

**Zoonotic Aspect of Methicilin Resistant Staphylococcus Aureus****19**

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**ABSTRACT**

Antibiotic-resistant bacteria have become an astoundingly painful issue for the security of global public health due to their exponential rise and persistence. A major player in antibiotic-resistant groups of bacteria is *Staphylococcus aureus*. It is a ubiquitous organism with superior adaptive and survival capabilities making it a perfect study model and an extremely hard enemy to deal with. *S. aureus* can gain resistance against various antibiotics and the most important one of those is the methicillin group. The specific group that gains resistance against this antibiotic group is known as Methicillin Resistant *Staphylococcus aureus* or MRSA. The emergence of MRSA is a primary issue for the healthcare sector as most of the antibiotics commonly used for the treatment of regularly occurring infections are the ones belonging to the methicillin group. Such circumstances call for the initiatives to battle antimicrobial resistance through the development of new antibiotics, the use of alternative medicine and the reduction of the misuse of antibiotics. Hence the researchers need to thoroughly comprehend the mechanism of methicillin resistance gene transmission to prevent its spread and save the human population from the abhorrent future of multi-drug resistant bacteria where every disease will become fatal and all antibiotics will be useless against them.

**Key word:** Resistant, Bacteria, MRSA, Antibiotic, Methicillin, *Staphylococcus aureus*.

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## 1. INTRODUCTION

AMR or Antimicrobial resistance is one of the major global health challenges of the 21st century. The approach of “One Health” is being thought out holistically as an important tactic to prevent the rise and spread of multi-drug resistant or MDR bacterial agents. This can help in the preservation of the efficacy of antibiotics already being used publically. The main concept of “One Health” is emphasizing the security of global health through an inter-connected approach of linking the health of humans with that of the environment and animals (pets, livestock and wild). Out of several bacterial pathogens, staphylococci are the ones that have been used as a model organism for the study of “One Health” relevant subjects. Many of the other organisms cannot be used because those species and their clones have been shown to “jump” across different types of ecosystems being considered for the study. *Staphylococcus aureus* or (*S. aureus*) generally behaves as a commensal. However, it can also act as an opportunistic pathogen that serves as an etiologic agent for causing various types of infectious diseases in both humans and animals. This bacterium has a major effect on public health, the general ecosystem and the production capacity of livestock production (Rossi et al. 2020). The presence of characteristics of *S. aureus* like anti-microbial resistance, virulence and, most importantly, adaptation to the host systems, are of immaculate importance for the public health sector. These characteristics raise concerns regarding livestock, pets and wild animals as they can serve as zoonoses reservoirs or intermittent hosts for reservoirs of zoonoses (Rossi et al. 2020). There has been an increase in interest regarding the exploration of methicillin-resistant *S. aureus* (MRSA) and its characteristics saving from the impact of antibiotics. Though old this trend has rejuvenated since the last decade. However, only a small amount of information is available regarding the global occurrence of MRSA isolates in wild animals. These trends need proper research despite wild animals being claimed as potential transmission vehicles or reservoirs for MRSA (Silveira et al. 2021).

## 2. METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS OR MRSA

Among the normal *S. aureus* organism, MRSA is present which is the reason for increased cases of hospital-based or nosocomial infections from 1980 to 2000. This rise in the number of cases was noticed in almost all parts of Europe and the world too ( Cuny et al. 2015). Only a few countries including the Netherlands and the Scandinavian countries, take serious actions to control and prevent MRSA in the populations (Köck et al. 2014). After this many other European countries also took action against MRSA which resulted in the stop of the high spread of MRSA infection in the last five years. The control measure was very effective in that the rise in infection declined which is seen in some European countries (Cuny et al. 2015). The major and basic control measure which became the cause of the rise in infection rate was the introduction of mandatory surveillance in some countries of Europe for the MRSA bacteria (Johnson et al. 2012). The surveillance was then followed by some search and follow-up techniques region-wide programmed for the control of MRSA in Germany (Ciccolini et al. 2013; Jurke et al. 2013). The healthcare-associated MRSA (HA-MRSA) is separated from the community-associated MRSA (CA-MRSA) based on epidemiological criteria and then grown independently according to the associated risk factors (Salgado et al. 2003). In some regions of the world for example South America and the United States, the infections by CA-MRSA are becoming a great problem of public health security. In European countries, the ratio of cases of CA-MRSA is very low (Li et al. 2014). The major difference between HA-MRSA and CA-MRSA is find out through their functional genomic and structural traits (Otto 2013). The precision of epidemiological differentiation between HA-MRSA and CA-MRSA can be decreased by the presence of HA-MRSA in the community (Tavares et al. 2013) and the presence of genotypic CA-MRSA infection through the nosocomial routes (Liu et al. 2008). Livestock-associated MRSA

(LA-MRSA) can be the reason for infection of MRSA in the community. LA-MRSA normally belongs to livestock (Huijsdens et al. 2006; Lewis et al. 2008; Layer et al. 2012). Using genotypic traits both the HA-MRSA and CA-MRSA can be differentiated due to their genome. The structure of the *S. aureus* species population is clonal and it involves the exchange of pieces of genetic information between different strains which is a rare condition. That is why, a test called multi-lit sequence typing (MLTS), identifies seven housekeeping genes and their allelic profiles. This resulted (sequence types also written as STs) in a strong genomic framework which shows the spread of MRSA at a high level. The clonal complexes (CCs) which are being grouped are sharing at least five of the total seven MLST alleles (Feil et al. 2003). For gene typing, Spa typing (Harmsen et al. 2003) is used around the world. The base of this test is the sequence polymorphism of the X-region of the spa gene. It also gives preliminary attribution to CCs. MRSA was first described as the methicillin-susceptible *S. aureus* (MSSA) which after time evolved with antibiotic resistance. By acquiring the SSCmec elements that had a mec gene (mecA, rarely mecC) it becomes MRSA. These mec genes have codes which can make an additional penicillin-binding protein. This protein has less attraction for the beta lactum group of antibiotics. Due to this low attraction, the capacity of resistance increases against all the members of the antibiotic group except ceftobiprole and ceftarolin. Almost 11 structurally different types of SCCmec have been discovered now (Palavecino 2014). Above mentioned methodologies are the base for major knowledge about the rise and spread of LA-MRSA. The next-generation sequencing techniques are economical, best for sequencing and make it possible for researchers to study the genome of whole bacteria. Ultimately this helps in studying the transmission and evolution of LA-MRSA more effectively as compared to the past studies (Price et al. 2012).

### 3. TRANSMISSION

The movement of animals across different habitats and their frequent contact with other livestock, wild animals and along with their indirect interception with the human population can increase the transmission of bacteria. This contact often increases the risks of MRSA colonization. Simultaneously, both animals and humans may also acquire infections (Porrero et al. 2014; Swift et al. 2018; Penna et al. 2021). Usually, the sources spreading antimicrobial-resistant bacteria are anthropogenic. These sources may include domestic wastewater effluents and industrial sanitary disposal, runoff from agricultural sites and their wastes. Such sources are suspected to play a major role in linking wild animals with AMR bacteria (Porrero et al. 2014; Rousham et al. 2018). Once a specific type of bacteria gets transmitted to the wild animal populations they can quickly become responsible for transmission of a large number of AMR genes, mobile genetic elements and epidemic clones (Porrero et al. 2014; Rousham et al. 2018). These examples increase the importance of control of bacteria and the implementation of control strategies throughout the ecosystem to decrease the rise in AMR traits of bacteria. MRSA is recognized as a multi-drug resistant (MDR) bacteria. It is most effective against beta-lactam antibiotics because it synthesises a modified form of penicillin-binding protein 2 (PBP2a/c) which cancels the effect of beta-lactam antibiotics. This PBP2a/c protein is encoded by mec genes which are the parts of staphylococcus cassette chromosome mec (SCCmec). These SSCmec genes are also known to be mobile elements of the genetic information which can harbour the gene's AMR for too long (Becker 2021). The origin of the mecC gene for causing MRSA has not been identified till now. In the beginning, the mecC was thought to be related to livestock-associated (LA)-MRSA but after that it was found that the gene is more related to the wild-life (Zarazaga et al. 2018). It means that mecC-MRSA can also be called wildlife-associated MRSA (WA-MRSA) (Zarazaga et al. 2018; Dube et al. 2021). The *S. aureus* is a suitable pathogen for study because of the large range of its hosts. Some of the clonal complexes (CCs) of MRSA have only specific hosts for example MRSA-CC398 in pigs and MRSA-CC5 in poultry. On the other hand, CC1 and CC130 show a large number of hosts in which they can cause infection (García-Álvarez et al. 2011; Raafat et al. 2020).

## ZOONOSIS

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Some of the clones of MRSA can transmit disease in different domains of "One Health". Due to this wide range of hosts, surveillance should be done at a high level to control the infection. The nasal oral discharge from wild animals (WHO 2014) is a major source of MRSA transmission in humans and other animals (Rahman et al. 2020). The rate of prevalence of CCs depends on the area (farmland or urban) and the frequency of interaction with the animals (Morand et al. 2014). The anatomy of the nasal cavity and buccal cavity of animals shows that there is a small path to the trachea and pharynx respectively which makes the entry of microbes in the trachea and pharynx way easier (Morand et al. 2014).

### 4. ZOONOSIS OF LA-MRSA TO HUMANS

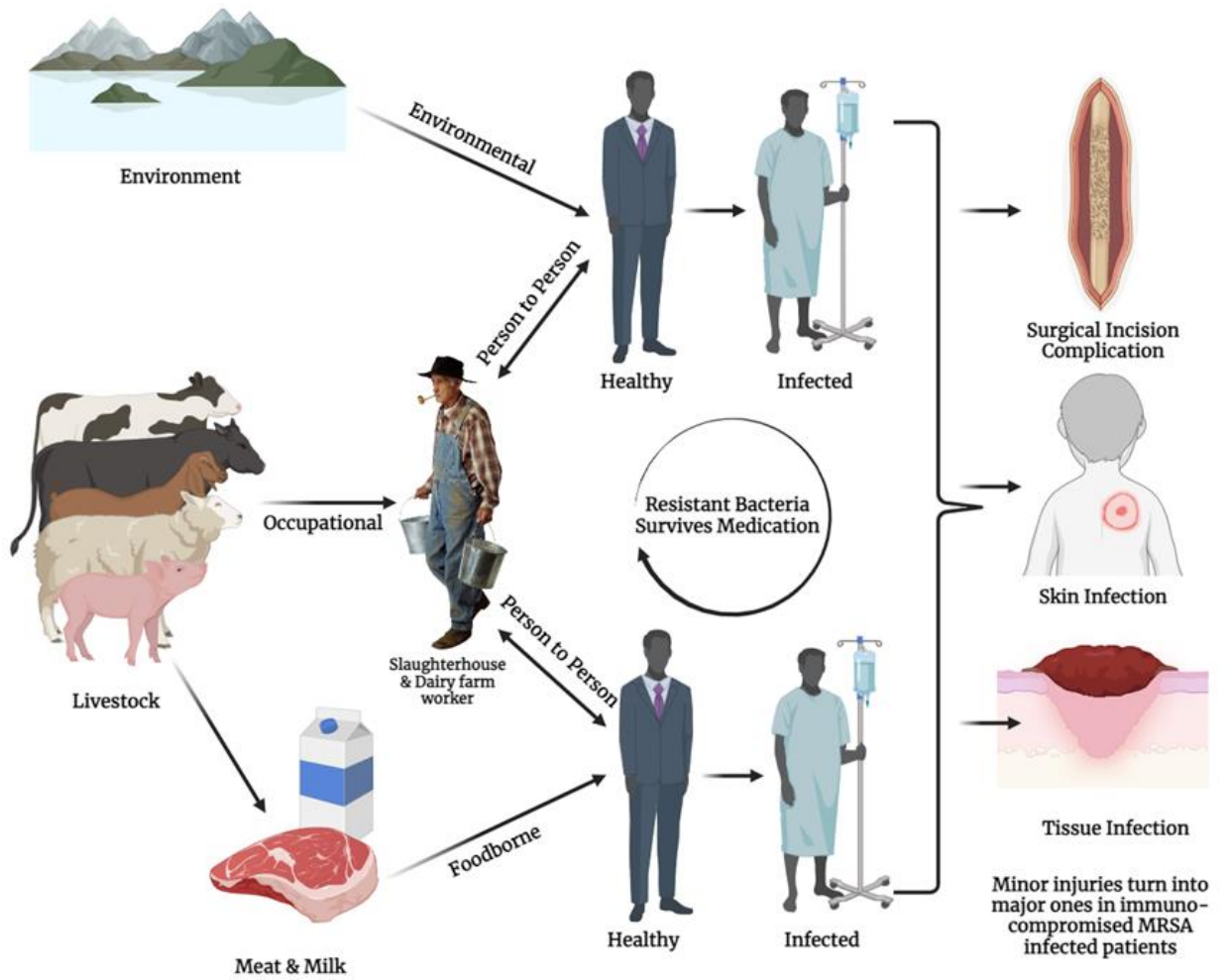
Transmission of *S. aureus* from one host to another primarily happens through physical contact made with the infected host (Fig. 1). The stables of pigs have dust with large amounts of MRSA-colonized contamination in them (Schulz et al. 2012). So, it can be safely assumed that the likelihood of a human getting an infection of MRSA increases in areas with high colonization of it which can be inhaled by humans (Bos et al. 2016). Colonization in the nasal region of humans has been found in 77%–86% of the cases while analyzing the MRSA-positive stables (Cuny et al. 2009; Van Den Broek et al. 2009). The growth of these colonies appears to be dependent upon the period of exposure to the aetiology along with the intensity of contact with the affected animals (Graveland et al. 2011).

### 5. ZOONOSIS OF MRSA THROUGH CONTACT

For a large number of farmers, the colonisation of MRSA continued even when regular contact with animals was terminated due to holidays (van Cleef et al. 2011; Köck et al. 2012). Other people living on the contaminated farms (e.g., household members) were found to be colonised with lesser frequency ranging from 4%–5% (Cuny et al. 2009). A longitudinal study with comparative analysis performed in Belgium, Denmark, and the Netherlands helped researchers discover that contact with pigs was the most important factor for the carriage and transmission of MRSA by farmers and their household members (Belgium 29%, Denmark 0%, Netherlands 6%). An increase in MRSA carriage rate was observed only in Belgium among household members of farmers. This increase was linked to the differences in country-specific species of pigs facing exposure (Garcia-Graells et al. 2013). A study that was performed in the region of Netherlands was used to conclude that living with an MRSA-positive pig farmer and working with sows meant you have to regularly come in contact with MRSA making it a major determinant of the carriage of MRSA to the household members of the farmers (van Cleef et al. 2015). In 2010 Netherlands initiated a crucial program at the national level to promote reduced usage of antibiotics in farm animals. A longitudinal study of MRSA in Germany considered the colonization of pigs and humans working on pig farms as well as their household members to study the decline in antibiotic resistance with a reduction in the usage of antibiotics. The report claimed a 44% fall in the use of antibiotics at the farms, that had entered in this study was linked with the declining prevalence of both MRSA in pigs as well as LA-MRSA in humans irrespective of the frequency and intensity of animal contact (Dorado-García et al. 2015).

### 6. RELATION OF HERD SIZE WITH MRSA OCCURRENCE

A study held in Taiwan revealed that the nasal carriage of LA-MRSA ST9 among the pigs was greater in larger herds which is 34% as compared to those with less amount of animals which is only 7%. Also, the risk of infection was high in humans dealing with larger herds was about 36.8% as compared to those who deal with smaller herds which is almost 9.1% (Fang et al. 2014). The colonization of LA-MRSA in the nasal region was found in the workers of slaughterhouses (Mulders et al. 2010) and veterinarians in



**Fig. 1:** Zoonotic Transmission of Methicillin-resistant *Staphylococcus aureus*.

Germany (Hermes et al. 2012) and in Belgium (Garcia-Graells et al. 2012). The risk of getting an infection of MRSA is greater in veterinarians due to the close association with livestock. The colonization of MRSA has been seen in the household members of veterinary industry staff (Verkade et al. 2014). To understand the colonization of LA-MRSA in family members of veterinarians whole-genome maps are used to check the possibility of LA-MRSA transmission in humans (Bosch et al. 2015). The major part of this data has been taken from studies which are about conventional farms. The research study in Germany shows that there was no CC398 strain of LA-MRSA in both humans and pigs at organic farms (Cuny et al. 2012). This study revealed that the prevalence of the CC398 strain of LA-MRSA is much less in organically grown pigs compared to those which are reared through conventional methods of farming in the Netherlands (Van de Vijver et al. 2014). The prevalence of LA-MRSA in humans far from farms is less, as proved by research on students of an institution with a large number of pig farming facilities in the northwest of Germany (Cuny et al. 2009). However, the tests of patients admitted to the hospital revealed that the prevalence of LA-MRSA is very high in the northwest region of the country as compared to the whole country (Köck et al. 2013). In the Netherlands, the number of livestock was identified as a risk for livestock-associated methicillin-resistant *S. aureus* (Feingold et al. 2012). Explosions of LA-MRSA were seen many times in the air emitted from pig stables. Research proved the

presence of LR-MRSA in the air expelled from pigs' stables ranges from 350 m downwind to 500 m on the surface of the soil (Friese et al. 2013a).

### 7. TRANSMISSION ROUTES OF LA-MRSA

The presence of LR-MRSA has also been recognized in the poultry droppings at poultry farms and the soil which is fertilized by poultry litter containing fertilisers (Friese et al. 2013b). Based on this, the discovery of LA-MRSA in the samples of stool collected from rocks in Austria is surprising for the researchers (Loncaric et al. 2013). After all these the main question was about the people living in the area which is surrounded by the livestock farms have a greater chance to get infected by LA-MRSA. So in these areas, the control and eradication of LA-MRSA is more important. In Lower Saxony in Germany, research has been conducted regarding the colonization of LA-MRSA cc389 in the nasal region of humans. This study revealed that the people living around traditional livestock farms have 1% of the nasal colonization of LA-MRSA CC398 (Bisdorff et al. 2012). An epidemiological survey was done in the state of Pennsylvania, USA and the outcomes of the survey were interesting. The state was well known for the high rate of skin problems and soft tissue infection due to the LA-MRSA in comparison to other states. Also, it has been recorded that the people living near the areas around the farms which are fertilized by animal dung are at greater risk of getting infection. This study was limited to some areas due to unfavourable circumstances. The major problem of this was the absence of the typing of several MRSA isolates which are enough to determine both the animal and human origin (Casey et al. 2013). It has also been reported that the isolates of MRSA have been found in dogs and cats. This transmission of LA-MRSA from pets to their human owner enlightens the need for more hygienic conditions in the daily routine (Idelevich et al. 2016). This proves that the case of human-to-human transmission of LA-MRSA CC398 is much less as compared to the zoonotic transmission. The latest studies reveal the data regarding LA-MRSA infection in humans having no contact with animals from Spain (Benito et al. 2014) and Germany (Deiters et al. 2015). The research data from the Netherlands shows that out of all the cases of LA-MRSA CC398 cases, 15% case were humans who never had contact with veal calves or pigs (Lekkerkerk et al. 2015) LA-MRSA infection is also found in person who has to deal with contaminated meat products. The main routes of transmission are human-to-human contact and environmental exposure. Most preferably this applies to food-handling personnel. A statistical study in the Netherlands shows that people with regular consumption of chicken meat have a high risk of getting LA-MRSA infection (Van Rijen et al. 2013).

### 8. PHENOTYPIC IDENTIFICATION OF MRSA AND VRSA

For the colonies of MRSA and VRSA identification can be done using respective antibiotics like the oxacillin (1µg) and vancomycin (30µg) placed on the activated colonies of *S. aureus* (0.5 McFarland) on agar plates of Muller Hinton respectively. The plates should be then incubated at 37°C for 24 hours. Growth inhibition zones can be observed around antibiotic discs and are measured by vernier callipers. These measurements are then compared with the standard inhibition zone diameters of the respective antibiotics as described in the Clinical and Laboratory Standard Institute (Javed et al. 2021). The isolates of bacteria with resistance towards the antibiotics are then named respectively. So, if one isolate is resistant to oxacillin discs it will be declared as the methicillin-resistant strain of *S. aureus* also known as (MRSA). On the other hand, the strain that was killed by antibiotics and found to be sensitive to oxacillin will be named methicillin-sensitive *S. aureus* or (MSSA). Similarly, the bacterial isolates showing resistance towards vancomycin discs were termed vancomycin-resistant *S. aureus* or (VRSA). Now the rest of the isolates that did not survive against vancomycin discs were claimed to be vancomycin-sensitive *S. aureus* or (VSSA) (Javed et al. 2021).

## 9. CONCLUSION

Methicillin-resistant *S. aureus* or MRSA has emerged on the horizon of public health as a cloud of disease blurring out the sunshine of health. It is an *S. aureus* with additional genes of resistance against the methicillin group of antibiotics. It can be simply identified by an antibiotic sensitivity test with antibiotic discs of the methicillin group. MRSA has antibiotic resistance due to special mec genes that encode for penicillin-binding protein. This protein helps the bacteria in nullifying the effectiveness of beta-lactam antibiotics.

MRSA genes are highly transmittable due to the ubiquitous nature of *S. aureus* bringing the difficulty of its control and eradication up by many levels. Although the rapid spread of MRSA worldwide has raised an alarm among public health entities. Additionally, its abundant routes of transmission make its control even harder. There are several varieties of MRSA known as clonal complexes (CCs) that infect both animals and humans. Most important and widespread of all these are CC398 and CC130 etc. Other classifications of MRSA include livestock-associated MRSA and wildlife-associated names according to their sources and reservoirs. Knowledge of types and sources can help humans understand MRSA transmission and formulate control policies accordingly as done successfully by various European countries.

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