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Methicillin-Resistant *Staphylococcus Aureus* (Mrsa) Remains a Major Threat to Public Health

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Abstract Methicillin-resistant *Staphylococcus aureus* (MRSA) represents a major public health challenge due to its antibiotic resistance and potential for severe infections in both humans and animals. This review examines the current state of MRSA as a global health threat, emphasizing its virulence factors, transmission mechanisms, and impact on public health. MRSA's resistance to methicillin and other antibiotics confounds treatment and control efforts primarily due to the encoding of penicillin-binding protein 2a (PBP2a) by the *mecA* gene which has a low affinity for β-lactams, resulting in resistance to the entire class of antibiotics. The ability of the bacterium to cause a spectrum of infections, from mild skin conditions to life-threatening diseases like toxic shock syndrome, pneumonia, endocarditis, bacteremia and osteomyelitis, highlights its clinical significance. MRSA's spread is facilitated by its presence in healthcare settings, community environments, and livestock, with significant implications for food safety and public health. The review underscores the urgent need for enhanced surveillance, novel treatment strategies, and effective infection control measures to combat MRSA's growing threat.

Keywords: *bacteremia, endocarditis, healthcare-associated infections, methicillin-resistant, public health, Staphylococcus aureus*

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1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a notable emergent zoonotic pathogen with significant implications for both public health and veterinary medicine. It presents serious issues in both human and animal populations, demonstrating resilience to harsh environmental conditions, including sunlight and desiccation [1]. *Staphylococcus aureus*, a Gram-positive bacterium, is known to colonize various body sites, such as the nares, axillae, vagina, pharynx, and damaged skin surfaces [2]. *Staphylococcus aureus* is a known commensal of both humans and animals. The bacterium could invade the skin, mucous membranes, and internal organs, causing severe illness in animals and humans. In humans, it is responsible for severe nosocomial and community-associated infections. Human diseases associated with *Staphylococcus aureus* include osteomyelitis, pneumonia, meningitis, arthritis, endocarditis, septicemia, deep tissue abscesses, and skin and soft-tissue infections, as well as toxic shock syndrome, among others [3,4].

Staphylococcus aureus is also a common cause of wound and urinary tract infections [5]. In animals, *Staphylococcus aureus* infections are most commonly reported as the cause of mastitis in dairy animals, osteomyelitis in poultry, and skin abscesses, mastitis, and septicemia in farmed rabbits [6,7,8,9]. The pathogenicity of *Staphylococcus aureus* is triggered by several factors, including invasive components, toxin-associated virulence factors, biofilm formation, and antibiotic resistance [10]. Despite surgical procedures and antimicrobial treatments, bacteremia caused by *Staphylococcus aureus* is often associated with high morbidity and mortality [11].

According to their ability to withstand antibiotics, *Staphylococcus aureus* is divided into two groups: methicillin-susceptible aureus (MSSA) and methicillin-resistant aureus (MRSA) [12]. According to the World Health Organization, MRSA infections are associated with noticeably increased rates of septic shock, post-infection hospital stays, ICU duration of stay, ICU mortality, and infection-attributable mortality [13]. Globally, antibiotic resistance caused over 100,000 deaths in 2019; MRSA played a significant role [14]. Compared to MSSA, MRSA is frequently linked to worse clinical outcomes and greater mortality rates; making it the primary cause of *Staphylococcus aureus* bacteremia cases worldwide [15].

Methicillin-resistant *Staphylococcus aureus* (MRSA)

infections represent a significant global public health challenge. In some regions, up to 90% of *Staphylococcus aureus* infections are MRSA, rendering them resistant to standard antibiotics. WHO reports indicate that MRSA is found in every province worldwide, elevating the risk of death by 64% due to its antibiotic resistance as compared to infections caused by drug-sensitive strains. The rise and spread of antibiotic-resistant MRSA strains have led to their increasing prevalence in both healthcare and community settings. MRSA's resistance to methicillin is attributed to the presence of penicillin-binding protein 2a (PBP2a), which renders it resistant to β-lactam antibiotics, including methicillin, and to the production of beta-lactamases [16]. Therefore, the primary aim of this review is to evaluate whether methicillin-resistant *Staphylococcus aureus* (MRSA) continues to pose a significant threat to public health.

2. Staphylococcus Aureus

Staphylococcus aureus is a member of the genus *Staphylococcus* [17]. This non-spore-forming, non-motile, gram-positive coccus commonly inhabits the skin and upper respiratory tract. As a major component of the body's microbiota, it is frequently linked to infections, particularly bacteremia. Pathogenic strains of *Staphylococcus aureus* can lead to a range of infections, from mild conditions to severe and potentially fatal ones like bloodstream infections and pneumonia. The rise of antibiotic-resistant strains, notably methicillin-resistant *Staphylococcus aureus* (MRSA), presents a significant global health challenge. MRSA poses a considerable risk in both healthcare and community settings due to its rapid spread [18].

MRSA is widely known for its quick dissemination and capacity to infect people [19]. Direct contact with sick people, contaminated materials, or polluted healthcare environments can all result in the transmission of the infection [20]. Its rapid spread in community and healthcare settings is facilitated by its ease of transmission [21]. MRSA has the ability to colonize the skin and mucous membranes without producing illness right away [22]. This allows the bacterium to proliferate and spread by building a reservoir. Because MRSA can survive and multiply in the presence of drugs, furthering its dissemination, its resistance to several antibiotics, including methicillin, thus affects treatment and control attempts [23].

MRSA frequently causes healthcare-associated infections, including surgical site infections, bloodstream infections, and pneumonia [24]. The close proximity of patients, weakened immune systems, and invasive medical procedures in healthcare settings can accelerate the spread of MRSA [16]. Additionally, MRSA can lead to infections in community environments, particularly among people who have close skin-to-skin contact, such as athletes participating in contact sports or individuals living in crowded conditions. These community-associated infections contribute to MRSA's widespread impact and rapid spread [25]. Most of the morbidity and mortality related to *Staphylococcus aureus* infections are due to MRSA. Its high prevalence and resistance to antibiotics make treatment challenging, highlighting the need for effective new therapies [26]. Antimicrobial Resistance of MRSA.

The rise of multidrug resistance (MDR) in MRSA presents a significant threat, leading to challenges in treatment and control. MRSA has developed advanced mechanisms to evade modern antibiotics, making it a dangerous pathogen for both humans and animals [27]. Antimicrobial resistance (AMR) occurs when microorganisms continue to grow or reproduce despite the presence of medications designed to inhibit or kill them [28]. MRSA is consistently resistant to multiple antimicrobial agents, including penicillin, methicillin, oxacillin, cefoxitin, amoxicillin-clavulanic acid, amoxicillin-sulbactam, quinolones, macrolides, cephalosporins, tetracycline, and chloramphenicol [1].

Microbes that have evolved to resist the effects of antimicrobial agents that are intended to kill or suppress them are said to have developed antimicrobial resistance (AMR). This resistance makes infections harder to cure, which increases the risk of disease transmission, more complex illnesses, and higher death rates [29]. Because there are fewer alternatives for treating bacterial infections, this scenario harms treatment results, increases treatment costs, and elevates mortality. This increasing prevalence of AMR pathogens poses a severe danger to the health of both humans and animals [30]. The worldwide prevalence of superbugs and germs resistant to drugs has led to a marked increase in morbidity and mortality rates [31]. Antimicrobial resistance is increasing at a rate that may surpass the creation of new antimicrobial agents [32].

2.1. Methicillin-Resistant *Staphylococcus aureus* (MRSA)

MRSA is now recognized as a high-priority pathogen according to the World Health Organization (WHO), since an emergence of these strains has been observed [33]. The global spread and emergence of MRSA are critical aspects of its epidemiology. MRSA spreads through two main methods: either by transmitting existing clones between humans and animals or through horizontal gene transfer of the SCC*mec* element [34]. The SCC*mec* element in MRSA strains encodes penicillin-binding protein 2a (PBP2a)., which has a low affinity for most β-lactam antibiotics. This makes these antibiotics ineffective at blocking the enzyme activity necessary for cell wall synthesis, thus granting resistance to a wide array of β-lactam antibiotics. [33] Additionally, some MRSA strains produce β-lactamase, an enzyme that breaks down β-lactam antibiotics, including methicillin [35].

MRSA was first discovered in 1960, shortly after methicillin was introduced to treat penicillin-resistant *Staphylococcus aureus*. MRSA shows antibiotic resistance through the PBP2a and PBP2c proteins, which are produced by the *mecA* and *mecC* genes, respectively. The staphylococcal chromosomal cassette mec (SCCmec) contains these genes, with *mecA* encoding PBP2a an alternative penicillin-binding protein that is responsible for MRSA's high-level methicillin resistance [36]. However, MRSA colonization increases the risk of infection, and infecting strains match colonizing strains in as many as 50–80% of cases. Colonization can persist for long periods of time. At the same time, colonization is not static, as strains have been found to evolve and even to be replaced within the same host Figure 1 [37].

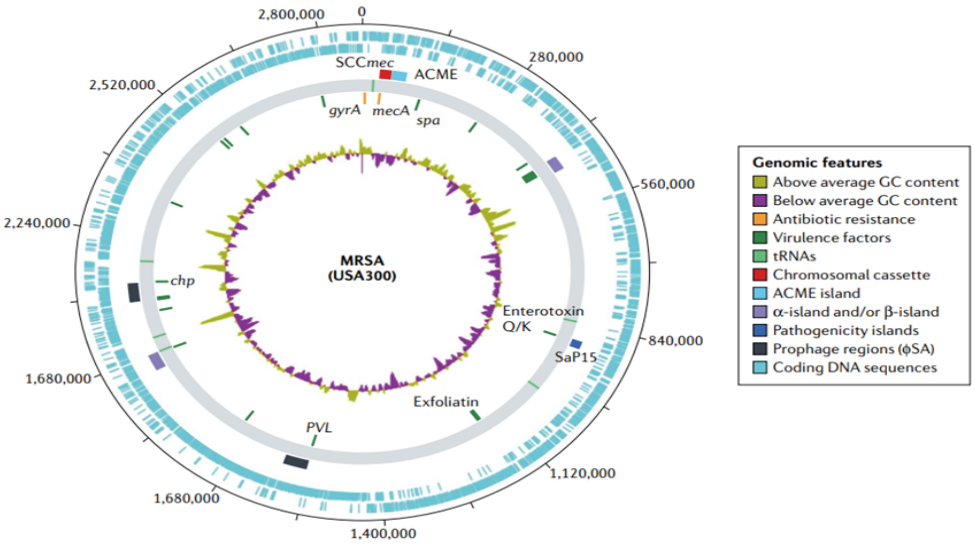

Fig. 1 | **Major genomic elements in methicillin-resistant *Staphylococcus aureus*.** Representative genomic map of the USA300 strain FPR3757 (REF.[77]). The innermost circular track (track 1) represents GC content. Moving outwards, track 2 displays select antibiotic resistance genes in orange and virulence factors in green. Track 3 shows the location of tRNAs. Track 4 displays select mobile genetic elements, with chromosomal cassettes in red, various pathogenicity islands in shades of blue through violet and prophages in black. The outer two tracks (5 and 6) represent coding sequences in blue. PVL, Panton–Valentine leukocidin. Selected annotation created using Artemis/DNAPlotter[166]. MRSA,methicillin-resistant *Staphylococcus aureus*.

Source – [37]

Figure 1. Major genomic elements in methicillin resistance Staphylococcus aureus

Table 1. Mechanisms of action and resistance of the most important classes of antibiotics

Class of Antibiotics	Mechanisms of Action	Mechanisms of Resistance
Penicillins Cephalosporins	Inhibition of cell wall biosynthesis	Production of β-lactamases; PBP's changed
Aminoglycosides Macrolides	Inhibition of protein synthesis by binding to the 30S ribosomal subunit	efflux pumps; modification of the target (ribosome).
Lincosamides	Inhibition of protein synthesis by binding to the 30S ribosomal subunit.	Modification of the target (ribosome).
Quinolones	Inhibition of DNA synthesis.	Target modification (DNA gyrase and DNA topoisomerase).
Tetracyclines	Inhibition of protein synthesis at the level of peptide elongation.	Efflux pumps; modification of the target (ribosome).
Phenicols	Inhibition of the peptidyltransferase reaction in the 50S ribosomal subunit.	efflux pumps; target modification (enzyme and ribosome).
Sulfonamides	Inhibition of folic acid synthesis	Target modification (enzymes).

Source – [33]

MRSA is a major pathogen present in both community and hospital settings. Methicillin acts by inhibiting penicillin-binding proteins involved in cross-linking peptidoglycan, a process crucial for cell wall synthesis. MRSA develops resistance by producing alternative penicillin-binding proteins that maintain essential functions, making methicillin ineffective [38]. The rise of antimicrobial-resistant staphylococci represents a global threat due to their contribution to severe illness and death from infections acquired in healthcare or community settings. MRSA was initially detected in hospital patients with a history of methicillin use but has also been found in healthy individuals with no hospital exposure. This suggests that MRSA can cause infections outside of medical environments. MRSA strains are classified based on their origin: healthcare-associated, livestock-associated, and community-associated [39]. MRSA with the ability to carry out certain biochemical mechanisms such as: enzymatic inactivation, efflux pumps, or target modification which can be specific for different classes of antimicrobials, as shown in Table 1 [33].

2.2. MRSA Transmission Between Humans and Animals

The transmission of *Staphylococcus aureus* depends on the expression of various secreted and cell surface-associated virulence factors. These factors operate on multiple levels: facilitating adhesion to host extracellular matrix components, altering host cells, and undermining the immune system [40] Healthcare-associated MRSA (HA-MRSA) spreads through several routes, including surface contact, aerosols, hand hygiene practices, and interactions with healthcare personnel [41]. HA-MRSA is mainly contracted in hospital settings from contaminated instruments, bedding, doors, and equipment. In contrast, community-associated MRSA (CA-MRSA) is typically transmitted through direct physical contact with infected or healthy individuals, as *Staphylococcus aureus* can be a commensal bacterium in the nasal passages of healthy people. Livestock-associated MRSA (LA-MRSA) is transmitted to humans through physical contact with animals or their environment [42].

2.3. MRSA Infections in Humans

The methicillin-resistant strain of *Staphylococcus aureus* (MRSA) is a growing concern that can cause both mild and severe infections in animals and humans. In humans, MRSA can lead to minor infections like skin and

soft tissue conditions, which include staphylococcal scalded skin syndrome (SSSS), pustules, impetigo contagiosa, abscesses, and papules, as well as more serious infections such as toxic shock syndrome (TSS), pneumonia, and TSS-like exanthematous disease in newborns [43]. Out of the approximately 100,000 MRSA infections reported each year, 20% result in death [44]. MRSA infections in humans have traditionally been categorized into two main types: community-associated MRSA (CA-MRSA) and healthcare-associated MRSA (HA-MRSA). HA-MRSA infections are commonly seen in athletes, children, and hospitalized individuals, while CA-MRSA typically causes a range of skin and soft tissue infections, from mild issues like furuncles and impetigo to severe conditions such as necrotizing fasciitis and pneumonia. Generally, CA-MRSA causes less severe infections compared to HA-MRSA in both humans and animals [25].

2.4. MRSA Infection in Food Animals

Staphylococcus aureus is a pathogen responsible for infections in both humans and animals, as well as for food poisoning [45]. Mastitis, a significant disease affecting dairy animals, is linked to extensive antibiotic use and results in substantial economic losses. Among the various pathogens causing mastitis, *Staphylococcus aureus* is the primary culprit globally. Livestock-associated MRSA (LA-MRSA) is also a notable cause of pustular dermatitis in dairy workers [46]. The first cases of antibiotic resistance in food animals were observed in turkeys in 1951, after streptomycin was fed to those animals. Since then, resistance to antibiotics, such as tetracyclines, sulfonamides, β-lactams, and penicillin, have increasingly been observed [33]. MRSA was first identified in cattle in Belgium in 1972, detected in milk samples, and likely spread through contamination from milker hands [47]. MRSA infections in the mammary glands of cattle can lead to reduced milk production or even cessation of milk flow in severe cases, causing significant financial impacts on the dairy industry [48]. The inflammation of the mammary gland is driven by lukMF9, a potent virulence factor of LA-MRSA. LukMF9 binds strongly to the CCR1 chemokine receptor in bovines, leading to severe inflammation and damage due to the increased accumulation of neutrophils in the mammary gland [49,50].

2.5. Public Health Importance of MRSA

MRSA contamination of milk and dairy products is a major contributor to food poisoning. This typically results in gastroenteritis symptoms, including vomiting and diarrhea. These symptoms are caused by consuming staphylococcal enterotoxins that develop in MRSA-contaminated milk and dairy products. Although cases of systemic toxicity, such as low blood pressure and fever, are uncommon, they usually resolve within 24 to 48 hours. The exact prevalence of MRSA-related food poisoning is not well known, but it is likely one of the leading causes of foodborne illness in the United States [51].

Risk assessment for milk and dairy products typically involves detecting classic bacteria and counting coagulase-positive *Staphylococcus* on selective Baird Parker media. Monitoring the progression of illness following consumption of these products, as well as detecting the presence and production of toxic cells, is crucial. In some countries, low levels of contamination by *Staphylococcus aureus* and MRSA are tolerated in various food products such as up to 10^3 CFU/g of *Staphylococcus aureus* in French cheese without posing significant public health risks [51,52].

3. Conclusion and Recommendations

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be a significant and intricate public health issue globally. The devastating effect of MRSA on global health is highlighted by its resistance to methicillin and other antibiotics, as well as its pervasive occurrence in food goods, animals, and humans. The versatility of the bacterium in healthcare and community settings makes it more difficult to contain infections and create efficient treatment plans. Multidrug-resistant strains (MDR-MRSA) are emerging, which exacerbates the issue and raises the mortality and disease rates. Stricter infection control protocols, enhanced surveillance, and continuous research are needed to mitigate the impact of MRSA on human health globally.

Based on the above conclusion;

- √ Improve monitoring of MRSA prevalence across healthcare settings, community spaces, and food production environments.
- √ Ensure rigorous infection control measures in healthcare settings, including consistent hand hygiene, thorough sterilization of equipment, and isolation of MRSA-positive patients to prevent the spread of the infection.
- √ Foster and enforce antibiotic stewardship programs to reduce the overuse and misuse of antibiotics, which contribute to MRSA resistance and spread.
- √ Increase public education on MRSA transmission and prevention. Highlight the importance of proper hygiene practices and the risks of untreated MRSA infections to minimize community spread and raise awareness.

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Authors Contribution

All authors contributed during the preparation of the manuscript.

Conflict of Interest

No conflict of interest was noticed among the authors

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