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Chapter 3

Methicillin-Resistant *Staphylococcus aureus* (MRSA) in Food-Producing and Companion Animals and Food Products

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Additional information is available at the end of the chapter

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a growing concern in companion and food-producing animals. The presence of multidrug-resistance with a wide range of extracellular enterotoxin genes, virulence factors, and Panton-Valentine leukocidin (*pvl*) cytotoxin genes confer life-threatening traits on MRSA and makes them highly pathogenic and difficult to treat. Clonal complex 398 (CC398), a predominant clonal lineage of livestock-associated-MRSA in domestic animals and retail meat, is capable of infecting humans. In order to monitor and prevent MRSA contamination, it is critical to understand its source and transmission dynamics. In this review, we describe MRSA in food-producing animals (pig, cattle, chicken), horses, pet animals (dogs, cats), and food products (pork, beef, chicken, milk, and fish).

Keywords: MRSA, companion animals, food-producing animals, food products, CC398

1. Introduction

Staphylococcus aureus is a pathogen that causes both human and animal infections and food intoxication [1–3]. It causes simple infections, such as furuncle, boil, stye, impetigo, carbuncle, and keratitis, and serious infections, including septicemia, necrotizing pneumonia, endocarditis, osteomyelitis, and pericarditis [4–7]. Shortly after the introduction of methicillin in clinical practice to control penicillin-resistant staphylococci, the first methicillin-resistant *S. aureus* (MRSA) was isolated [8]. MRSA is one of the most important hospital-acquired pathogens that are resistant to various antimicrobials, thereby making their treatment complicated [9]. MRSA

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in humans is usually divided into two groups: hospital-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) [10]. A third group of MRSA, known as livestock-associated MRSA (LA-MRSA), now has emerged and infects livestock, pets, and wild animals.

LA-MRSA was first detected in milk with bovine mastitis from Belgium in 1972 [11–13]. Thereafter, MRSA reports in various food and companion animals, such as pigs, cattle, chickens, dogs, cats, and horses, have increased [11, 14]. A novel strain of MRSA belonging to multilocus sequencing type (MLST) 398 (ST398) and related strains collectively grouped into clonal complex 398 (CC 398) have been frequently found in pigs, chickens, veal calves, dairy cattle, horses, dogs, and milk in various countries [11]. Both methicillin-susceptible *S. aureus* (MSSA) and MRSA have been associated with companion and food production animals [15–19]. The most significant of these is intramammary infection of dairy cattle leading to mastitis, which causes a substantial economic loss to the dairy industry worldwide [6, 20, 21]. The CC398 *S. aureus* isolate was more prevalent in nasal swabs of pig and cattle farmers than of non-farming human controls [22, 23]. An examination of livestock-associated MRSA (LA-MRSA) in human case isolates in the Netherlands indicated an increase from 0% in 2002 to greater than 21% in mid-2006 [23] and 35% in 2009 [24]. In most European countries, CC398 remains the most commonly identified type of LA-MRSA [15, 25–27]. However, the epidemiology of LA-MRSA differs in other geographic areas. A different strain of LA-MRSA, CC9, appears to be the prominent type in several Asian countries [28–32]. Poultry may harbor CC398 strains [16, 33, 34] but CC5 [33, 35] and other types unrelated to CC398 have also been reported [36]. The diversity of LA-MRSA in the USA appears to be higher than that identified in Europe or Asia, with reports of both CC398 as well as a variety of "human" types of *S. aureus* in livestock.

LA-MRSA infections among livestock animals and associated farmers are of great concern as these sources could potentially serve as reservoirs for zoonotic infections [14]. Contamination of food with enterotoxin producing *S. aureus* leads to over 240,000 cases of food-borne illness in the United States annually. Although most *S. aureus*–related food-poisoning incidents are self-limiting and go away within 2 days, some serious infections have been reported as well [4, 5]. A large number of the reported staphylococcal food-poisoning outbreaks can be traced back to a human source harboring *S. aureus* producing certain staphylococcal enterotoxins (SEs) [1, 37]. Most of the LA-MRSA strains, particularly the ST398 group, do not appear to code for any of the known SEs [11, 38–42]. However, genes for SEs B, K, and Q have been detected in MRSA CC398 strains isolated from geographically diverse pig farms in Germany [43]. The acquisition of enterotoxin genes along with the virulence factors, such as Panton-Valentine leukocidin (*pvl*) genes by LA-MRSA may eventually pose a threat to humans, suggesting that animals have the potential to be a source of primary contamination as well [16, 44].

2. MRSA in food-producing animals

2.1. Porcine MRSA

In 2005, pigs were reported as an animal reservoir of *S. aureus* in France, including MRSA [17]. Pig farmers were more frequently colonized than nonfarmers and one of the most

prevalent strains of *S. aureus* in pig farmers was CC398 [45–49]. Forty-five percent of veterinarians attending pig farms in the Netherlands were positive for MRSA [48]. In Belgium and Denmark, the prevalence of MRSA in veterinarians was 9.5% and 1.4%, respectively [47]. German researchers reported that MRSA ST398 that carried SCC*mec* IV or V, accessory gene regulator type I and capsule type 5 [25] in pig primary production herds was higher in their country (45–70%) than in the rest of the European Union [45, 46]. In an interesting report, 12.5% of attendees at an international meeting concerning pig health carried MRSA and 91.2% (31/34) of them CC398 [50]. While early studies on farms and of meat identified CC398 strains in animals, farm workers, and meat products [51, 52], other studies also documented CC398 in populations with no obvious livestock contact [53–55]. The emergence of this strain was also reported in pigs and pig farmers in the Netherlands [22, 56, 57], Denmark [58], Germany [59], and Canada [60]. Detection rates of MRSA in breeding and production herds were 46%, 43.5%, and 40% in Spain, Germany, and Belgium, respectively, but no single strain of MRSA was found in Finland and Denmark in 2008 [61]. The majority of LA-MRSA lineage belonged to ST398, accounting for 92.5% of the MRSA isolates. Other ST types, human-associated MRSA ST1 and cattle-associated ST97 in finishing holdings, and ST9 in the same animal species in Europe [62], CC9, and CC49 in Switzerland [63] have also been reported.

Various farm types in the Netherlands were reported to have MRSA in 23–71% of their pigs, and it was especially high in farms with finishing pigs (pigs are almost ready to be sent to market) [49, 57, 64]. The presence of MRSA is dependent on pig production type and herd size and increases from 31 to 86% depending upon small-, medium-, and large-sized farms carrying <250, >500, and >1000 animals, respectively [45, 62, 64, 65]. MRSA prevalence also varied with farm type, e.g., fattening and closed (farrow-to-finish) farms exhibited 94 and 56% MRSA, respectively [66]. Transportation from farm to slaughterhouse [38, 67], lairage [38], national and international trade [57], and slaughter house employees all have been reported to enhance MRSA contamination and may play important roles in transmission of the bacteria [68]. It was proposed that MRSA contamination in piglets is dependent on the status of sows [69]. When a sow was colonized with MRSA, 100% piglets were MRSA-positive. However, 84% piglets were MRSA-positive when there was no MRSA contamination in a sow. Higher numbers of MRSA were isolated in suckling (52.9%) and weanling piglets (53.4%) than sows (38.3%) [64]. Prevalence of MRSA in pigs has been linked to their age but the data are not conclusive. MRSA were identified in 100% of 9–12-week-old pigs, whereas in adult animals it decreased to 36% [51]. On the other hand, Weese et al. [69] reported that MRSA was more prevalent in post-weaning (85%) than preweaning pigs (34.5%) in pig farms without antimicrobial treatment. Percent of MRSA colonization in Canadian piglets on days 1, 28, 56, and 70 were 1, 34, 50, and 42%, respectively [69]. Khanna et al. [60] reported no variation in MRSA prevalence based on age groups. MRSA does not seem to cause serious infection in pigs, but there have been a few reports of MRSA from exudative epidermitis lesions of piglets on a breeding farm [70] and in pigs suffering from infection of the urinary-genital tract, skin infection, and metritis-mastitis-agalactia syndrome [71]. While MRSA ST398 isolated from diseased pigs did not carry the major virulence genes, such as toxic shock syndrome toxin 1, *pvl*, and exfoliative toxins, they carried some virulence genes, such as α- and δ-hemolysins, proteases, capsule type-specific genes, microbial surface components recognizing adhesive matrix

molecules, biofilm-associated, and enterotoxin genes [44]. Their MLST, *spa*, and SCC*mec* types were identified as ST398, t011, and IV, respectively.

The epidemiology of livestock-associated *S. aureus* in the USA appears to be notably different than that in European countries. Most of the porcine MRSA isolates in Canada, Europe, Peru, and USA were CC398 [65]. A human epidemic clone, Canadian MRSA-2 (CMRSA-2, USA100, CC5), was found in nasal and rectal swabs of pigs in Canada [60]. This isolate was the most common cause of health care-associated infections in Canada. CMRSA-5 (USA500, ST8) also isolated from retail pork in Canada, is a human epidemic strain that also has been documented in horses and horse personnel [72]. Three *spa* types (t011, t034, t108) within CC398 were the most frequent in breeding and production herds in Europe, and t108 was most popular only in the Netherlands among European countries. On the contrary, prevalence of t899 in Italian breeding and production herds was between 24% and 27% [62, 65]. In Italy, CC1 and CC97 lineages among MLST types that do not belong to CC398 were significantly high in the primary production of pigs [62]. In one study carried out in a jail setting in Texas, CC398 isolates made up of 13.2% of all MSSA identified within this population. Apart from CC398, other human strains of *S. aureus* have also been found in USA livestock. Studies carried out on swine farms in the USA have identified human strains within the noses of live animals [55, 73, 74] and farm dust [75]. Several papers have reported CC5 strains rather than CC398-associated types to be the dominant strain isolated from pig farms in both Iowa and Ohio [75, 76], whereas others have found CC398 to be the most common molecular type [51, 76]. Studies on workers on pig farms and in processing plants found substantial diversity within *S. aureus* isolates, including CC398, CC5, and CC8 strains, among others [77–79]. MRSA attributed to ST5 was recently reported in pigs in the USA [38]. A different swine-associated MRSA strain, CC9, is circulating among pigs and pig farmers in China and Malaysia [29, 30, 80, 81]. MRSA ST22, known as human epidemic clone EMRSA-15 in the UK, was also discovered in pigs and in hospitalized patients in Singapore with an elevated frequency [82, 83]. High frequency of MRSA CC9 with *spa* types t899 and t4358 was reported in porcine samples in Asian countries, whereas it was not found as much in Europe or the USA [28–30, 84]. In Thailand, porcine MRSA ST9 isolates had a unique *spa* type (t337) and SCC*mec* type (SCC*mec* IX) that were different from other LA-MRSA ST9 strains found in Asian countries [28]. In 2012, Lim et al. [85] reported two ST types, livestock-associated ST398 and human-associated ST72, from pigs, which was the first finding of ST398 in Korean pigs.

2.2. Bovine MRSA

The first report of MRSA in farm animals was published in the early 1970s, when the bacteria were isolated from the milk of dairy cows with mastitis in Belgium [86] and clustered in the CC398 group [87]. Devriese and Hommez [88] suspected that these samples were most likely contaminated by humans. In the past few years, MRSA has been isolated from cows or their milk in Korea [89–91], Hungary, Mexico, and the Netherlands [89, 92, 93]. There have also been numerous reports of MRSA from cows or their milk in Brazil, Italy, Pakistan, Nigeria, Turkey, and the USA [94–96]. Subsequently, several reports have described bovine udder infections caused by LA-MRSA CC398 [97]. In Dutch farms, MRSA was detected in 18–31% of veal calves [98]. In 2010, the European Union reported that 20% of veal calves in Germany

carried MRSA [99]. A survey of 51 veal calf farms in the Netherlands indicated that an average of 38% of farmers and 16% of family members were colonized with LA-MRSA [19, 100]. Recently, another group of LA-MRSA strains (CC130, CC425, and CC1943) that were initially thought to be bovine-specific lineages emerged in humans [101]. A number of multidrug-resistant MRSA were isolated from bovine mastitis in Germany [97, 102], the majority of which were MRSA ST398 related to animal strains, but an isolate of the clonal complex group CC8 was identified as a human epidemic MRSA strain Irish-01 [103]. In 2010, Hata et al. first discovered MRSA in cow's milk in Japan and the genotypes (ST5-SCC*mec* II) were the same as or similar to human strains [104]. There has been a dramatic surge in human CC398 infection and colonization in the Netherlands, increasing from 0% in 2002 to more than 21% in 2006 [23]. A recent Dutch study indicated that the annual incidence of MRSA in humans more than tripled from 2001 to 2006 where 23%, 26%, 16%, and 10% of the patients acquired MRSA from a foreign hospital, animals, nosocomial transmission, and the community, respectively [105]. The presence of MRSA CC398 in pig farms with a concomitant increase in CC398 infections in humans clearly suggests that pigs or cattle are specifically a risk factor and CC398 MRSA colonization and prevalence in humans is associated with animal contact [23, 46, 106, 107]. The above argument is further strengthened by the findings that the CC398 carrier status of farm workers decreased dramatically when they took a break from direct animal care duties [19, 100]. People who visited farms to collect samples for a shorter duration carried MRSA transiently as compared to those who had prolonged visits, suggesting that a prolonged contact with animals is probably an important factor for higher rates of colonization [49].

While a majority of the MRSA collected from dairy cattle belonged to ST398 [89], other ST types, such as ST1-t286-SCC*mec* IV, ST72-t324 [108], ST59-t437–V [91], ST10-t127-SCC*mec* IVa genotype [92], SCC*mec* types IVg [109], CC97, t4795, and t1730 [110], and a *mecA* variant ($mecA_{LGA251}$) known as *mecC*, are also reported from MRSA CC130 and ST425 isolates [111]. The *mecC* type was also detected in Danish MRSA CC130 isolated from a cow and the genotypic characteristics, such as *spa* type (t843), MLVA (MT429) and PFGE profiles of bovine isolates were the same as the human isolates, implying transmission between humans and ruminants [112]. The geographic variation in the prevalence and origin of CC398 colonization and incidence of infection in humans is quite interesting. MRSA has been detected in retail beef, but nasal and fecal sampling of nearly 500 Canadian feedlot cattle, shortly before slaughter, detected no MRSA [113]. Moreover, while CC398 MRSA infection in humans is a leading cause of CA-MRSA infection in some European countries, it is rare in North America despite the presence of CC398 in livestock [114]. The reasons for the low incidence of CC398 infections in the USA may include differences in direct and indirect contact with food animals, much lower population density in North American pig-rearing regions, and the common presence of other competing MRSA strains in people in the general population. Although some studies suggested that the MRSA present in cattle is bovine-specific, most of the reports indicated that MRSA found in cattle were derived from humans [89, 92, 115, 116]. Bovine, porcine, canine, feline, and equine MRSA isolates containing the *pvl* gene and other virulence factors, such as *chp*, *scn*, *seb*, *sek*, and *seq*, toxic shock syndrome toxin 1 (*tsst1* or *tst*) gene [91, 117], hemolysin, protease, superantigen-like protein, capsule, and biofilm-associated genes [118–121], may pose a potential threat to public health.

2.3. Poultry MRSA

CC398 is not limited to large livestock animals alone; it has also been reported in poultry [18, 122], manure from chicken farms and soil fertilized with this manure [123]. However, the numbers of MRSA ST398-t011-SCC*mec* V isolated from chickens are lower (0–28%) than in pigs (82–92%) on the same farm [124]. In another study from Belgium [109], MRSA present in 0.8–1.8% layers and broilers (chickens raised for meat) was clustered into two ST types, ST398 (t011, t899) and ST239 (t037). Two other studies from Belgian broiler farms [18, 125] reported 12.8–14.3% of randomly selected Belgian broiler farms to be positive for CC398. In 2010, the Federal Institute for Risk Assessment reported a contamination rate of 32% in turkey meat in Berlin, Germany [126]. Similar contamination frequencies were reported from Canada and the USA [72, 127], as well as from Taiwan [128]. Moon et al. [91] reported that the *S. aureus* isolated from chicken carcasses contained 1.3% MRSA, which was more than the MRSA isolated from other animal carcasses (0.3%) in Korea. Poultry-associated *S. aureus* isolates belonging to genotypes other than CC398 have also been reported from different geographic regions [36, 129–131]. Mulders et al. [132] reported that 6.9% of MRSA present in broiler chickens in the Netherlands represented the ST9-t1430 genotype. A single *spa* type, t1456, in poultry was seen and distinguishable from the *spa* types of ST398 observed in other animals in Belgium [125]. Genotypic and antimicrobial patterns between 14 MRSA isolates from broilers and pigs were identical [133]. The MRSA isolates from Korea had the genotype of ST692-t2247–III [91] and the MRSA isolates from Hong Kong exhibited the genotypes ST9-t899–IV [81] and CC9 (t899, t1234) [134]. A study from Denmark analyzed the isolates from infected poultry and detected a predominant common human epidemic clone CC5 [129]. Using a population genomics approach, Lowder et al. [36] examined the origin of *S. aureus* isolates from diseased and healthy poultry from four continents and found that the majority of isolates belonged to a single clonal complex CC5 belonging to a known human-associated lineage. The poultry isolates were more closely related to each other than to human CC5 isolates, but were most similar to a subclade of CC5 that was circulating in Polish hospitals in the 1980s. In a study conducted in Korea, 930 food samples were collected, and four strains of the CA-MRSA CC5 human clone were identified [135]. In a human case study, a 63-year-old Dutch woman who owned a chicken farm developed a life-threatening endocarditis; the infecting MRSA isolate was identified as CC398 [136], similar to an isolate found in a pig farm nearby and to MRSA isolates previously found in other pig farms in the Netherlands.

2.4. Other meat products

S. aureus is found frequently in a variety of retail meat products. A Dutch Food Safety Agency analyzed 2217 samples of various kinds of meats from the retail stores and found that 11.9% of 2217 samples had MRSA [137]. The distribution of MRSA within various meat types was listed as follows: beef, 10.6%; veal, 15.2%; lamb and mutton, 6.2%; pork, 10.7%; chicken, 16.0%; turkey, 35.3%; fowl, 3.4%; and game, 2.2%. Of all the MRSA isolates, 85% of the isolates belonged to ST398; the other STs were possibly of human origin [137]. Another Dutch survey found that 46% of retail meat samples contained *S. aureus* strains, of which two (2%) were MRSA: one was CC398 and the other was USA300 [138]. Studies in Switzerland and Japan showed the prevalence of *S. aureus* in meat products to be 23 and 65%, respectively [122, 139].

A USA survey of 120 retail meat samples indicated that 39.2% contained *S. aureus* strains, 5% of which were MRSA of the types USA100 (ST5) and USA300 (ST8) [127]. A Canadian survey [72] found that 7.7% of retail meat samples harbored MRSA; 30% belonged to the clonal complex CC398, 40% were CC8, and 30% were CC5, a strain commonly found in humans in both the USA and Canada.

2.5. Milk

In general, the occurrence of MRSA in bovine mastitis isolates is well studied and its prevalence seems to be very low [140]. Following the initial reports of isolation of MRSA from mastitic cows [86], sporadic cases of MRSA in dairy cattle were detected among *S. aureus* isolates from clinical or subclinical mastitis. In one of the studies from Korea [109], MRSA were isolated from the milk of cows with an isolation ratio of 0.18%. In one report on dairy farms in Belgium, a high percentage (15%) of MRSA was found in lactating cows [140]; these cows had a previous history of MRSA. The long-term low prevalence of MRSA mastitis is quite surprising, given the number of years since the first identification of MRSA in cattle and the close contact of humans with the udders of dairy cattle. In Germany, the highest proportion of positive samples (45%) was found in nasal swabs from veal calves at slaughter and the lowest rate was 4.1% in bulk tank milk. Most isolates, irrespective of origin, were from *spa* types t011 and t034 belonging to the clonal complex CC398 [141]. The finding of LA-MRSA CC398 in tank milk suggests udder colonization and possibly cases of subclinical mastitis in dairy cattle in Germany [141]. Close contact of dairy cattle with humans could lead to a transfer of strains between them. In one of the reports from Hungary, MRSA isolates from mastitic cows and a worker were found identical by phenotypic and genotypic analysis indicating a transfer between cows and human [92].

2.6. Fish

Fish is not a normal host for staphylococci and its presence on fish is either due to disease in the fish, contamination, or poor personnel hygiene. The first report of the isolation of MRSA from Tilapia was published in 2010, where 559 *S. aureus* isolates from the brain, eyes, and kidneys of tilapia from 11 farms collected for a period of 2 years were analyzed and 50% were identified as MRSA [142]. In another study [143] from Korea that analyzed 165 *S. aureus* strains isolated from different food samples between 2003 and 2006, four were identified as MRSA. Two of these were from beef and two from fish. The two fish isolates, one from sea bass and other from rockfish, were identified as ST1 and ST72, respectively. An analysis of 200 ready to eat (RTE) fish samples collected from 10 shops belonging to four supermarket chains in Japan, 5 were MRSA and 5 others were identified as coagulase-negative MRSA [144]. Molecular typing of two MRSA isolates by *spa* sequencing and MLST typing identified t1767 and ST8, respectively. Interestingly, MRSA ST8 strains have been predominantly isolated from humans in the USA and Europe but are of rare occurrence in foods in Japan. It is not certain if the MRSA in fish was from human or fish origin. In another report from Greece, one hundred samples from RTE fish products were examined and two were reported to have MRSA belonging to the *spa* types t316 (ST359) and t548 (ST5) [145]. In a recent report, a patient developed foot infection with MRSA after a fish pedicure [146], but the origin of the MRSA

could not be determined in this case. Reports of fish from Egypt, India, and Yemen have also been reported to harbor as much as 3.5% MRSA [147]. In this report, two of the MRSA isolates were found to harbor the enterotoxin genes *seg* and *sei*. Since the global spread of multi-drug-resistant bacteria has increased in the past decade, the finding of enterotoxigenic MRSA in fish should be of concern. The global trade of fish increases the possibility of intercontinental transmission of multidrug-resistant and enterotoxigenic *S. aureus* and its potential influence on consumer health worldwide should be monitored.

3. MRSA in food processing environment

After carcasses leave the slaughter-house chillers, residual MRSA on carcass surfaces can be transmitted during further processing through human hands, cutting tools, and any surfaces with direct meat contact. Manual handling during processing also can facilitate the entry of human MRSA strains into the production units. Recent surveillance data suggest that 22.5–64.8% of retail beef, pork, chicken, and turkey meats in five different geographical locations in the United States were contaminated with *S. aureus* [148–150]. A Swiss meat-processing plant reported the presence of *S. aureus* on 22.7% of the received chilled pork hind quarters from 18 European suppliers [151]. While investigating German pork processing units, Kastrup [139] determined a MRSA detection frequency of 6% on meat trimmings, 2% on processing equipment, and 5% on employees. Beneke et al. [152] obtained a similar detection rate in the processing area of a German abattoir. In an experimental setting, *S. aureus* at a contamination level of 5–7 log CFU/100 cm^{-2} was detectable on dry stainless steel for at least 96 h. In The Netherlands, de Jonge et al. [39] assessed the presence of MRSA in three meat-processing facilities and two institutional kitchens. MRSA was not isolated from any human nose or hand swabs, but 33% of the participants carried MSSA and only 14.3% of the meat samples were contaminated with MRSA. A Dutch study [138] which found that 46% of the retail meat samples, the majority of which came from a single retail shop and contained *S. aureus*, had a high degree of clonal relationship, indicating cross-transmission at some point during processing in the shop.

To pin point the exact source of contamination, it is necessary that the process of slaughtering be analyzed critically. Slaughter and meat processing involve several steps, any of which could introduce contamination with MRSA. Scalding, the first step in the slaughter process, is carried out at 60–62°C for 6–8 min in scalding tanks with rotating bars or through long scalding tanks [153] to loosen the hair from the carcass. An analysis of the effect of scalding on the quantity of coagulase-positive *S. aureus* (CPS) on pig carcasses in two Swiss abattoirs indicated variable data [154]. CPS, isolated from 96 to 100% of all carcasses, was reduced to 18 and 20% along the slaughter line after scalding from one abattoir, but in the second abattoir, it increased to 99% at the end of the line. Dehairing that follows scalding is another critical step that involves mechanical treatment of the carcass with rotating scrapers and rubber flails. This step has a potential to increase dissemination of porcine bacteria from mouth, nose, skin, and intestinal tract due to the accumulation of detritus in the machine. Singeing, which involves the exposure of the carcass for 10–15 s at 900°C, has been reported to decontaminate the surface of pig carcasses and lead to a 2.5- to 3-log reduction in total bacterial counts [153, 155].

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Using a probabilistic model, Vossenkuhl et al. [156] found that a high MRSA prevalence at the beginning of the slaughter line was reduced to a low level at the end of the slaughter line (**Figure 1**). However, some investigators reported no effect of singeing on the microflora [157], whereas others have indicated that the reduction achieved by singeing is frequently reversed by polishing, that cleans intensively a skin surface [158–160]. Evisceration of the intestinal tract is another source of contamination with fecal bacteria on the surface of carcasses [154, 161]. To minimize the bacterial contamination, pig carcasses are usually chilled overnight using conventional single-stage chilling regimes, spray chilling, ice bank chilling in humid air at 2°C, and rapid or ultra-rapid chilling [162, 163]. Spescha et al. [154] reported a 77% decrease in the proportion of *S. aureus*-positive carcasses after chilling. Freeze chilling at temperatures of −10 to −25°C for 45–60 min, followed by chilling at 2°C for 23 h reduced *S. aureus* by 1 log CFU cm^{-2} on untrimmed carcasses [151]. It is clear from the published reports that handling of carcasses, proper maintenance of equipment, and personal hygiene play critical roles in the control and spread of *S. aureus* in the final end product.

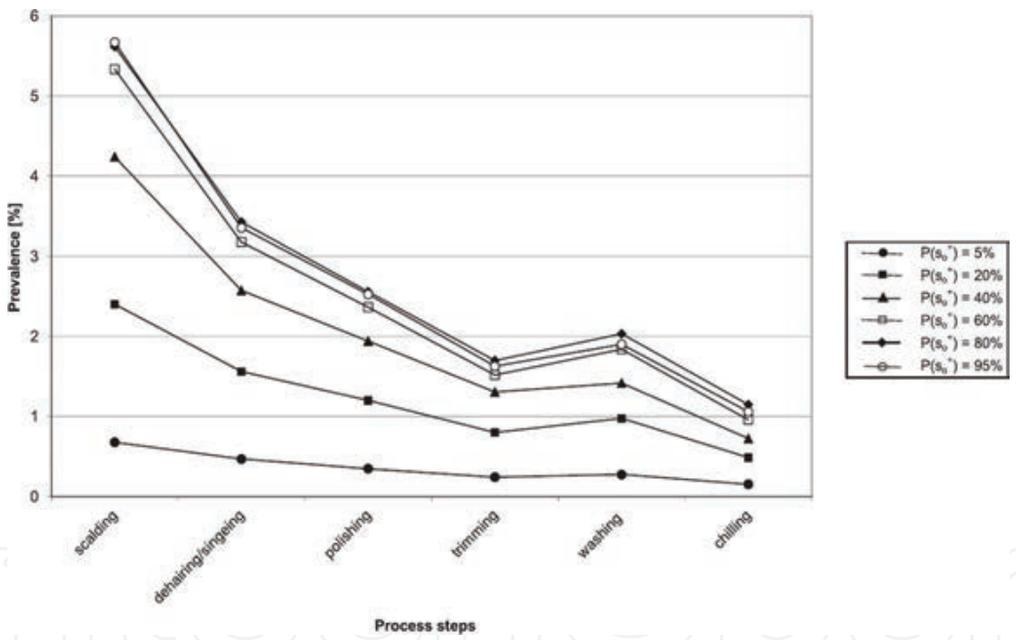


Figure 1. Change in MRSA prevalence along the slaughter line depending on the variation of the initial MRSA prevalence $P(s_0^+)$ [156]. Reproduced with permission of Elsevier.

4. Molecular epidemiology of *S. aureus* CC398

The emergence of LA-MRSA strains in humans [16, 17, 25, 56] and the presence of an identical MRSA CC398 in pigs, farm workers, veterinarians who attended to the same pig farms and their nonexposed family members [47, 48] suggests animal-to-human or human-to-animal transmission. In an interesting report from the Netherlands, it was shown that farm visitors were positive for CC398 MRSA directly after a farm visit but tested MRSA negative after

24 h [19, 41]. These and other studies indicate that CC398 appears to be frequently shared between animals and humans and is capable of causing infections in both species [25, 70, 164]. Transmission of MRSA between animals and humans is not new, but the MRSA isolates, in most cases, represent an initial human-to-animal transmission [24, 49, 165, 166].

Analysis of MRSA and MSSA from animals and humans spanning 19 countries and four continents indicated that the CC398 lineage originated in humans as an MSSA [167]. The whole-genome sequencing analysis by Price et al. [167] demonstrated that livestock-associated MRSA CC398 lost an immune-evasion cluster (IEC) as it evolved from its human-adapted MSSA. All of the HA-MSSA strains carry ØSa3 prophage in association with human innate immunomodulatory genes that play crucial roles in human niche adaptation (**Figure 2**) [167]. The prophage-associated virulence and adaptation genes are not necessary for nonhuman hosts, therefore, ØSa3 is mostly absent in livestock strains. After their introduction to livestock, MSSA CC398 acquired resistance to methicillin and tetracycline. Since tetracycline is heavily used in animal farming, the tetracycline resistance gene *tet*(M) is nearly universal among livestock-associated MRSA CC398 and MSSA isolates. The MSSA and MRSA CC398 isolates found in humans with direct livestock contact exhibited the same molecular patterns (i.e., ØSa3 prophage negative, *tet*(M)-positive) as the livestock-associated strains, indicating human re-adaptation [167], and were also reported in isolates epidemiologically associated with human-to-human transmission in multiple countries and continents [168]. During the host jump from humans to animals, MRSA CC398 strains also acquired resistance to copper and zinc because of their use in animal feed [130]. The vast majority of LA-MRSA CC398 strains carry SCC*mec* type Vc, which contains the *czrC* gene that confers resistance to copper and zinc.

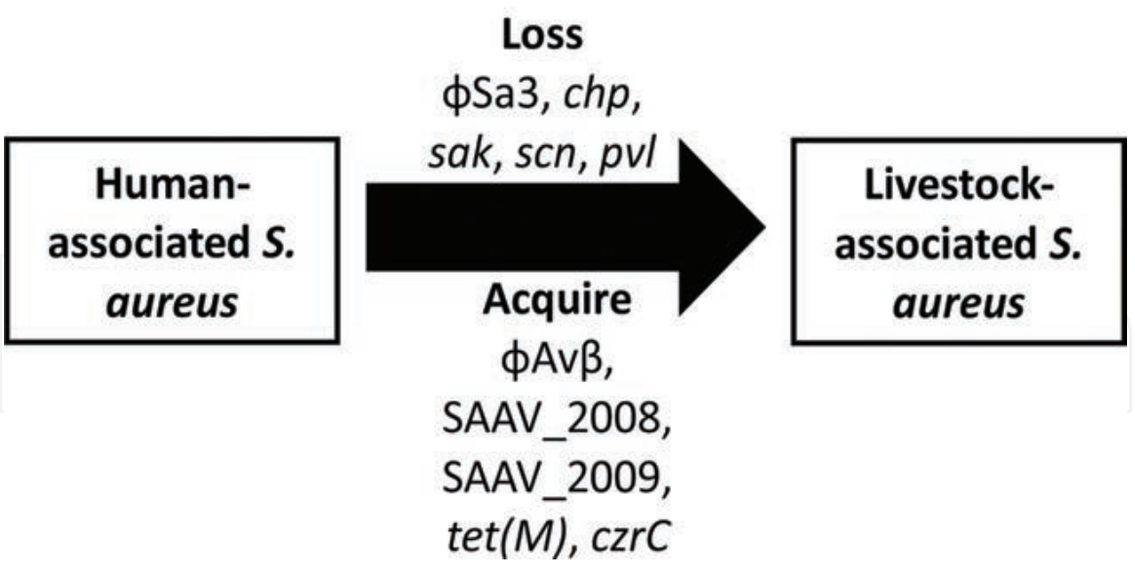


Figure 2. Gain or loss of genes as *S. aureus* jumps from human to livestock animals.

It is quite possible that LA-MRSA CC398 strains would eventually acquire certain genetic traits (additional antibiotic resistance and virulence factors) that would allow *S. aureus* to colonize both hosts and become a more formidable zoonotic agent [167]. Since ST398 strains are deficient in one or more restriction modification systems [169, 170], this adaptation process may have already occurred, as *pvl*-positive ST398 MRSA strains have been isolated from

severe cases of community-acquired infections [20, 21]. These *pvl*-positive ST398 MRSA strains are also lysogenized with ϕSa3 phage coding for the human-specific virulence factors *sak*, *scn*, and *chp*. LA-MRSA *S. aureus* CC398 is not alone in the ability to adapt. A phylogenetic study of *S. aureus* CC97 strains that originated from livestock and caused human infections in Asia, Europe, and North and South America indicated that in the process of adapting to the human host, CC97 acquired either the SCC*mec* IV or V cassette and the ϕSa3 containing an immune evasion cluster [123]. A more recent study in the United States demonstrated that 22% of 30 veterinary students who were initially MRSA negative became positive after visiting MRSA-positive pig farms in Iowa but were negative again by 24 h after the visit [75]. The predominant *spa* type most commonly detected among the students was associated with ST5, suggesting a possible expansion of LA-MRSA to include ST5 [75].

Bayesian phylogenetic analysis of the poultry isolates with the CC5 clade indicated that it arose due to a single human-to-poultry host jump in or near Poland, where CC5 poultry strains acquired an MGE (mobile genetic element), presumably from other resident staphylococcal strains [36]. In addition to gene acquisition, loss of staphylococcal protein A (SpA) has occurred in avian isolates; it encodes virulence factors involved in human disease pathogenesis but is not needed for avian pathogenesis. The lack of protein A expression is a characteristic of the poultry biotype as defined by Devriese et al. [148]. In addition to the CC5 poultry clade, several other poultry isolates had identical or closely related STs to strains commonly associated with humans but had acquired MGE unique to avian strains, indicating that human-to-poultry host switches may be happening relatively frequently. A recent study demonstrated frequent contamination of poultry meat products with *S. aureus* ST5 and ST398 isolates, both of which have human origin [171]. Host adaptation of ST5 from humans to chickens was associated with a loss of genes contributing to human pathogenesis, and this was followed by the acquisition of avian-specific virulence determinants [36, 172]. Further, the presence of a cysteine protease encoded by a plasmid and widely distributed within avian strains suggests its potential role in avian-specific pathogenesis [173]. The adaptation from one host to another appears to be dependent upon the acquisition or loss of MGEs that code for key elements necessary for survival in new host [167, 174]. These cases have not only been associated with livestock [19] but have also occurred in cases with no known livestock contact [53, 54], suggesting a broader transmissibility capacity than originally thought. Further research is required to characterize the full scope of the genetic changes associated with the shift from humans to livestock and vice versa.

5. ST398 evolution and genetic diversity

In spite of similarities between LA- and HA-MRSA isolates, significant amounts of genetic diversity among *spa* and SCC*mec* cassette types have been documented in ST398 [6, 57, 175]. For instance, ST398 appears to have evolved by multiple acquisitions of the SCC*mec* elements, such as SCC*mec* types II, III, IV, IVa, and V [176]. In the Netherlands, two farms were found to have MRSA ST398 with identical *spa* types, but different SCC*mec* types, suggesting that divergent SCC*mec* elements were inserted into the clonal MSSA [57]. Similarly, MSSA ST398 (*spa* type t899), MRSA ST398–IVa (*spa* type t899), and MRSA ST398–V (*spa* type t108)

were found in dust samples, nasal swabs, and a blood isolate from workers on the same pig farm [177], suggesting multiple acquisitions of SCC*mec* cassettes by MSSA precursors. Coagulase-negative staphylococci in the farming environment are suspected as sources of SCC*mec* [176], and the progeny of emerging MRSA strains are spreading locally rather than globally [178–180]. While SCC*mec* acquisition seems to be fairly common in MRSA ST398, the transfer of staphylococcal toxin genes, including the Panton-Valentine leukocidin gene (*pvl*) appears to be rarer [20, 43, 44, 57, 165, 181–184]. Only a handful of studies have found *pvl* positive ST398 [20, 165, 185–187]. Additionally, horizontal transfer of the protein A gene has been suggested, due to the finding of the *spa* type t899 in both ST398 strains and ST9 strains [29, 30, 80, 177].

6. MRSA in companion animals

6.1. Canine and feline MRSA

The first MRSA from pet animals was isolated from dogs in Nigeria in 1972 [188]. *S. intermedius* is the strain most isolated from dogs [189]. However, the predominant canine species among staphylococci was *S. sciuri* in Japan [190]. Various coagulase-positive and -negative staphylococci have been reported in pet animals [191]. Among coagulase-negative staphylococci, *S. felis* was dominant in Brazil [116], and a coagulase-positive *S. intermedius* was dominant in canine species in the UK [192, 193]. The prevalence of canine MRSA was 0.7% in Portugal, 2.3–9% in UK, and ≤20% in Canada [194–197]. Conversely, in cats, it was 1.48% in the UK, ≤4% in Portugal [195, 198] and 21.4% from wounds and skin lesions of cats in the USA [199]. *S. aureus* was found in 8% of dogs with inflammatory skin disease in the USA and one isolate was MRSA [200]. In addition, one MRSA was detected among the *S. aureus* strains isolated from 29% of 48 cats suffering with inflammatory skin disease and two MRSA were found among the *S. aureus* strains from 20% of 50 healthy cats [201]. Previous surgery, hospitalization, antimicrobial agent treatment, contact with humans possessing MRSA, and use of implant devices are regarded as risk factors for MRSA infection in companion animals [195, 202]. Rich and Robert [203] reported that MRSA were isolated from 1.4% of the postoperative and wound infection samples of pet animals in the UK. Lilenbaum et al. found 3% MRSA in Brazilian cats [193]. Southwest Pacific clone-associated community-acquired MRSA (USA1100) and methicillin-resistant *S. pseudintermedius* (MRSP)-associated with the European clone (ST71) were first reported in South America in cats [204].

MRSA isolates from Austria, Belgium, Germany, Ireland, and Portugal were resistant to ciprofloxacin and enrofloxacin, perhaps because of the fluoroquinolone approval for use in companion animals in Europe in the middle of 1990 (**Table 2**). MRSA ST398 that was identified in dogs and cats in France carried a chloramphenicol acetyltransferase gene, *cat*, that mediates resistance to nonfluorinated phenicols [117]. On the other hand, MRSA isolated in Portugal and Thailand from dogs and Germany from cats possessed a florfenicol-chloramphenicol exporter gene, *fexA*, that mediates resistance to both fluorinated and nonfluorinated phenicols [205–207]. MRSA ST398 isolated from an Austrian dog suffering from vaginitis harbored the *vatC* gene that inactivates streptogramin A [208]. An ABC transporter gene, *lsaE* (responsible

for combined resistance to lincosamides, pleuromutilins, and streptogramin A), and a lincosamide nucleotidyltransferase *lunB* gene (confers resistance only to lincosamides), were present in the MRSA ST45 isolated from dogs in Thailand [205]. In France, an MRSA strain (*agr* III-t008–IV) isolated from a synovial fluid of dog was positive for *pvl* [117]. It carried *sek* and *seq* genes and was suspected to be a USA300 variant that was imported from the USA. *tsst1*-positive MRSA (*agr* II-t002-SCC*mec* I-truncated) was recovered from pet animals in France (**Table 3**). Leukotoxin genes, most prevalently *lukF* and/or *lukS* followed by *lukD* and/or *lukE*, are reported to be present in most of the MRSA isolated from companion animals, but those from dogs, cats and horses in Austria and the USA did not possess any leukotoxin genes. MRSA isolates CC5-t002–II, CC5-t062 and CC22-t032–IV, isolated in Portugal from a dog, a horse and human, respectively, harbored IEC genes suggesting adaptation to different hosts [206]. The presence of host-adaptive, virulence, and toxin genes makes the companion animal MRSA isolates prime candidates for zoonotic transfer. The first outbreak of human MRSA associated with cats was reported in a rehabilitation geriatric ward in the UK in 1988 [209] but others have since been reported in Australia, Canada, Germany, New Zealand, South America, and the Netherlands [193, 210–212]. Human-associated MRSA, such as EMRSA-15 and CMRSA-2, show a close relationship with pet-associated MRSA [211–214]. Since MRSA ST398 has been isolated from many farm animals, this MLST type found in dogs or cats may have originated from them or people who had contact with them [215]. MRSA SCC*mec* II strains, which are those most frequently affiliated with nosocomial human infections, have been isolated from cats [216].

6.2. Equine MRSA

Since the first report of MRSA from mares with metritis in Japan [217], many isolates have been found in Europe, North America, and Asia (**Table 2**) [142–144, 218–220]). Haenni et al. [221] identified four *mecC*-positive MRSA from horses in France exhibiting *spa* types, t208, t843, t6220, t11015 and ST types ST49, ST130, and ST1245. Among them, MRSA CC130 (ST130, ST1245) and CC49 (ST49) were documented in animals and humans, respectively. Multidrug-resistant ST8 MRSA was detected in Belgium, Germany, Switzerland, and the USA. A single locus variant of ST8 classified as ST254 MRSA was isolated from horses in Austria, Germany, Ireland, and the UK [183, 208, 222, 223]. Twelve different MLST types have been reported and most of the MRSA strains were grouped into the CC8 or CC398 classes [224]. The CC8-SCC*mec* IV genotype in horses was likely from a contaminated veterinary hospital and later spread to various clinics [219]. This genotype was reported in veterinary hospitals in Canada and the USA [118, 225]. It was first found in infected horses in Ireland and thereafter reported in the Netherlands, Austria, and Germany [226–228]. Many MRSA isolates from Canada showed ST8-SCC*mec* IV-t064 genotype [93]. They were designated as a Canadian epidemic MRSA-5 (CMRSA-5) and were very close to a human clone, USA500. Although the CC8-SCC*mec* IV genotype has been the most frequently found, CC398-SCC*mec* IV has recently become a major genotype. CC398-SCC*mec* IV was first found from infected horses in the Veterinary University of Vienna in Austria [222]. CC398 isolated from nasal samples of horses in the Netherlands and Belgium exhibited high prevalence rates, 9.3 and 10.9%, respectively [227, 229]. More than 25 *spa*-types have been reported, and three types, such as t011, t064 and t451, were the most

Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
Belgium	B†	398	*			+**			+			+	+	+				+	+		+	+			[87]
Belgium	B	398			+	+			+			+	+	+					+		+	+			[133]
Belgium	C†	239, 398		+	+		+		+		+	+	+			+		+	+	+		+			[34]
Belgium	C	398				+			+					+					+			+			[133]
Belgium	P†	ST9, 80, 239, 398			+	+	+		+		+	+	+		+	+		+	+	+		+	+	*aacA-aphD, aadD, aphA3-sat, blaI, blaR, blaZ, cfr, dfrS1, ermB, ermC, fexA, fosB, lnuA, tetK, tetM, vgaA*	[121]
Belgium	P	398				+			+			+	+	+					+		+	+			[256]
Belgium	P	398			+	+			+		+	+	+	+					+		+	+			[66]
Belgium	P	398			+	+			+			+	+	+		+			+		+	+			[133]
Brazil	B	398		+		+	+					+						+	+		+			*ant4, aac(6')-aph(2"), blaZ, mecA, tetK, tetM*	[257]
Central Europe	P	9			+		+		+										+				+		[258]

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Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
China	P	6, 9, 63, 627	+	+	+		+		+	+					+		+		+	+				*aadE, erm33, fexA, lnuB, lsaE, mecA, spw, tetL, vgaA*	[259]
China	P	5, 9			+	+	+		+			+							+				+		[260]
China	P	NA		+	+	+	+		+			+							+				+	*acc(6′)/aph2″, ant(4′, 4″), aph(3′)-III, ermC, mrsA, tetK, tetM*	[261]
China	P	398		+	+	+	+		+			+				+			+				+		[262]
Finland	P	1, 398		+		+	+		+										+					*aadD, blaZ/I/R, ermB, lnuB, mecA, tetK, tetK/M*	[120]
Germany	B	398	+		+		+		+			+	+	+		+	+		+	+		+	+	*aacA-aphD, aadD, aphA3, blaZ-I-R, dfrK, ermA, ermB, ermC, ermT, fex, spc, tetL, tetK, tetM, vgaA, vgaC*	[97]

Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
Germany	B	398	+					+	+										+						[102]
Germany	P	398	+	+	+		+	+	+	+		+	+				+		+	+			+	*aacA-aphD*, *aadD*, *blaZ*, *dfrG*, *dfrK*, *ermA*, *ermB*, *ermC*, *fexA*, *mecA*, *qacC*, *tetK*, *tetL*, *tetM*, *vga vgaA*	[44]
Hong Kong	C	9	+	+	+		+	+	+	+		+	+	+		+	+	+	+	+		+	+	*aacA-aphD*, *aadD*, *aadE*, *blaZ/I/R*, *dfrK*, *ermC*, *lnuB*, *lsaE*, *mecA*, *spw*, *tetL*	[134]
Hong Kong	P	9			+	+	+		+			+							+					*ermB*, *ermC*	[81]
Hong Kong	P	9	+	+			+	+				+	+				+	+	+	+		+		*aacA-aphD*, *aadD*, *aadE*, *blaZ/I/R*, *dfrK*, *ermC*, *lnuB*, *lsaE*, *mecA*, *tetL*, *spw*	[134]

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Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
Hong Kong	P	9			+	+	+		+		+					+			+				+	*ermC, fexA, tetK, tetM*	[263]
Hungary	B	1	+						+										+						[92]
Ireland	P	CC398	+		+				+			+	+	+			+		+		+	+		*aacA-aphD, aadD, blaZ, dfrG, dfrK, ermA, ermB, fexA, spc, tetK, tetL, tetM*	[264]
Italy	B	CC97		+		+	+		+			+	+			+		+	+	+		+		*aacA-aphD, aadD, blaI, blaR, blaZ, cat, ermB, ermC, mecA, qacC, sdrM, tetK, tetM, vgaA*	[110]
Italy	B	1		+		+			+			+	+					+	+	+		+		*aphA3, blaZ, ermC, mecA, sat, tetK, sdrM*	[119]
Italy	P	1, 9, 97, 398, 1476			+	+	+		+			+	+					+	+			+			[62]

Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
Italy	P	CC97		+		+	+		+			+	+			+		+	+	+		+		*aacA-aphD*, *aadD*, *blaI*, *blaR*, *blaZ*, *cat*, *ermB*, *ermC*, *mecA*, *qacC*, *sdrM*, *tetK*, *tetM*, *vgaA*	[110]
Italy	P	1		+		+	+		+			+	+					+	+	+			+	*aacA-aphD*, *aadD*, *blaI*, *blaR*, *blaZ*, *cfr*, *dfrS1*, *ermA*, *ermC*, *ermR*, *fexA*, *mecA*, *qacC*, *sdrM*, *tetK*, *tetM*, *vgaA*	[119]
Italy & Spain	P	1	+			+	+		+			+	+						+	+		+		*aacA-aphD*, *aadD*, *blaZ*, *cat*, *dfrA*, *ermA*, *ermC*, *lnuA*, *mecA*, *tetK*, *tetL*, *tetM*, *vgaA*, *vgbA*	[265]

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Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
Korea	B	NA	+	+		+	+		+			+	+						+						[89]
Korea	B	1, 72							+			+							+						[108]
Korea	B	NA	+				+		+			+	+						+						[90]
Korea	C	692				+	+		+										+					*ermB, ermC, tetL, tetS*	[91]
Korea	C	NA	+	+			+		+																[89]
Korea	P	398				+	+		+										+						[85]
Korea	P	5, 72, 398, 541			+	+	+		+		+	+	+		+	+			+	+				*aac(6′)-le-aph(2″), ant(3′)-IIIa, anat(4′)-la, cfr, ermA, ermC, ermT, fexA, lnuB, tetK, tetL, tetM*	[91]
Netherland	B	398	+									+							+		+		+		[266]
Netherlands	P	398					+		+			+	+						+		+				[22]
Netherlands	P	398							+			+	+	+					+						[70]
Portugal	B	398			+	+	+	+	+	+			+						+					*aphA3, ermC, fexA, tetK, tetM*	[206]

Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
Portugal	P	NA				+	+		+			+	+						+	+		+	+	*aacA-aphD, aadD, apmA, dfrK, ermC, fexA, qacG, qacJ, tetK, tetM, vgaA*	[206]
Spain	P	398, 1379					+		+			+	+					+	+		+		+	*aacA-aphD, aadA, aadD, aphA3, dfrA, dfrG, dfrK, ermC, ermT, msrA, str, tetK, tetM, tetL*	[255]
Spain	P	398					+		+			+									+		+		[234]
Spain	P	1, 398, 1965, 1966, 1967, 1968, 1969		+	+	+			+		+	+		+		+		+	+			+			[267]
Switzerland	B	1, 398	+	+			+		+										+					*aphA,blaI, blaR, blaZ, ermC, mecA, tetM*	[42]

Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
Switzerland	P	398	+	+			+		+			+							+				+	*blaI, blaR, blaZ, ermA, mecA, tetK, tetM*	[42]
Switzerland	P	398		+			+		+					+				+	+						[63]
Taiwan	P	9			+	+	+		+			+							+				+		[268]
Thailand	P	9		+	+		+					+							+				+		[31]
Thailand	P	9, 2136		+		+						+					+		+	+		+	+	*blaZ, aac-aphD, tetM, vgaA*	[269]
USA	P	398					+		+							+			+						[51]
USA	P	5, 72, 398, 1340	+				+		+			+				+			+				+		[38]

B†: cattle, C†: chicken, P†: pigs, *: not tested or sensitive, **: resistant, AMP: ampicillin, CEF: cefoxitin, CHL: chloramphenicol, CIP: ciprofloxacin, CLI: clindamycin, ENR: enrofloxacin, ERY: erythromycin, FLO: florfenicol, FUS: fusidate, GEN: gentamicin, KAN: kanamycin, LIN: lincomycin, LIZ: linezolid, QD: quinupristin/dalfopristin, SPE: spectinomycin, STR: streptomycin, TET: tetracycline, TIA: tiamulin, TOB: tobramycin, TRI: trimethoprim, SXT: trimethoprim-sulfamethoxazole.

Table 1. Antimicrobial resistance pattern of bovine, poultry, and porcine MRSA isolates.

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Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
Austria	D†	22, 254, 398	*			+**			+			+							+				+	*aacA-aphD, dfrA, ermC, tetK, tetM, vatC*	[208]
Austria	C†	1, 5, 398				+	+		+			+							+					*aacA-aphD, ermC, tetK, tetM*	[208]
Austria	H†	1, 254, 398				+	+		+			+							+				+	*aacA-aphD, dfrA, ermC, tetK, tetM, vatC*	[208]
Austria	H	1, 254, 398					+		+			+							+					*aph2"-aac6', ermC, mecA, tetM*	[222]
Belgium	D	398			+	+			+			+	+	+					+		+	+			[133]
Belgium	C	398			+	+			+					+		+			+						[133]
Belgium	H	8, 398, 2197	+	+			+	+	+			+		+					+			+			[270]
Belgium	H	398					+		+			+		+					+			+			[229]
Brazil	C	30		+																					[204]
Brazil	C	NA	+																						[193]
Canada	D	NA	+			+	+	+	+		+	+							+				+		[271]
Canada & USA	H	NA			+			+	+			+							+			+			[272]
China	C, D	59, 398					+					+							+					*aacA-aphD, ermB, mecA, linA, tetK*	[273]

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Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
France	C, D	CC398		+	+			+	+		+		+	+					+		+			*aadD, blaZ, cat, dfrA, erm(A), fosB, mecA, qacA, tetK, tetM, vgaA*	[117]
Germany	C, D, H	CC5, 8, 9, 22, 398, 599			+		+	+	+			+	+						+				+		[274]
Germany	C	398	+	+	+		+		+					+		+	+		+				+	*blaZ, dfrK, ermC, fexA, mecA, tetK, tetM*	[207]
Germany	C, D	22			+	+	+		+															*ermC, mecA*	[210]
Germany	H	8, 22, 254, 1117																						*aacA-aphD, aadD, aphA3, blaI/R, blaZ, cat, dfrA, ermA, ermC, fosB, mecA, qacA, sat, tetK, tetM*	[183]
Hong Kong	D	NA			+	+	+		+		+	+							+				+		[275]
Ireland	D	NA	+			+			+					+					+						[276]
Ireland	D	NA	+			+			+					+					+						[226]
Ireland	H	NA	+			+			+			+	+					+	+		+	+			[226]
Israel	H	5				+	+		+			+													[277]
Israel	H	5				+	+		+			+													[278]

Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
Japan	D	5, 30				+			+			+	+					+	+						[279]
Japan	D	NA	+						+			+							+						[280]
Korea	D	72		+																					[281]
Korea	D	NA	+		+	+		+				+									+		+		[282]
Malaysia	D	59		+					+									+	+						[283]
Malaysia	C	55		+					+			+						+	+						[283]
Netherlands	D	NA	+					+	+			+		+											[284]
Nigeria	D	NA		+	+	+	+		+			+							+				+		[285]
Portugal	D	22, 105, 398			+	+	+		+	+			+						+					*fexA, ermA, ermC, tetM*	[206]
Portugal	C	5, 22				+	+		+		+													*ermC, fusC, mphC, msrA,*	[206]
Portugal	D	22				+	+		+		+	+	+			+			+		+			*aac(6')-aph(2"), ant(4')-Ia, aph(3')-III, ermB, ermC, msrA, tetM*	[286]
Portugal	H	5, 398					+		+		+	+	+						+			+		*aacA-aphD, blaZ, dfrK, ermC, fusC, tetM*	[287]

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Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
Portugal	H	5					+		+		+	+	+						+			+	+	*aacA-aphD, dfrK, ermC, fusC, tetM*	[206]
Switzerland	H	8, 398				+	+		+			+	+					+	+			+		*aac(6′)-le-aph(2′)-la, ant(6)-Ia, aph(3′)-III, blaZ, dfrG, dfrK, ermC, mecA, mphC, msrA, str, tetK, tetM*	[288]
Thailand	D	45			+	+	+					+	+			+		+	+	+		+		*aac(6′)-Ie-aph(2′)-Ia, ant(4′)-Ia, ant(6′)-Ia, blaZ, dfrA, fexA, lnuB, lsaE, mecA, mupR, tetL, tetM*	[205]
USA	D	5	+			+	+		+															*blaZ, ermA, mecA*	[289]
USA	D	NA	+			+	+	+	+			+							+				+		[290]
USA	D	5, 8, 105, 986	+					+	+			+							+						[118]
USA	C	5, 8	+					+	+										+						[118]
USA	C	NA	+	+			+	+	+			+													[291]
USA	D	NA	+																						[291]

Country	Animal	ST	AMP	CEF	CHL	CIP	CLI	ENR	ERY	FLO	FUS	GEN	KAN	LIN	LIZ	QD	SPE	STR	TET	TIA	TOB	TRI	SXT	Genotype	References
USA	C, D	NA			+		+	+	+			+							+				+		[292]
USA	D	NA				+	+		+										+						[293]
USA	C	NA				+	+		+										+						[293]
USA	C	NA			+		+	+	+			+							+				+		[216]
USA & UK	D	NA				+	+	+	+			+		+									+		[294]
USA	H	8, 830	+						+			+							+				+		[118]

C[†]: cats, D[†]: dogs, H[†]: horses, *: not tested or sensitive, **: resistant, AMP: ampicillin, CEF: cefoxitin, CHL: chloramphenicol, CIP: ciprofloxacin, CLI: clindamycin, ENR: enrofloxacin, ERY: erythromycin, FLO: florfenicol, FUS: fusidate, GEN: gentamicin, KAN: kanamycin, LIN: lincomycin, LIZ: linezolid, QD: quinupristin/dalfopristin, SPE: spectinomycin, STR: streptomycin, TET: tetracycline, TIA: tiamulin, TOB: tobramycin, TRI: trimethoprim, SXT: trimethoprim-sulfamethoxazole.

Table 2. Antimicrobial resistance pattern of feline, canine and equine MRSA isolates.

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Country	Animals	Leukotoxins	Hemolysins	Enterotoxins	Immune-invasion factors	Protease	Superantigen-like proteins	Biofilm-associated	Capsule	Miscellaneous genes	References
Austria	Horses			*seb*							[208]
	Dogs			*sei*							
	Cats			*sei*							
Belgium	Pigs	*lukD/E, lukF, lukPV, lukS, lukX, lukY*	*hla, hlb, hld, hlIII, hlgA*	*seg, sei, sem, sen, seo, seu*	*hysA1, hysA2, isaB, isdA*	*splA, splB*	*ssl1, ssl2, ssl3, ssl4, ssl5, ssl6, ssl7, ssl8, ssl9, ssl10, ssl11*	*bbp, cflA, cflB, cna, ebh, ebpS, eno, fib, fnbA, fnbB, icaACD, map, mprF, sasG, sdrC, sdrD, vwb*	*capH5, capH8, capI8, capJ5, capJ8, capK5, capK8*	*edinB, etd, setC*	[121]
China	Pigs			*sec, seg, sei, sem, sen, seo, seh*							[260]
Finland	Pigs			*seh*				*fnbB*	*cap5, cap8*		[120]
France	Cats and dogs	*lukF-PV, lukS-PV*		*sea, sec, sed, seg, sei, sej, sek, sel, sem, sen, seo, seq, ser, seu*						*tst*	[117]
Germany	Pigs			*seb, sek, seq*							[44]
	Horses	*lukD/E, lukF, lukS*	*hl, hla, hlb, hld, hlIII-aII, hlgA*	*sea, seb/k/g, sec/l, sed/j/r, seg/i/m/n/o/u, sep*	*chp, sak, scn*	*splAB/E, splE, sspA/B/P*					[183]

Country	Animals	Leukotoxins	Hemolysins	Enterotoxins	Immune-invasion factors	Protease	Superantigen-like proteins	Biofilm-associated	Capsule	Miscellaneous genes	References
Italy	Cattle	*lukD, lukE, lukF, lukS, lukX, lukY*	*hl, hlIII, hlb, hlgA*	*seh*	*hysA1, hysA2, isaB, isdA, sak, scn*	*aur, splA, splB, sspA, sspB, sspP*	*ssl1, ssl2, ssl3, ssl4, ssl5, ssl6, ssl7, ssl8, ssl9, ssl10, ssl11*	*bbp, clfA, clfB, cna, ebh, ebpS, icaA, icaC, icaD, eno, fib, fnbA, fnbB, sasG, sdrC, sdrD, vwb*	*cap8, capH8, capI8, capJ8, capK8*	*lmrP, mprF, hsdS2, hsdS3, hsdSx*	[119]
	Pigs	*lukD, lukE, lukF, lukS, lukX, lukY*	*hl, hla, hlIII, hlb, hlgA*	*seh*	*isaB, isdA, hysA1, hysA2*	*aur, splA, splB, splE, sspA, sspB, sspP*	*ssl1, ssl2, ssl3, ssl4, ssl5, ssl6, ssl7, ssl8, ssl9, ssl10, ssl11*	*bbp, clfA, clfB, cna, ebh, ebpS, icaA, icaC, icaD, eno, fib, fnbA, fnbB, sasG, sdrC, sdrD, vwb*	*cap8, capH8, capI8, capJ8, capK8*	*lmrP, mprF, hsdS2, hsdS3, hsdSx*	
Italy & Spain	Pigs	*lukX*	*hlb*	*entH, entU, entX, entY*							[265]
Korea	Pigs	*lukE/D*		*sed, seg, sei, sej, sem, sen, seo, sep, ser*	*chp, sak, scn*					*tsst1*	[91]
	Chicken	*lukE/D*		–	–						
	Cattle	*lukE/D, pvl*		*seb, sed, seg, sei, sej, sek, sem, sen, seo, seq, ser*	*chp, sak, scn*					*tsst1*	

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Country	Animals	Leukotoxins	Hemolysins	Enterotoxins	Immune-invasion factors	Protease	Superantigen-like proteins	Biofilm-associated	Capsule	Miscellaneous genes	References
Portugal	Pigs	*lukF, lukS*	*hla, hld*	–	–						[206]
	Dog	*lukD, lukE, lukF, lukS,*	*hla, hlb, hld*	*sec, sed, seg, sei, sej, sel, sem, sen, seo, seu, ser*	*chp, sak, scn*						
	Horse	*lukF, lukS, lukD, lukE*	*hla, hlb, hld*	*seg, sei, sem, sen, seo, seu*	*chp, sak, scn*						
	Calf	*lukF, lukS*	*hla, hld*	–	–						
Spain	Pigs	*lukD, lukE*	*hla, hlb, hld, hlg, hlg-v*							*eta*	[255]
Switzerland	Pigs	*lukF, lukS, lukY*	*hla, hld, hlgA*	*entX, entY*							[42]
	Calf	*lukF, lukS, lukY*	*hla, hld, hlgA*	*entX*							
	Cattle	*lukD, lukE, lukF, lukY*	*hla, hld, hlgA*	*entH, entX, entY*							
Thailand	Pigs			*entG, entI, entM, entN, entO*							[269]
USA	Dogs	*lukSF-PV*		*sea, seb, sec, sed, seg, sei, sej, sem, sen*				*clfA, clfB, fnbA, fnbB*			[118]
	Cats	*lukSF-PV*		*sec, sed, seg, sei, sej, sek, sem, sen*				*clfA, clfB, fnbA, fnbB*			
	Horses			*sea, seb, seg, sek, sei, sej, sek*				*clfA, clfB, fnbA, fnbB*			

Table 3. Virulence profiles from food-producing and pet animals.

widespread [230]. In addition, only three SCC*mec* types (IV, V, VI) have been discovered from horses [218]. Interestingly, no MRSA was isolated from 300 horses on 14 farms in Slovenia, 497 horses on 50 farms in Canada, 87 horses in Austria, and 200 horses in the Netherlands [231–233]. ST22 and ST1117 isolates from horses in Germany had IEC genes, such as *chp*, *sak*, and *scn* [183]. On the other hand, ST8, ST254, and ST398 strains did not carry those genes.

6.3. Antibiotic resistance and enterotoxin genes in LA-MRSA CC398

An analysis of MRSA and MSSA from animals and humans spanning 19 countries and four continents indicated that the CC398 lineage originated in humans as MSSA [167]. After its transmission to livestock, CC398 became resistant to tetracycline, probably because of the heavy tetracycline use in pig production [22]. However, many tetracycline-resistant MRSA strains are found in horses despite the fact that tetracycline is either not used much [229] or sparingly used [93, 229]. Among bovine MRSA isolates tested, most of them were resistant to β-lactam antibiotics [34] as well as tetracycline, erythromycin and gentamicin. CC398 has also been reported to be highly resistant to several other antibiotics, such as ciprofloxacin, tobramycin, clindamycin, and trimethoprim-sulfamethoxazole [234]. Antimicrobial resistance patterns of MRSA and MSSA isolates in Hong Kong were very similar [81]. The only MRSA CC398 isolate that has exhibited resistance against daptomycin and intermediate susceptibility to vancomycin has been described in a case-report from an Italian hospital [235]. Two other isolates, one from a ventilator-associated pneumonia of a farmer and one additional porcine isolate, were also described as resistant to linezolid and possessed the *cfr* gene which is located on transferable plasmids [235]. An outbreak with HA-MRSA ST125 containing *cfr*, reported from a Madrid hospital in 2010 [236], was followed by reports on the emergence of nosocomial coagulase negative staphylococci containing *cfr* [40]. This gene was previously found in staphylococci from animals in Europe [237, 238] but has also been reported in humans in Colombia and the USA [239, 240]. Distribution of the *cfr* gene in MRSA isolates is alarming because, besides linezolid, it confers resistance to oxazolidinones, phenicols, lincosamides, streptogramin A, and pleuromutilins, including the topical antibiotic retapamulin that is used for treatment of human skin infections [239, 241, 242].

About 50% of LA-MRSA CC398 isolates, besides being resistant to antimicrobial agents, also exhibit resistance to copper and zinc mediated by the *czrC* gene [130, 243]. The use of zinc as feed additives may have favored spread of the *czrC* gene in LA-MRSA [130]. So far, this gene has only been found in LA-MRSA [130, 243] but an extended use of copper coating of biomaterials in orthopedic surgery and traumatology, as well as copper surfaces in hospitals, might select for *czrC*-positive HA-MRSA as well. The trimethoprim-resistance gene *dfrK*, located close to *tetL* in LA-MRSA ST398, has also been found on a plasmid [244]. The *tetL* gene was identified in MRSA isolated from diverse livestock animals and meats from different regions of the world [97, 245, 246]. Kadlec and Schwarz demonstrated the presence of plasmid pKKS25-associated resistance genes, *ermT, dfrK*, and *tetL*, in MRSA obtained from a nasal swab of a young sow in Germany [247]. A porcine MRSA ST398 was shown to contain a transposon Tn*6133* carrying *ant(9)-Ia* and *ermA* genes and a plasmid pKKS825 [248, 249] harboring the resistance genes *vgaC* and *vgaE, aadD, tetL*, and *dfrK* [248–250]. In Germany, the *vgaE* gene was detected in MRSA ST398 isolated from cattle, turkeys, and chicken and turkey meats

[251]. An apramycin resistance gene, *apmA*, was discovered in a bovine MRSA ST398 [252] and in porcine MRSA ST398 [206, 253]. In Denmark, the quaternary ammonium compound-resistant genes, *qacC* and *qacG* were detected in MRSA CC30 isolates [254]. Wendlandt et al. identified a plasmid pV7037-associated multidrug resistance gene cluster, including the novel resistance genes *lsaE* and *spw*, and other resistance genes, such as *mecA, blaZ/I/R, tetL, dfrK, ermC*, and *aadD*, from frozen or chilled chicken carcasses in Hong Kong. The antimicrobial resistance patterns and associated genes from bovine, porcine, and poultry isolates are summarized in **Table 1** and those from companion animals are shown in **Table 2**.

Most of the animal isolates are negative for the *pvl* gene, but Belgian MRSA ST80–IV isolates from healthy pigs were positive for the *pvl* gene and corresponded to the community-acquired CA-MRSA ST80–IV European clone [121]. One Belgian pig CC80 strain contained an exfoliatin (*etd*), an epidermal cell differentiation inhibitor (*edinB*), and staphylococcal exotoxin-like protein (*setC*) and IEC genes (*isaB, isdA, hysA1, hysA2*) [121]. A comparison of the *pvl*-positive MRSA isolates (ST8-t008–IVa) from American pig and pet animals indicated the presence of common virulence profiles (*lukSF-PV, clfA, clfB, fnbA*, and *sek*) except for the *fnbB* gene of a canine isolate [118]. Spanish ST1379/CC97 porcine isolates carried an exfoliatin (*eta*), a leukotoxin (*lukE/D*), and a gamma-hemolysin (*hlg-2*) but were negative for *etb, etc, tst, pvl*, and enterotoxins [255]. The occurrence and prevalence of enterotoxin genes in MRSA isolates from food-producing or companion animals is summarized in **Table 3**. The presence of multidrug-resistant MRSA in companion and food animals, combined with the enterotoxin genes, will require constant monitoring and evaluation of mitigation strategies.

7. Conclusions

MRSA contamination in food-producing and companion animals poses a serious threat to public health. Incidences of identical LA-MRSA strains in pig farms and persons in close contact with food producing and companion animals suggest a clear link for transmission of these strains between humans and animals. While MRSA isolates from companion and food-producing animals are known to infect humans, the reverse is also true. Studies reviewed in this report indicate an initial transfer of MSSA from humans to animals by deletion of immunomodulatory genes and prophage ØSa3, necessary for human infection but not required for infection in animals, and acquisition of tetracycline and methicillin resistance genes (**Figure 2**). The MRSA that evolved in animals started showing up in humans that were in close contact with them and exhibited traits specifically found in animal isolates, indicating a reverse transmission from animals to humans. Initial reports of MRSA in animals did not indicate the presence of host adaptation, enterotoxin, virulence, and antimicrobial resistance genes in them but they are becoming more prevalent and it is feared that these animals could serve as a reservoir for such strains and play an important role in zoonotic transfers.

Documentation of MRSA isolates (ST59-t437–V) from cattle containing the *pvl* gene and other virulence factors, such as *chp, scn, seb, sek*, and *seq*, toxic shock syndrome toxin 1 (*tsst1* or *tst*) gene and hemolysin, protease, superantigen-like protein, capsule, and biofilm-associated genes make them powerful pathogens that could cause a medical nightmare.

A livestock-associated CC398 lineage MRSA is well known to transfer from animals to humans and other MRSA isolates of different clonal complex groups are also known to be associated with zoonotic transfers. A human pandemic community-associated CC97 lineage MRSA harboring the antimicrobial resistance genes *mecA* and *mecC* has been shown to have originated from animals.

A comprehensive study of the emergence, dissemination, prevention and control of MRSA colonization is required to mitigate the risks to both animal and human health. Rapid advancement of whole genome sequencing technology has the great power of discriminating closely associated MRSA isolates from different sources and could be used for source tracking and differentiating between animal and human origin isolates. In addition, it can be applied to monitor the emergence and dissemination of MRSA isolated from various environments and determine the characteristics of virulence factors and evolution of multi-antimicrobial resistance.

Disclaimer

The views expressed herein do not necessarily reflect those of the US Food and Drug Administration or the US Department of Health and Human Services.

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