

Methicillin-resistant *Staphylococcus aureus* in food products: cause for concern or case for complacency?

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Abstract

The widespread use of antimicrobial agents, in combination with insufficient infection control measures, is the main driver of the current pandemic of antimicrobial resistance in human pathogens. The use of antimicrobials in food animal production also contributes, because resistant organisms and resistance genes can spread from animals to humans by direct contact or through the food chain. An important, traditionally human, pathogen, methicillin-resistant *Staphylococcus aureus* (MRSA), is currently endemic in many hospitals around the world and has also emerged in the community. Recently, a new reservoir of MRSA has been identified in food production animals and people in contact with these animals. This involves a specific clone, multilocus sequence type 398 (ST398), which has spread extensively among animals. ST398 has also been found in up to 11.9% of retail meat samples in several surveys from different parts of the world, posing a potential threat to human health.

Keywords: Food production animals, food safety, meat, MRSA, pigs, review

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Introduction

Antimicrobial agents are widely used not only in human and veterinary medicine, but also in animal husbandry and other agricultural activities. This has contributed to an alarming increase in antimicrobial resistance [1,2]. Transmission of resistant bacteria from farm animals to humans can occur not only by contact with the animals but also through contact with, or ingestion of, food products of animal origin [3,4]. Depending on the virulence of the microorganism involved, this can lead to human disease that is more difficult to treat because of the presence of antimicrobial resistance. Additionally, ingested resistant bacteria can transfer their resistance genes to bacteria of the human commensal flora [5,6]. The objective of this review is to describe the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) in humans and animals, its occurrence in food products, and its consequences for human health.

Colonization and Infection with *S. aureus*

S. aureus is a Gram-positive, coagulase-positive coccus of the family *Staphylococcaceae*. Staphylococcal species occur worldwide as commensal colonizers of the skin of animals and humans. They are additionally found on mucous membranes of the upper respiratory tract and lower urogenital tract, and transiently in the digestive tract. Staphylococci are resistant to dehydration and are stable for months in the environment [7]. Colonization with *S. aureus* may occur on mucous membranes of the respiratory and/or intestinal tract, or on other body surfaces, and this is usually asymptomatic [3,8]. The prevalence of nasal colonization with *S. aureus* among the human population is relatively high (c. 30%), whereas the prevalence of nasal colonization with MRSA among the same group is low; the highest rate reported in a population-based survey was 1.5% [9,10]. Some individuals are colonized transiently and some persistently [11]. In healthy people, carriage is associated with

a minor risk of developing an infection. However, when the integrity of the skin is broken, the risk of infection increases dramatically. One of the first reports clearly demonstrating this relationship, in 1952, was performed among miners who suffered from beat disorders (bruises and skin lesions) of the knees and elbows [12].

The situation in miners can be compared to that of patients in hospitals, whose breaks in skin integrity also provide an entry for *S. aureus*. This is especially true for surgical patients, but non-surgical patients are also at risk, owing to the use of invasive devices (e.g. patients on dialysis, patients with human immunodeficiency virus, patients with organ transplants, patients with Wegener's granulomatosis, patients in the intensive-care unit, or patients with intravascular catheters) [13].

MRSA: Underlying Mechanisms, Epidemiology and Clinical Relevance

The methicillin resistance of *S. aureus* is conferred by the *mecA* gene, which codes for a variant of penicillin-binding protein (PBP), PBP2a. PBPs, which are normally present at the cell membrane of *S. aureus*, are bound by penicillin and, consequently, cell membrane synthesis is discontinued, resulting in bacterial death. However, PBP2a has a reduced affinity for β -lactam antibiotics, leaving the cell membrane intact and the organism alive [14]. The *mecA* gene resides on a mobile genetic element, the staphylococcal cassette chromosome *mec* (SCC*mec*) [15]. SCC*mec* contains a *mec* complex, which includes the *mecA* gene and one or two regulatory genes, and a cassette chromosome recombinase (*ccr*) gene complex, which regulates the insertion and excision of the cassette into the bacterial chromosome. So far, eight different *mec* complexes and four different *ccr* genes have been described [15–17].

MRSA was first reported in 1961, shortly after methicillin became available. However, it took several decades before it became a clinical problem. For example, in the USA and the UK, the proportion of *S. aureus* strains causing bacteraemia that were methicillin-resistant started to increase around 1990; by the start of the 21st century, approximately half of the strains causing bacteraemia were resistant [18]. At present, hospital-acquired MRSA is globally endemic, except in Scandinavian countries and The Netherlands, where it is controlled by extensive measures called 'search and destroy'.

Recently, new strains of *S. aureus* with diverse genetic backgrounds have acquired the methicillin resistance cassette, because of the emergence of smaller and more easily acquired cassettes (types IV and V) [19]. These community-acquired strains of MRSA successfully compete with suscepti-

ble strains outside of the hospital, and can cause epidemics in closed communities and healthcare institutions.

Observational cohort studies have consistently found that MRSA infection is associated with excess healthcare costs and prolonged hospital stay for surgical and critically ill patients, after adjusting for comorbidities and hospital events before infection [20]. In addition, in two cohort studies from Canada and the UK, MRSA did not replace methicillin-susceptible *S. aureus*, but accounted for increasing rates of *S. aureus* bacteraemia [21,22]. A survey of all US hospitals estimated the occurrence and effects of *S. aureus* infections over time [23]. Infections increased from 258 000 in 1998 to 480 000 in 2005. In 2003, the associated incremental costs of staphylococcal disease were c. \$14.5 billion. Another study estimated the occurrence of invasive MRSA infections in the USA in 2005 to be 100 000, and the number of associated deaths to be 19 000 [24].

MRSA in Animals

The isolation of MRSA from animals was first reported in 1972, following its detection in milk from mastitic cows [25]. Since then, MRSA has been isolated from many different animal species, including dogs, cats, horses, sheep, pigs, dairy cows, veal calves and fowl. This was recently reviewed by Leonard and Markey, who suggested that MRSA may be an emerging pathogen in companion animals and horses [26]. However, a distinction should be made between food production animals and individually housed animals, which are, predominantly, kept for companionship and leisure activities. When it is found in companion animals, the presence of MRSA is mainly due to transmission from a human reservoir [27–29]. In food production animals, a new strain of MRSA (ST398; see below) emerged recently [11,30,31], and people working with living pigs or veal calves were found to be colonized from these animal reservoirs. A French group that studied the occurrence of *S. aureus* in pigs and pig farmers at the turn of the century first mentioned this animal reservoir [32]. They found that pig farmers were more frequently colonized with *S. aureus*, including MRSA, than non-farmers. In addition, the strains from non-farmers and farmers were different, whereas strains from pig farmers were identical to the strains in pigs. One of the types that was found only in pig farmers was multilocus sequence type 398 (ST398). A few years later, Voss *et al.* [33] reported ST398 in pig farmers and pigs in The Netherlands. This prompted additional investigations into the epidemiology of MRSA in pigs, showing that ST398 had spread extensively. Dutch studies have reported prevalences at the farm level varying from 23% to

81% [34,35] (Broens *et al.*, Proceedings of the 1st American Society of Microbiology Conference on Antimicrobial Resistance in Zoonotic Bacteria and Foodborne Pathogens, 2008, Abstract A19). Later studies from Belgium (Dewaele *et al.*, Proceedings of the 1st American Society of Microbiology Conference on Antimicrobial Resistance in Zoonotic Bacteria and Foodborne Pathogens 2008, Abstract A36), Denmark [36], Germany [37], France [32], the USA (Smith *et al.*, International Conference on Emerging Infectious Diseases, 2008, Abstract A17) and Canada [38] also reported the occurrence of this strain in pigs and pig farmers. A case-control study confirmed that humans colonized with ST398 had a strong relationship with pig farms, defining MRSA as a zoonotic pathogen [39]. In addition, this study showed a strong relationship with exposure to veal calves. Subsequent studies of veal farms revealed high prevalences of ST398 as well; 88% of the farms and 28% of the calves tested positive (Graveland *et al.*, Proceedings of the 1st American Society of Microbiology Conference on Antimicrobial Resistance in Zoonotic Bacteria and Foodborne Pathogens, 2008, Abstract B84). Finally, ST398 has also been linked to poultry, but its relationship to human carriage must be confirmed in larger surveys [30,31,40].

Several observations have confirmed the potential of ST398 to spread and cause disease among humans. However, both the transmissibility and the virulence of ST398 are likely to be less than those of other MRSA types, according to two observational studies [41,42]. Therefore, the impact of ST398 on public health may be limited, but close monitoring of its evolution over time will be required.

MRSA in Food: Presence and Consequences

Contamination of food products with *S. aureus* is an important cause of food poisoning. This is a form of gastroenteritis that is manifested clinically as emesis, with or without diarrhoea. It results from ingestion of one or more preformed staphylococcal enterotoxins on food that has been contaminated with *S. aureus*. Signs of systemic toxicity, such as fever and hypotension, are rarely observed in cases of staphylococcal food poisoning. It is a self-limiting condition that typically resolves within 24–48 h of onset. The exact incidence is unknown, but it is probably the most common cause of food poisoning in the USA.

Risk assessment in foodstuffs relies on classic microbial detection and quantification of coagulase-positive staphylococci on a selective Baird–Parker medium. For the development of disease after consumption, the presence of bacterial toxins cells above a certain threshold, as well as the produc-

tion of, is required. Therefore, in many countries, low-degree contamination by *S. aureus* is tolerated in most foodstuffs (e.g. up to 10^3 CFUs/g in raw milk cheeses in France), as this is not considered to be a risk for public health [43]. Indeed, *S. aureus* is found frequently in retail meat. Studies in Switzerland and Japan showed prevalences of *S. aureus* in meat products of 23% and 65%, respectively [44,45]. The Swiss survey traced the contamination of meat products back to certain abattoirs.

The emergence of ST398 has prompted surveys for the presence of MRSA in meat. During slaughtering of MRSA-carrying animals, contamination of carcasses with MRSA may occur, and consequently the meat of these animals may become contaminated. A contemporary review of the presence of MRSA in food was recently released by the European Food Safety Authority (http://www.efsa.europa.eu:80/cs/BlobServer/Scientific_Opinion/biohaz_op_993_mrsa_en.3.pdf?ssbinary=true). The most important and well-designed surveys are described here. The Dutch Food Safety Agency sampled various kinds of meat collected from the retail trade. MRSA was isolated from 264 (11.9%) of 2217 samples analysed. Isolation percentages for the meat species were 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%. The majority (85%) of the isolated strains belonged to ST398; the other STs were possibly of human origin [46]. Another Dutch survey found that 36 of 79 (46%) retail meat samples contained *S. aureus* strains, of which two (2%) were methicillin-resistant: one was ST398 and the other was USA300 [47]. This study used molecular typing, and demonstrated that there was a high degree of clonal relationship among *S. aureus* strains from samples that came from a single retail shop, indicating cross-transmission at some point during processing in the shop. Therefore, the strain in the sample may not always be indicative of the strain that was carried by the animal at source. In a US survey, among 120 retail meat samples, 47 (39.2%) contained *S. aureus* strains, six (5%) of which were MRSA. The types found were USA100 (ST5) and USA300 (ST8) [48]. A Canadian survey found that 31 of 402 (7.7%) retail meat samples harboured MRSA (Weese *et al.*, 19th European Conference on Clinical Microbiology and Infectious Diseases, 2009, Abstract O94). Three major types were obtained: ST398 (30%), ST8 (40%) and ST5 (30%). ST8 has also been found frequently in horses, which may represent a source of contamination of meat. ST5 is a strain commonly found in humans in both the USA and Canada.

It is clear from the aforementioned surveys that MRSA is currently present in food, posing a potential risk for human health. As mentioned, the main risk arising from the presence of *S. aureus* in food is the development of food poisoning. However, methicillin resistance is not a relevant

factor for the production of enterotoxins, and food poisoning is not a disease that is treated with antibiotics. Therefore, MRSA should not pose a greater risk of food poisoning than methicillin-susceptible *S. aureus*. In fact, ST398 rarely possesses toxin genes [49].

The second risk is the development of invasive disease following the ingestion of contaminated food; this is a rare event, and has only been reported once in the literature, in the context of a large hospital outbreak of MRSA, due to contamination of food products, in a hospital ward in Erasmus Medical Centre in Rotterdam, The Netherlands [50]. In this outbreak, a patient was probably infected following ingestion of MRSA-contaminated food, and severe sepsis developed subsequently, leading to death. The patient was severely immunocompromised and received both antacids and antibiotics, to which the outbreak strain was resistant. Therefore, under these extreme conditions, it may be possible to develop invasive infection after ingestion of *S. aureus*-contaminated food, but this is unlikely to be a risk for the majority of individuals.

The third potential risk is the possibility of becoming colonized with MRSA during food processing or consumption. When meat is cooked properly, the potential risk related to consumption is probably not relevant. Handling the meat before cooking, however, does involve a risk of becoming colonized. The risk largely depends on the hygienic measures taken, the amount of MRSA present, and the ability of the strain itself to colonize the host. In this regard, it should be noted that, in the studies on retail meat mentioned above, the amount of *S. aureus* present in meat samples was very low.

Conclusions and Recommendations

Over the past decades, the epidemiology of MRSA has changed significantly. Traditionally considered a nosocomial pathogen, MRSA has recently also entered the community, causing serious infections. Additionally, MRSA infection and colonization have been documented in several animal species. At the turn of the century, MRSA ST398, a novel clone linked to food production animals, has also emerged in humans. Molecular typing methods support the relationship between this particular strain in food production animals and humans who have been in contact with these animals. From the animal reservoir, MRSA can be introduced into hospitals, and serious infections and outbreaks can occur, as has been reported incidentally so far. How critical this new development is for human health, and the possibilities for appropriate infection control, are currently being studied. Considering the significant spread among production animals, it is unlikely

that this reservoir will be eradicated easily. At present, MRSA is also found commonly in retail meat, with a potential for widespread dissemination in the population. On the other hand, there are indications that ST398 does not spread easily among humans and that its virulence is less than that of other MRSA clones [41].

However, this assumption needs to be confirmed in well-designed studies before control measures are modified. Considering the potential implications of the reservoir in food production animals and the widespread presence in meat, the epidemiology of ST398 in humans needs to be monitored carefully.

Transparency Declaration

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