*008 strain in dolphins, although this strain has already been randomly isolated from human patients, as well as from other animals [49]. Previous studies already expressed a concern for the potential pathogenicity of *S. aureus* in those animals [58–61]. However, the authors of this study consider that the predisposing factors impairing the immune system of these dolphins played a central role in their death. Consequently, the isolated bacteria should not be considered as the primary cause of their decease. However, these findings support the need for a continuous monitoring plan to be implemented in both wild animals and domestic animals under human care, both in open and closed water systems.

Hower et al., 2013, identified the presence of MRSA ST8 and ST72 in short-finned pilot whales in a marine mammal rehabilitation center. In this study, in addition to samples from animals, samples from human volunteers, sand and seawater were also analyzed. After characterizing the MSSA and MRSA isolates, the authors concluded that there was a certain degree of similarity between the strains isolated from the environment, whales and volunteers. PGFE analysis indicated that most of the MRSA isolates obtained were identical or highly similar to the human strain USA300 [53]. Because of their natural habitat, it was unlikely that these animals were previously colonized with human-associated strains of MRSA, such as USA300. Nevertheless, studies have reported the presence of MRSA and drug-resistant *S. aureus* in animals with no previous contact with antibiotics, or in animals living in areas with a very low antimicrobial selection pressure [62–64]. The authors suggest that the source of contamination was the beach sand that may have acted as a bacterial reservoir for adjacent waters where the whales were exposed during initial events. Indeed, studies have shown that the water near beaches may be a reservoir of antimicrobial resistant bacteria, including MRSA [65–68]. Thus, this study supports the idea that there is a potential for the transmission of this agent from humans to animals, either directly through contact with them or indirectly through sand or seawater. To prevent or reduce *S. aureus* spread in these facilities, the authors suggest showering prior to entering the rehabilitation and hand washing. Besides that, protocols to increase flow and filtration of water at rehabilitation sites are also reasonable based on these results.

Colonization by *S. aureus* has also been reported in other aquatic animals such as white swan and common porpoise. One *S. aureus* isolate belonging to the clonal complex CC133 associated with a white swan and an isolate CC112 in a common porpoise has been identified [35].

Other studies of high importance have also revealed the presence of MRSA in marine animals for human consumption. In a study by Rhee and Woo, the authors proposed to determine the susceptibility of *S. aureus* isolates from food samples, as well as to characterize the virulence of MRSA isolates using MLST and PFGE techniques. In this work, 165 strains of *S. aureus* from different origins (meat, fish and processed foods) were analyzed. The 165 isolates obtained exhibited different resistance profiles, with the vast majority (90.9%) being resistant to at least one antibiotic. From a general point of view, most of the isolates were resistant to beta-lactams such as penicillin (72.7%) and ampicillin (72.7%). The high percentage of resistance to the antibiotics penicillin and ampicillin is, according to the authors, related to the massive administration of these drugs in animal production in Korea. Furthermore, MRSA strains isolated from fish had high minimum inhibition concentrations (MICs) for gentamicin, presumably due to the frequent use of this antibiotic in Korean aquaculture [52]. Of the 165 isolates of *S. aureus*, four (2.4%) were identified as MRSA because they were resistant to oxacillin and carried the *mec*A gene. Of the four strains, one was identified as ST1 and originated from a sea bass sample, two ST72 (meat and rockfish sample) and the remaining sample from a single locus variant of ST72 (ST72 slv) (meat sample). The ST1 strain has already been identified as the largest epidemic clone related to food poisoning incidents in Korea, in addition to being reported as the clone most commonly identified in drug addicts and the homeless, while ST72 is identified as

the largest CA-MRSA genotype and even caused a community outbreak in the country between 2004 and 2005. These results reinforce the evidence that there is an increasingly large transmission of resistant pathogens, which are a central cause of food poisoning in Korea [52]. Therefore, it is important to improve hygiene in food production practices to limit the spread of antimicrobial-resistant organisms via food [69,70].

In India, a study of the route of MRSA contamination within a fish market revealed the presence of MRSA in several species of fish and shellfish. According to the authors, since *S. aureus* and MRSA are not native residents of the fish flora, the contamination of these animals must occur through water or through their inadequate handling [50]. Murugadas et al., 2017, collected samples from the locations of the dock to the fish market. In total, 17 samples were collected, and the sampling process was repeated the following week to validate the procedure. After the isolation procedure and molecular confirmation by PCR, it was confirmed that 35.2% and 23.5% of the samples (1st and 2nd week of samplings, respectively) contained MRSA. Through the *spa*-typing technique, it was possible to identify several *spa*-types (t186, t121, t311 and t15669) and trace the contamination route. According to the authors, the sources of contamination of fish and seafood were the lake water and ice used during the handling and conservation of the fish on the dock, which was later transferred to the fish market, indicating a community risk of MRSA infection associated with livestock activity [50]. Although MRSA prevalence is not at a significant level, it is important to be aware that, in the long run, these MRSA clones may become endemic persistent microbial contaminants in seafood and may pose a risk to the public. The authors suggest a continuous documentation of prevalent MRSA clones in the fisheries sector to control the spread of these organisms.

Othman et al., 2018, and Egege et al., 2020, reported the presence of MRSA and MSSA in shellfish samples with resistance to several antibiotics. The first investigated the occurrence of MRSA in a total of 80 samples of green mussel and cockle [48]. Samples were randomly collected from various fish and seafood markets in Malaysia over a 5-month period. The authors used a combination of two techniques (most probable number (MPN) and multiplex polymerase chain reaction (mPCR)) to identify the occurrence of *S. aureus* and MRSA in these samples. In fact, the occurrence of *S. aureus* and MRSA in these samples was 15% and 8.5%, respectively, with a microbial load ranging from <3 to 12.2 MPN/g. The authors also tested the susceptibility of the isolates to 17 antibiotics using the disk diffusion method. The results showed that all isolates were resistant to amikacin and penicillin. However, there was no resistance to the remaining antibiotics tested. Furthermore, coagulase-negative Staphylococcus were reported [51].

It is known that the occurrence of *S. aureus* is linked with high-protein foods, such as seafood. Heating, sanitizing agents, proper handling practices and a higher quality of raw fish could be good measures to prevent the spread of *S. aureus* and other pathogenic bacteria [71,72]. In these studies of marine animals for human consumption, fish and shellfish are of high importance as these are generally consumed raw or partially cooked, so there is a high risk of transmission to humans.

Although only a few studies have been conducted regarding the presence of MRSA and MSSA in aquatic animals, the most common clonal lineage among these animals was ST8-t008. This particular clone is also known as the USA300 and is one of most widespread *S. aureus* clones [73]. Initially, this clone was associated with CA-MRSA, but it has been isolated from patients in healthcare facilities, animals and the environment [73–76]. USA300 gained much attention recently due to its pathogenic properties and virulence which were linked to severe infections [77]. MRSA USA300 strains had a few specific features such as belonging to SCC*mec*IV and being PVL-positive [74]. However, most of the studies mentioned above did not investigate the SCC*mec* type, nor the presence of PVL. MRSA ST72 was detected in two animals, namely, whales and sea bass, from the USA and Korea, respectively. ST72 was the most significant and prevalent CA-MRSA clone in South Korea [78]. Nevertheless, this clone has been identified in the meat and milk production chain in Korea [79,80]. CC133 and CC97 were also detected in aquatic animals. Both `clonal`

lineages were associated with ruminants and were reported in [81,82]. Other MRSA and MSSA clonal complexes found among aquatic animals, such as, CC1, CC12 and CC15, were common in human strains, either causing infections or colonizing the organism [83].

5. Conclusions

The results obtained in different studies show that *S. aureus* is widely distributed in the aquatic environment, presenting a huge diversity of genetic lineages. Some of these strains have previously been associated with humans and other animals. Strain 398 is the strain that manages to infect a wider spectrum of hosts, having been identified in several different species. Furthermore, many of these strains have virulence factors and antibiotic resistance genes, in part due to the use of these drugs in aquaculture. For this reason, it is increasingly important to distinguish between the different reservoir-adapted clades of MSSA and MRSA to better control the spread paths and to implement more focused measures to prevent MRSA from spreading.

This review, as with some previous studies in this field, highlights that particular attention must be paid to the early recognition of a scenario in which MRSA from animals could readapt to humans and be retransmitted to animals, where it can become a frequent colonizer and transmit once again to humans and have a pronounced capacity to spread.

In future studies, we suggest that DNA sequencing (such as whole-genome sequencing) will be helpful to elucidate the process of MSSA or MRSA re-adaptation and to better understand the type of the transmission.

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