

# **METHICILLIN RESISTANCE *STAPHYLOCOCCUS AUREUS*: A COMPENDIUM OF CURRENT DEVELOPMENT ON EPIDEMIOLOGY, TRANSMISSION, PREVALENCE, ASSOCIATED FACTORS, PATHOGENESIS, IDENTIFICATION OF PATTERNS OF ILLNESS IN HOSTS, NEW THERAPY, AND CONTROL STRATEGIES**

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## **I. INTRODUCTION**

Most healthy individuals usually have *Staphylococcus aureus* in their noses and on their skin. It is a coccus-shaped, gram-positive, non-motile, non-spore-forming bacterial species (Tigabu et al., 2018). It is a human pathogen in addition to being a commensal bacterium. Approximately thirty percent of people are infected with *S. aureus*. In addition to bacteremia and infective endocarditis, it is the main cause of infections associated with other body parts, including skin and soft tissue infections, pleuropulmonary infections, and osteoarticular disorders (Tong et al., 2015).

The host range that *S. aureus* can infect is diverse as well, encompassing domestic cats and dogs, horses, goats, sheep, cattle, rabbits, pigs, and poultry (Peacock and Paterson, 2015). Although several illnesses have been identified in these species, mastitis in dairy cattle and

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other ruminants is the most commercially significant (Grinberg et al., 2004). *S. aureus* is a common cause of infections in both the community and healthcare settings (Shibabaw et al., 2013). In 135 countries, *S. aureus* was the most common cause of bacterial deaths, accounting for the majority of deaths globally among adults over the age of 15 (Ikuta et al., 2022). Resistance strains of *S. aureus* have arisen as a result of the widespread use of antibiotics in both human and veterinary medicine (Grema et al., 2015).

One of the crucial gram-positive bacteria for medicine is methicillin-resistant *S. aureus* (MRSA), which is primarily found in the nasal cavity. A person colonized by both *S. aureus* and MRSA has a gradually increasing chance of contracting another infection (Reta et al., 2019). To render penicillin resistant to penicillinase, its structure was altered in the late 1950s, yielding methicillin, a semisynthetic derivative of penicillin. Like other penicillins, methicillin works by inhibiting the production of bacterial cell walls (Boswihi and Udo, 2018).

Since the 1960s, MRSA has been identified as a primary cause of bacterial infections in both community and clinical settings. It emerged and migrated around the globe. The MRSA burden varies significantly among regions, nevertheless, for a variety of reasons, including differences in local infection control practices and pathogen-specific characteristics of the circulating clones. (Lee et al., 2018). Methicillin resistance is determined by the acquisition of a non-self-gene that codes for a penicillin-binding protein (PBP2a), which has a significantly decreased affinity for  $\beta$ -lactams. Due to this resistance, the objective of  $\beta$ -lactams, cell-wall production, can proceed even at antibiotic dosages that would ordinarily be inhibitory concentrations of antibiotic (Peacock and Paterson, 2015).

Even though bacteria naturally develop resistance to many antibiotics, the alarming growth in pathogenic germs resistant to these drugs is attracting attention on a global scale. A new AMR indicator was added to the SDG monitoring framework in 2019. This indicator measures the frequency of bloodstream infections brought on by two different drug-resistant pathogens: methicillin-resistant *Staphylococcus aureus* (MRSA) and *E. Coli* resistant to third-generation cephalosporin (3GC). Global Antimicrobial Resistance and Use Surveillance System (GLASS) received data on MRSA bloodstream infections from 25 nations, territories, and regions in 2019. Even though the data are still not nationally representative, the median rate of methicillin-resistant *S. aureus* that was discovered was 12.11% (IQR 6.4–26.4) (WHO, 2015).

According to a systematic review and meta-analysis, the pooled global prevalence of MRSA in 119 studies totaling 164,717 individuals from 29 countries was 14.69% (95% CI 12.39–17.15%; 16,793/164,717). This is about the colonization rate of MRSA in aged care center residents worldwide (Hasanpour et al., 2023).

Even though WHO reported different findings about MRSA across the globe still results are not nationally representative. Also, there is a gap in mapping the distribution of MRSA clones in sub-Saharan Africa, especially East Africa. The prevalence of MRSA varies globally, having greater rates. Its spread is facilitated by patient demographics, monitoring of antibiotics, and community-associated MRSA. The World Health Organization

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(WHO) states that new antibiotic substitutes are critically needed for certain high-priority illnesses. This list was released in 2019 and was recognized as a worldwide recovery in 2024 (WHO, 2024). In light of the review's main topic, antimicrobial resistance (AMR) was recently ranked by the World Health Organization (WHO) as one of the top ten threats to world health because of its effects on human health (WHO, 2019). The most prevalent antimicrobial-resistant bacteria in hospitals worldwide is MRSA (Álvarez et al., 2019). Compared to developed countries, research on MRSA prevalence, associated factors and antimicrobial susceptibility patterns in sub-Saharan Africa is scarce. Most importantly, the transmission of HA-MRSA has been a serious concern among patients in recent years. HA-MRSA can spread by carriers or by health care workers (HCWs) using fomites and irregular practices (Arshad et al., 2017). Information about MRSA prevalence and related factors in Somalia is scarce. This gap in knowledge hinders researchers from understanding how these antibiotic-resistant strains spread and evolve within the region, making it difficult to implement effective strategies to contain outbreaks and prevent the spread of drug-resistant infections.

## II. AIM OF REVIEW PAPER

This review paper aims to provide an overview of the present state of research on methicillin-resistant *S. aureus*, covering topics such as epidemiology, transmission, prevalence, related variables, pathogenesis, identification of patterns of illness in hosts, new therapy, and control strategies.

## III. LITERATURE REVIEW

**1. Epidemiology of MRSA:** *S. aureus* is a well-known human pathogen that infects people in both hospitals and the community. Despite the focus on the methicillin-resistant "variant" MRSA, the methicillin-susceptible counterpart (MSSA) remains a major species in infections. The epidemiology of *S. aureus* has altered dramatically in the last few years, especially with MRSA. MRSA has evolved from being a typical nosocomial multidrug-resistant disease to being increasingly common in both the community and among farmed animals because of its ability to modify and adapt to varied situations. Global surveillance has shown that MRSA is a concern in all continents and nations where research has been done, leading to a rise in mortality and the requirement for the use of costly, and last-resort medications. *S. aureus* is prone to quickly developing antibiotic resistance, and MRSA is well known for being multidrug-resistant (Monaco et al., 2017).

The introduction and widespread spread of MRSA have been among the most important advances in the epidemiology of infectious illnesses. Although MRSA was first discovered in the early 1960s (Lee et al., 2018). There have been reports of high (>50%) MRSA rates in the USA, Asia, and Malta; intermediate (25–50%) rates in Africa, China, and Europe; and, depending on the research location and sample size, relatively lower than 50% prevalence rates in some parts of Europe. (Mejía et al., 2010).

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**HA-MRSA:** Global data over the preceding 25 years has indicated an increase in the frequency of hospital-associated HA-MRSA. It is discovered that HA-MRSA strains lack SCC mec types I, II, or III and instead have genes that encode PVL. Antimicrobial drugs other than  $\beta$ -lactams, such as aminoglycosides, macrolides, lincosamides, and fluoroquinolones, are frequently met with resistance in HA-MRSA. They are associated with nosocomial infections such as endocarditis (Kateete et al., 2019).

**CA-MRSA:** MRSA infections that are brought on by CA-MRSA can happen outside of medical facilities (Cuny et al., 2015). The more recent and virulent strain CA-MRSA, which has a distinct genome, first surfaced in the late 1990s. It is known that these strains can infect young, healthy people who have never been to a hospital with skin and soft tissue diseases (Kong et al., 2016). Most CA-MRSA strains typically feature SCC-mec types IV or V and are susceptible to non- $\beta$ -lactam drugs. Additionally, occasionally CA-MRSA endocarditis carries Panton-Valentine-Leukocidin (PVL), a cytotoxin associated with heightened virulence that encodes the genes *lukS-pv*, and *lukf-pv* (Kateete et al., 2019). The epidemiology of MRSA has changed significantly since these strains were introduced into the hospital setting, with CA-MRSA emerging as a primary source of infections associated with healthcare endocarditis. Because of their higher potential for transmission and pathogenicity, CA-MRSA clones have replaced standard hospital MRSA clones in several areas (Choo, 2017).

**LA-MRSA:** Some Staphylococcal infections are currently caused by livestock-associated MRSA (LA-MRSA). It was first associated with animals. The majority of MRSA cases have a connection to clonal complex CC398. Almost half of the traditional pig farms had animals colonized with LA-MRSA CC398 without any symptoms. It has been found that nasal carriage occurs in approximately 77%–86% of individuals who work with pigs; interruptions in exposure can cause it to disappear. It is only 4%–5% of family members who live on the same farms that are colonized. Less frequently, the spread beyond this demographic occurs. Disinfectant use, farm size, farming practices, and zinc in feed all appear to have an impact on the LA-MRSA's prevalence in animals. The same bacteria that cause *S. aureus* and MRSA infections in general can also cause LA-MRSA CC398 infections in humans (Cuny et al., 2015).

**Distribution of MRSA Clones:** MRSA epidemiology is characterized by the emergence and spread of new clones, which cause ongoing alterations on a worldwide scale (Turner et al., 2019). For example, the two most prevalent CA-MRSA clones, ST5 and ST93, have been steadily increasing in Australia (Bloomfield et al., 2020), whereas in China, ST239 has replaced ST59 (Li et al., 2018). Furthermore, in Canada and the United States of America, there has been a decline in ST5 instances and a rise in ST8 cases (Guthrie et al., 2020) (See et al., 2020).

The epidemiological picture reveals distinct clonal types in various nations and regions, and Africa has reported varying prevalence rates of MRSA (Wangai et al., 2019). According to the results, sequence type (ST) 5 and ST239/241 were the two most common pandemic MRSA clones all over the continent. However, some clones were unique to particular regions (ST612 in South Africa, for example) or regions (ST80 in

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North Africa). Furthermore, CA-MRSA (ST8 and ST88) was detected in both clinical and non-clinical venues (Agabou et al., 2017). Africa is classified as an endemic zone for Panton-Valentine leukocidin (PVL). Additionally, among MRSA recovered from human infections and pregnancy in Africa, the PVL prevalence ranged from 0.3% to 100%. Despite these findings, there is still a lack of knowledge on MRSA's clonal origins in Africa (Schaumburg et al., 2014).

The three most prevalent CA-MRSA clones with African ancestry are ST88-IV, ST5-IV, and ST239-III. A clone known as ST88-IV has been found in both community infections and hospitals. According to reports, European ancestry originated in sub-Saharan Africa (EMRSA-16) (Steger et al., 2014).

A Nigerian study found that in MLST mapping, seven distinct sequence types (ST-1, ST-9, ST-55, ST-93, ST-97, ST-80, and ST-463) were grouped into spa-CC 07 and spa-CC 003, and ten distinct spa-types of MRSA strains were found to be distributed among two groups and two singletons (Shuaibu et al., 2019). Nine different CCs, twelve STs, and fifteen spa types were found in Kenya; CC8 and CC152 were the most common. Across three CCs—CC5-ST39, CC8-ST241, CC8-ST4705, ST8, and CC152—MRSA isolates were dispersed (Kyany'a et al., 2019). Ethiopia contains a diverse range of *S. aureus* and MRSA strains, 56 distinct spa types, a prevalence of 32.9% t355, and 11 new spa types, with 22.2% of MRSA isolates being spa-CC 239 with SCC mec III (Ibrahim et al., 2023).

There is a gap in mapping the distribution of MRSA clones in sub-Saharan Africa, especially East Africa. Researchers find it challenging to comprehend how these antibiotic-resistant strains propagate and change within the area due to this knowledge gap, which makes it challenging to put into practice efficient containment and drug-resistant infection prevention tactics. Since MRSA is a severe public health concern, minimizing its financial and healthcare burden is essential. Consistent surveillance and monitoring can aid in understanding epidemiological changes.

- 2. Prevalence of MRSA:** The following overall reported range of *S. aureus* AMR proportion percentages was recorded worldwide, according to the Antimicrobial Resistance Global Report on Surveillance (2014): region of the Americas 21–90%, Eastern Mediterranean Region 10–53%, European Region 0.3–60%, South-East Asia Region 10–26%, Western Pacific Region 4–84%, and African Region 12–80%. (WHO, 2014). Based on a comprehensive review and meta-analysis of 55 studies spanning 24 countries and 110,654 pregnant women, the global prevalence of maternal methicillin resistance *S. aureus* colonization was found to be 3.23% (95% CI, 2.40-4.17%). Europe (0.79%, 0.28-1.51%) and Africa (9.13%, 4.36-15.34%) had the lowest and highest rates of colonization, respectively. This analysis estimates that 4.5 million pregnant women worldwide are colonized by MRSA (Nourollahpour Shiadeh et al., 2022).

A ten-year prospective cohort research conducted at a hospital in Saudi Arabia revealed 3395 cases of *S. aureus* infections overall, representing 27% of all *S. aureus* isolates, with an annual MRSA incidence of 25 cases per 100,000 patients. Although 64% of MRSA infections occurred in healthcare settings, the isolation rate of CA-MRSA increased

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dramatically from 23% in 2006 to 60% in 2015, outpacing that of healthcare-associated (HA)-MRSA. The skin and soft tissues, the lungs, and the bloodstream were the most common sites of infection; in pediatric patients, these settings accounted for 20% to 35% of MRSA infections. The surgical wards and critical care units were the sites of most MRSA infections in inpatient settings (Al-Hamad et al., 2018).

In Karachi, Pakistan, a cross-sectional study conducted from January 2015 to June 2017 sought to ascertain the frequency rate of MRSA out of a total of 346 *S. aureus* strains, as well as the prevalence of methicillin resistance and multidrug resistance (MDR) among clinical isolates of *S. aureus* and the antimicrobial susceptibility profile of MRSA to the commonly prescribed antibiotics (Siddiqui et al., 2017).

In a Malaysian tertiary hospital, a retrospective analysis of MRSA infection in general surgery wards shows that 8.53% of MRSA incidence in surgical wards, out of 598 patients, were isolated with *S. aureus*. It was found that 51 patients' samples had MRSA infections. The death rate is 11.76%. Risk factors include patients who are older than 60 years old, lengthy hospital stays, a history of antibiotic usage, and comorbidities such as diabetes mellitus, hypertension, and chronic kidney disease, which account for 5.9%, 47.1%, and 35.3% of the patient population, respectively. (Zainol Abidin et al., 2020).

A meta-analysis study conducted in Ethiopia found that the combined prevalence of MRSA was 32.5% (95% CI: 24.1 to 40.9%). Furthermore, it was discovered that methicillin-resistant *S. aureus* strains had a pooled resistance ratio of 99.1, 98.1, 97.2, and 97.1% to penicillin, ampicillin, erythromycin, and amoxicillin, respectively. Conversely, comparatively low vancomycin resistance ratios of 5.3% were observed. (Eshetie et al., 2016).

To ascertain the prevalence of MRSA nasal carriage among healthcare workers, a hospital-based cross-sectional study was carried out among staff members at the Ocean Road Cancer Institute (ORCI) and two regional hospitals in Dar es Salaam, Tanzania: Temeke and Amana. The study's findings revealed that the overall frequency of *S. aureus* nasal carriage among staff members at the hospitals was 157/379 (41.4%). MRSA made up 59 (37.6%) of the 157 isolates of *S. aureus*. Consequently, 59/379 (15.6%) HCWs had an overall prevalence of MRSA nasal carriage (Moyo et al., 2018).

A total of 232 nasal swabs were collected from HCWs in a cross-sectional study conducted in Nepal to determine the rate of nasal carriage MRSA among HCWs at Manmohan Memorial Medical College and Teaching Hospital, Kathmandu. Of these, 34 (14.7%) were found to be carriers of *S. aureus*, and 12/34 (35.3%) HCWs were found to be MRSA carriers. It was discovered that the overall MRSA distribution was 5.2% (12/232) (Giri et al., 2021). Similar research carried out in a Referral Hospital in Zabol, Iran between March and September 2017 revealed that 46.7% of the isolates were MRSA and 10.8% of HCWs were carriers of *S. aureus* (Mir et al., 2019)

HCWs at Kampala International University Teaching Hospital participated in a cross-sectional study between September 2016 and July 2017. 13 (46.4%) of the 97 subjects

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had cefoxitin resistance, making 28 (28.8%) of the participants nasal carriers of *S. aureus* (Abimana et al., 2019). In a different cross-sectional investigation, 140 healthcare workers at the University Teaching Hospital in Lusaka had their nose and hand swabs collected. Of these, 17.1% (24/140) had *S. aureus* carriage overall. 13.6% (19/140) of these had nasal carriage (Chakolwa et al., 2019).

In a different hospital-based cross-sectional investigation, the total prevalence of MRSA and *S. aureus* was found to be 12% (29/242) and 5.8% (14/242) in the Tigray area of eastern Ethiopia, respectively, at the Wukro and Adigrat general hospitals. The study also looked for risk variables, drug susceptibility patterns, and nasal carriage of MRSA. Of the 29 *S. aureus* samples, 48.3% (14/29) had MRSA antibodies. MRSA transmission in this study was much greater among nursing staff (7.8%) and in the surgical unit (17.1%) (Legese et al., 2018). Similar studies on healthcare personnel at Dessie e Referral Hospital in Northeast Ethiopia reveal that 12.7% of MRSA and 28.8% of *S. aureus* were nasally carried by HCWs overall (Shibabaw et al., 2013).

### 3. Associated Factors on MRSA Particularly HCWs Nasal Carriage

- **Sociodemographic Factors:** A cross-sectional study conducted at a tertiary hospital in Ecuador to determine the prevalence of colonization with *S. aureus* (SA) and MRSA strains in health care workers (HCWs) as well as the risk factors associated with carriage found that being male (OD 2.78) and older (OD 1.09) are risk factors for both MRSA and SA colonization (p-value < 0.001) (Baroja et al., 2021).

Another cross-sectional study in a New Delhi, India, tertiary care hospital revealed that 31.66% of MRSA strains and 41.66% of *S. aureus* strains were isolated. In this study, the carriage rate of MRSA was higher in females than in males, and a significant prevalence rate of MRSA was seen in the age group of 21 to 40. Nurses had the highest MRSA carriage rate (Gupta et al., 2015).

- **Clinical Factors:** In Harar, Eastern Ethiopia, two public institutions (Jugol Institutions and Hiwot Fana Specialized University Hospital) hosted a cross-sectional study from May 15 to July 30, 2021, which revealed that among healthcare workers, 11.2% of MRSA nasal carriage and 15.6% of *S. aureus* prevalence were present. According to this research, there was a significant difference (P = 0.001) between nasal carriage of MRSA with antibiotic use and having a chronic illness (Wolde et al., 2023). A similar study at the hospitals in Adigrat and Wukro, Tigray, Northern Ethiopia, found a statistically significant correlation between MRSA colonization and diabetes (Legese et al., 2018).
- **Behavioral Factors:** A cross-sectional study carried out at the hospitals in Adigrat and Wukro, in Tigray, Northern Ethiopia, shows that the use of hand rubs was statistically significant when MRSA colonization occurred (Legese et al., 2018).

At Kutahya Health Science University in Turkey, a cross-sectional study revealed that the carriage of *S. aureus* is considerably lower in the group of smokers and among

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staff members who wear gloves when performing procedures on patients. The more often one washes their hands, the lower the *S. aureus* culture positive (Genc and Arikan, 2020).



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**Table 1:** Summarizing Prevalence and Common Associated Factors of MRSA in Different Countries

Year	Sample size	Country	Prevalence	Sample source	Common risk factors	References
2017	346	Pakistan	52%	Clinical isolates	*	(Siddiqui et al., 2017)
2020	598	Malaysia	8.5%	Surgical ward patients	being above 60 prolonged hospitalization	(Zainol Abidin et al., 2020).
2015	481	Ecuador	5%	HCW	being older in age being male	(Baroja et al., 2021)
2019	232	Nepal	5.2%	HCWs	*	(Mir et al., 2019)
2018	157	Tanzania	15.6%	HCWs	antibiotic use within the past three months	(Moyo et al., 2018).
2016	97	Uganda	46.4%	HCWs	*	(Abimana et al., 2019)
2021	295	Ethiopia	11.2%	HCWs	Having a chronic disease	(Wolde et al., 2023)
2021	787	Pakistan	24.59%	Bovine milk	-	(Lodhi et al., 2021)

\*Not applicable

In this context, the majority of studies among different countries in the world reveal a high prevalence of MRSA particularly amongst HCW (Table 1.), including in different hospital units and highly associated with Having a chronic disease, antibiotic use within the past three months, prolonged hospitalization and being older in age.

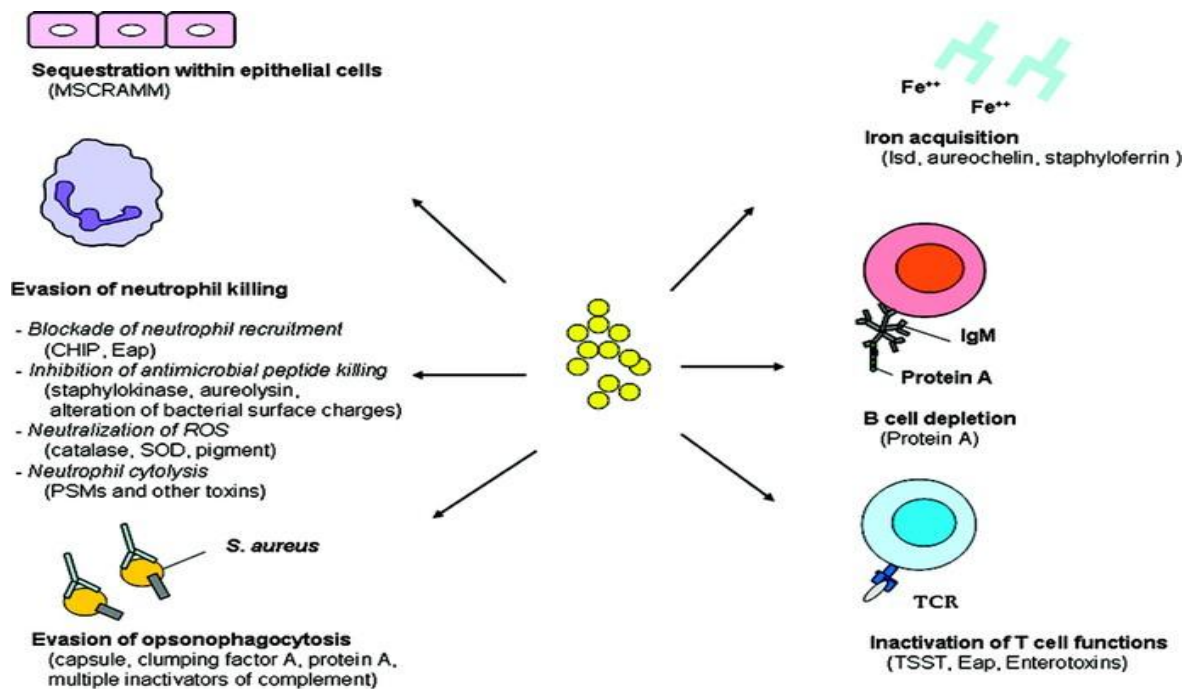
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- **Transmission of MRSA:** Since *S. aureus* is a commensal bacteria found in the nares of healthy individuals, CA-MRSA is typically acquired by direct contact with an infected or healthy person, whereas HA-MRSA is largely acquired through hospital environments, including contaminated instruments, bedding, doors, and equipment (Shoaib et al., 2023a). Also, HA-MRSA can be spread by carriers or by health care workers (HCWs) using fomites. The primary source of MRSA is HCWs who have been colonized with the bacteria on their nasal nares (Arshad et al., 2017). From vertebrate animals, MRSA can infect humans. The transmission of *S. aureus* to vertebrate animals is similarly facilitated by humans. “Amphixenoses” are illnesses that can affect humans and animals and spread both ways, like *S. aureus* illnesses. Human contact with animals and the environment can result in the transfer of LA-MRSA to humans (Crespo-Piazuelo and Lawlor, 2021). The factors that raise the possibility that companion animals may contain LA-MRSA were highlighted in another investigation. Veterinarians, chronic antibiotic use, bodily illnesses, and animal health status were identified as important risk factors for the spread of MRSA to humans among these risk variables. Pets could enter bedrooms as well (Shoaib et al., 2020).
- **Current Updates on Pathogenesis:** *S. aureus* is a commensal and pathogenic bacteria that usually live in the anterior nares of humans and other animals. It can colonize the groin, the axillae, and the digestive tract. The key phases in the pathogenesis of infection are colonization, virulence, infection onset, abscess formation, systemic infection, regulation, and adaptation with the help of several virulence factors. *S. aureus* has remarkable virulence traits that allow it to survive harsh conditions inside the human body. In most healthy body parts, it raises the risk of serious infection by controlling the number of virulence factors that are produced.
- **Colonization and Disease:** *S. aureus* is a pathogen as well as a commensal bacterium. For *S. aureus*, the anterior nares represent the primary ecological niche. 30% of people have sporadic nasal *S. aureus* colonization, while 20% of people have permanent nasal colonization. Nevertheless, a wide range of additional locations, such as the groin, axillae, and digestive system, might become colonized. The process of colonization establishes a reservoir through which germs can infiltrate a host when its defenses are weakened, such as during surgery, aspiration, shaving, or the implantation of an indwelling catheter. Colonization increases the risk of infection later on (Kluytmans et al., 1997). In a study on bacteremia, blood isolates from 82% of patients matched nasal isolates exactly (von Eiff et al., 2001). *S. aureus* can also spread between people in community and medical settings favorable to colonization. Although the process of *S. aureus* colonization is complex and poorly understood, it appears to depend on the bacteria's ability to attach to host cells and evade the immune system, as well as the host's interaction with the germs (for example, through other carriers) (Gordon and Lowy, 2008).

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- **Progression of *S. aureus* Infection:** The class of surface proteins on *S. aureus* known as "microbial surface components recognizing adhesive matrix molecules" (MSCRAMMs) is in charge of mediating attachment to host tissues. MSCRAMMs bind molecules such as collagen, fibronectin, and fibrinogen, and many MSCRAMMs can bind to the same host-tissue component (Figure 1). MSCRAMMs appear to have a major impact on the development of endovascular, bone, joint, and prosthetic device infections. *S. aureus* can endure by creating biofilms, or slime, on the surfaces of hosts and prosthetics, which allows it to evade host defenses and antibiotics. *S. aureus* has several other characteristics that contribute to its capacity to evade the host immune system while an infection is underway. The main defense mechanism of most clinical isolates is the production of type 5 or type 8 antiphagocytic microcapsules. Moreover, *S. aureus* may release the extracellular adherence protein or the staphylococci chemotaxis inhibitory protein, which blocks neutrophil chemotaxis and extravasation to the infection site. Also, *S. aureus* produces Leukocidins, which penetrate leukocytes' cell membranes and kill them. Leukocidins, which break through the cell membrane and kill leukocytes, are another substance that *S. aureus* produces. Enzymes such as lipases, elastase, and proteases are produced by *S. aureus* during infection. The bacteria can multiply and destroy host tissues because of these enzymes. It is also possible for *S. aureus* to cause septic shock. This is achieved by its interaction and activation of the host immune system and coagulation pathways. There may be a role for peptidoglycan, lipoteichoic acid, and alpha toxin. Several toxicoses, such as toxic shock syndrome and food poisoning, are brought on by superantigens produced by certain *S. aureus* strains. Different from the structural elements discussed earlier, these superantigens can trigger a "cytokine storm," which can lead to a disease similar to sepsis. Further, some strains produce toxins known as epidermolysins, which act as an exfoliant and cause scalded skin illness or bullous impetigo (Gordon and Lowy, 2008). *S. aureus* lipoprotein and peptidoglycan are detected by host pattern recognition molecules. Pro-inflammatory signaling is further enhanced by endogenous toll-like receptor ligands (DNA, RNA, and HMGB1) and breakdown products of hyaluronan released by necrotic tissues during infection. This ultimately leads to the activation of local immune cells and the migration of neutrophils and macrophages. The fact that *S. aureus* may grow both within and outside of host cells is generally accepted. *S. aureus* needs to avoid being opsonized by antibodies and complement in the extracellular milieu. This may lead to the death of *S. aureus* or the uptake of phagocytes through complement or Fc receptors, either directly or indirectly. *S. aureus* eludes opsonophagocytosis by expressing a capsule, clumping factor A, protein A, and several complement inhibitors on its surface. All of these methods function to deactivate or halt the host (Liu, 2009).

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**Figure 1:** Strategies for *S. aureus* survival during infection. TCR, T cell receptor; SOD, superoxide dismutase; Eap, extracellular adherence protein; MSCRAMM, microbial surface components recognizing adhesive matrix molecules; Isd, iron-regulated surface determinant; TSST, toxic shock syndrome toxin; and TCR, iron-regulated surface determinant. Image Courtesy of (lui, 2009)

- Immunopathogenesis of *S. aureus* Infection:** The immune response to *S. aureus* involves the activation of both the innate and adaptive immune systems. The first defense against infections is the innate immune response, which is promptly triggered by pattern recognition pathways that recognize non-specific signs of microbial disease. One of the primary outcomes of this is the activation of phagocytic cells, such as neutrophils and macrophages. Given that deep-seated infections can occur in both humans and animals with inherited and acquired neutrophil abnormalities, it is clear that neutrophils are critical for the acute response and are an important weapon in the battle against *S. aureus*. Later on in the infection, the innate response produces a cytokine milieu that influences the adaptive immune response, which is triggered by the presentation of bacterial antigens by antigen-presenting cells. The adaptive immune response uses T-cell activation and B-cell antibody production to target particular bacterial antigens. This aids in forming a "memory" against that specific pathogen in the event of further infections. Apart from their direct antibacterial effects, antibodies and T cells can enhance the function of innate immunity cells by augmenting the recruitment and destruction of phagocytes, among other ways (Karauzum and Datta, 2017).
- Immune Evasion:** Immunity against microbes is significantly influenced by immunological evasion mechanisms. Among the proteins implicated in these

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pathways in *S. aureus* are staphylokinase (encoded by Sak), chemotaxis inhibitory protein (Chp), and staphylococcal complement inhibitory protein (Scn) (Figure 2). Furthermore, particular enterotoxins that are encoded by genes such as *sep*, *seq*, *sek*, and *sea* are also implicated. It seems possible that by undermining the neutrophil response and establishing a protected niche, superantigens expression aids *S. aureus* in surviving in the host. The bacterium can escape into the cytoplasm due to the actions of  $\delta$ -toxin or the combined effects of  $\beta$ -toxin and phenol-soluble modulins (PSM $\beta$ ). After adhering to a target cell, *S. aureus* can be found in the cytoplasm and membrane of both professional and non-professional phagocytes, such as cells of the epithelium or endothelium. The surface characteristics and penetration into tissue or circulation make this possible. *S. aureus* detected in the phagocytes of people with cystic fibrosis is probably caused by  $\alpha$ -hemolysin breaking down the phagosomal membrane (Giese et al., 2009). Furthermore, in transit, phagocytes may become infected with intracellular microorganisms. Furthermore, *S. aureus* lyses host cells using cytolytic toxins. Polymorphonuclear leukocytes are thought to die as a result of exposure to phenol-soluble modulins (PSM), a genus-specific class of cytolytic peptides. In both professional and nonprofessional phagocytes, phagosomal escapes of PSM $\alpha$  mutants are not conceivable. Fortunately, the strains of *S. aureus* that produced Panton-Valentine leukocidin, PSM $\beta$ ,  $\delta$ , and  $\beta$ -toxins were able to escape just as well as the strains that produced them (Grosz et al., 2014).

- 4. Virulence Determinants in *S. aureus* Particularly MRSA:** It is commonly known that *S. aureus* can lead to a broad range of dangerous infections in humans. This capacity is associated with the synthesis of many proteins that aid in the pathophysiology of infection and allow the bacteria to adhere to surfaces and bodily tissues, elude or penetrate the immune system, and infect the host. Together, these components are known as virulence determinants. They are classified as secreted (exotoxins) and cell-surface-associated (adherence) factors (Table 1; Figure 2) and can be divided into cell-surface-associated (adherence) and secreted (exotoxins) factors (Costa et al., 2013).

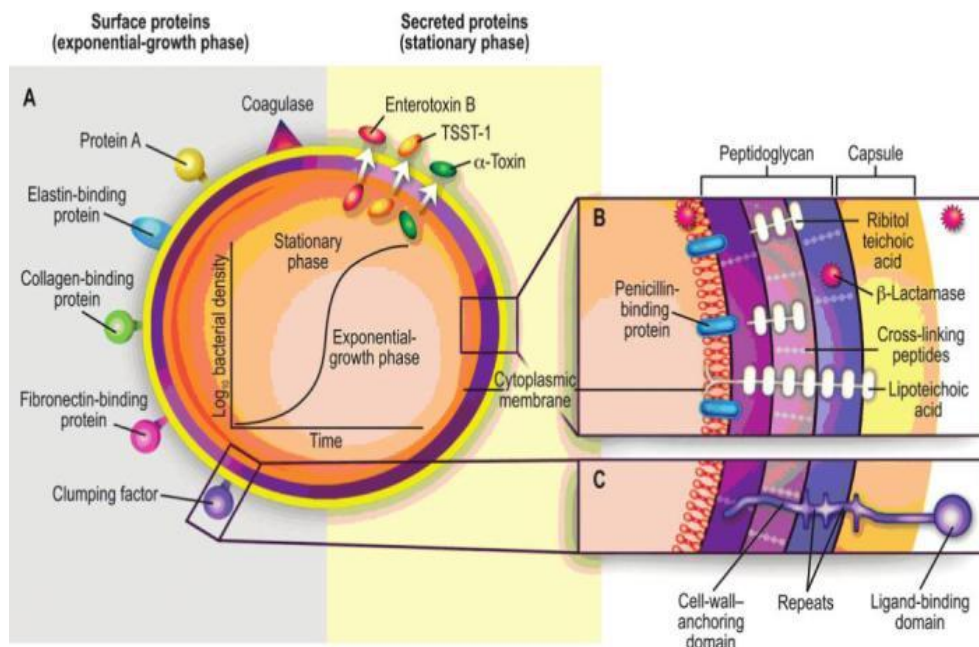
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**Table 1:** Virulence Determinants of *S. aureus*.

Virulence Factor	Putative Function
<b>CELL SURFACE FACTORS</b>	
1. Microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) ✓ Staphylococcal protein A (SpA)	Bind to IgG, interfering with opsonisation and phagocytosis
✓ Fibronectin-binding proteins (FnbpA and FnbpB)	Attachment to fibronectin and plasma clot
✓ Collagen-binding protein	Adherence to collagenous tissues and cartilage
✓ Clumping factor proteins (ClfA and ClfB)	Mediate clumping and adherence to fibrinogen in the presence of fibronectin
2. Capsular polysaccharides	
3. Staphyloxanthin	Resistance to neutrophil reactive oxidant-based phagocytosis
<b>SECRETED FACTORS</b>	
<b>1. Superantigens</b>	
✓ Staphylococcal enterotoxins (SEA, B, C, D, E, G and Q)	Massive activation of T cells and antibody-presenting cells
✓ Toxic shock syndrome toxin-1 (TSST-1)	Massive activation of T cells and antibody-presenting cells
	Cytolysins
✓ $\alpha$ -hemolysin	Induce lysis on a wide spectrum of cells, mainly platelets and monocytes
✓ $\beta$ -hemolysin	Hydrolysis of sphingomyelin of the plasmatic membrane of monocytes, erythrocytes, neutrophils, and lymphocytes; makes cells susceptible to other lytic agent
✓ $\gamma$ -hemolysin	Induce lysis on erythrocytes and leukocytes
Leukocidin family ✓ Leukocidins E/D and M/F-PV ✓ Panton-Valentine leukocidin (PVL)	Induce lysis on leukocytes Induce lysis on leukocytes
<b>3. Various exoenzymes</b>	

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<ul style="list-style-type: none"> <li>✓ Lipases</li> <li>✓ Nucleases</li> <li>✓ Proteases</li>   <li>• Serine (e.g. exfoliative toxins ETA and ETB)</li> <li>• Cysteine (e.g. staphopain)</li> <li>• Aureolysin</li> <li>✓ Hyaluronidase</li> <li>✓ Staphylokinase (SAK)</li> </ul>	<p>Inactivate fatty acids                  Cleave nucleic acids</p> <p>Inactivate neutrophil activity; activate T cells (only ETA and ETB)                  Block neutrophil activation and chemotaxis                  Inactivate antimicrobial peptides                  Degrade hyaluronic acid                  Activate plasminogen; inactivate antimicrobial peptides</p>
<p>4. Miscellaneous proteins</p> <ul style="list-style-type: none"> <li>✓ Staphylococcal complement inhibitor (SCIN)</li> <li>✓ Extracellular fibrinogen binding protein (Efb)</li> <li>✓ Chemotaxis inhibitory protein of <i>S. aureus</i> (CHIPS)</li> <li>✓ Formyl peptide receptor-like 1 inhibitory protein (FLIPr)</li> <li>✓ Extracellular adherence protein (Eap)</li> </ul>	<p>Inhibit complement activation</p> <p>Inhibit complement activation</p> <p>Inhibit chemotaxis and activation of neutrophils</p> <p>Inhibit chemotaxis of neutrophils</p> <p>Inhibit neutrophil migration</p>



**Figure 2:** *S. aureus* pathogenic virulence factors include both structural and secreted components, which function as virulence factors. A, Proteins secreted and on the surface. Cell envelope cross sections B and C. Toxic shock syndrome toxin 1, or TSST-1. Image Courtesy of (Gordon and Lowy, 2008).

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- 5. Novel Mechanisms for MRSA Virulence:** Researchers in the United States have shown that MRSA frequently altered the *sarZ* gene, which increased the severity of bloodstream infections in mouse models. The *sarZ* gene is a transcriptional regulator that regulates the expression of virulence genes, and the study, which was published in *Cell Host and Microbe*, claims that MRSA has altered the gene repeatedly. This has caused bloodstream infections in mouse models to become more severe. Utilizing its limited genetic variation and recent introduction into hospitals, the researchers were able to identify mutations that contribute to the effectiveness of USA300 in a novel setting. The altered regulation of virulence is observed in USA300 infections, according to the researchers. They identified the genes causing this condition by using comparative genomics, and they also determined that the transcriptional regulator *sarZ* had independent and recurrent mutations. In a mouse model of BSI, these changes led to an increase in the pathogenicity of the isolates of USA300 BSI. The *sarZ* mutations increased the production and expression of the surface protein ClfB, which is crucial for the pathophysiology of USA300 BSI isolates (Dyzenhaus et al., 2023).

**Leukocidin A/B (LukAB):** Recently, it was shown that the toxin leukocidin A/B (LukAB) kills primary human phagocytes; however, the precise mechanism of cell death is yet unknown. Using a variety of ex vivo and in vitro infection and poisoning scenarios, Melehani et al. found that LukAB promotes necrosis, stimulates IL-1 $\beta$  production, and activates Caspase 1 in human monocytes. Additionally, they found that in THP1 cells, a model for human monocytes, necrotic cell death and IL-1 $\beta$  production mediated by LukAB need the inflammasome components NLRP3 and ASC. It has been shown that *S. aureus* depends on LukAB to kill human monocytes in both intracellular and exterior ex vivo infection scenarios (Melehani et al., 2015).

**Emergence of *mecC* MRSA:** The discovery that MRSA codes for a distinct *mecA* gene was extremely important. The 2011 discovery that MRSA encodes a divergent *mecA* gene was extremely important. *S. aureus* susceptible to methicillin is a homolog known as *mecC* that presents diagnostic challenges and maybe mistakenly identified, which could have serious ramifications for both the monitoring of MRSA and specific patients. Microbiologists studying humans and animals are interested in the emergence of *mecC* MRSA (Paterson et al., 2014).

## 6. Laboratory Diagnosis

### Phenotypic Methods

**Culture-Based Methods:** Mannitol Salt Agar (MSA) is inoculated with collected samples. After 24 hours of incubation at 37<sup>0</sup> C, the formation of golden yellow colonies on MSA surrounded by yellow zones provides a positive result for *S. aureus*, which is needed to validate the fermentation of Mannitol. These isolates are cultivated for 24 hours at 37<sup>0</sup> C on blood agar. To confirm *S. aureus*, colony morphology, Gram staining, and biochemical tests like catalase and coagulase are carried out (Brown et al., 2005).



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Since it has been in use for so long, Mannitol-salt agar containing oxacillin, or MSA-OXA, has demonstrated the lowest detection rates and sensitivity when compared to other selective media. A modified form of MSA known as oxacillin-resistant agar base (ORSAB) has demonstrated low sensitivity and specificity. Even though ORSAB has outperformed MSA-OXA, chromogenic media still have a higher degree of reliability. The use of chromogenic medium has revolutionized culture-based diagnostics. Chromogenic selective medium comprising a combination of antibiotics and chromogenic enzymatic components has been accessible since the 1990s. These media have several advantages over traditional selective media, including increased sensitivity and specificity, a lowered need for confirmatory testing, and a quicker turnaround time (Aghamali et al., 2017).

**Minimum Inhibitory Concentration Methods:** The E-test, agar dilution, and broth dilution are the three types of procedures available in clinical microbiology laboratories for determining minimum inhibitory concentrations (MIC). Low-level oxacillin-resistant MRSA isolates may remain undetected even in situations where minimum inhibitory concentration (MIC) techniques are sufficiently precise. Investigations have revealed that the agar dilution method's results were comparable to those of the *mecA* gene PCR, which was the gold standard for figuring out antibiotic sensitivity before the PCR technology was developed. Even with the right sensitivity of broth dilution, reliable results are labor- and time-intensive and need a high level of competence (Aghamali et al., 2017). Sensitive to vancomycin *S. aureus* strains having minimum inhibitory concentrations (MIC) of less than 2 µg/ml are classified as *S. aureus* according to the new Clinical Laboratory Standards Institute (CLSI) criteria. When a *S. aureus* strain's minimum inhibitory concentration (MIC) falls between 4 and 8 µg/ml, it is categorized as Vancomycin-Intermediate *S. aureus*; if it exceeds 8 µg/ml, it is categorized as vancomycin-resistance *S. aureus* (CLSI, 2018).

**Agar Diffusion Method:** Disk diffusion using 30 µg of cefoxitin on Muller Hilton Agar, in particular the oxacillin disk diffusion method, is regarded as the most widely used standard clinical laboratory procedure for MRSA detection using Kirby-Bauer disc diffusion. After incubating at 33–35<sup>0</sup> C for 24 hours. It is possible to identify the inhibitory zone. All MSA isolates that have a Cefoxitin concentration of less than 24 mm are categorized as MRSA. Every isolate from MSA ≤ 24 mm of cefoxitin is classified as MRSA. Oxacillin testing, however, might not identify heteroresistant bacteria. According to earlier research, oxacillin tests often have good sensitivity but low specificity. Cefoxitin disk diffusion has been suggested as a more reliable option for MRSA detection, especially for heteroresistant bacteria, due to its better sensitivity and specificity when compared to oxacillin. Furthermore, the cefoxitin disk diffusion test has low specificity but the same sensitivity as PCR-detected *mecA*, according to numerous investigations (Aghamali et al., 2017).

**Penicillin-Binding Protein 2a Latex Agglutination Method:** PBP2a latex agglutination is a fast latex slide agglutination test that detects PBP2a in MRSA by using highly specific monoclonal antibodies that have been sensitized against PBP2a. This approach shows a good correlation with *mecA* gene PCR and is more economical than the PCR

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method. Additionally, it is simpler, more responsive, and faster (20 minutes after primary separation) for processing large numbers of samples (Aghamali et al., 2017).

**Automated Methods:** For microbiological diagnostics, automated antimicrobial susceptibility testing devices are frequently employed. Clinical laboratories are interested in this approach because of its shorter turnaround time, same-day findings, cost, and ease of use. Vitek is a well-liked automated susceptibility testing technique that yields accurate results quickly. The automated mass spectrometry and software system known as matrix-assisted laser desorption ionization-time of flight, or MALDI-TOF, aims for rapid MRSA detection. The assay is based on analyzing bacterial protein spectra and sequentially comparing them to those in a reference database (Aghamali et al., 2017).

**Molecular Detection of MRSA:** It is generally accepted that PCR-based *mecA* gene identification is the most reliable technique for identifying MRSA. The *mecA* gene is amplified in typical PCR, and the results are available the same day, which is quicker than traditional susceptibility testing methods. PCR techniques offer greater specificity and sensitivity than culture techniques. It is not a good technique, nevertheless, for directly detecting MRSA from non-sterile clinical specimens. The diagnostic utility of this approach is called into question by the possibility of false-positive results since these specimens frequently include a mixed population of methicillin-resistant CoNS and *S. aureus*. One useful method for differentiating SCCmec kinds is the PCR test. SCCmec-type characterization improves the ability to distinguish between community-onset and hospital-acquired MRSA clones. Even though SCCmec typing is a helpful technique for interpreting surveillance data meaningfully (Aghamali et al., 2017).

- 7. Antimicrobial Resistance and its Impact on MRSA Treatment:** The extensive use of antibiotics as growth enhancers in animal feed, their widespread and sometimes inappropriate use, and the relative ease with which MRSA can cross geographic barriers through regional and international travel are all factors that have contributed to the evolution of antimicrobial resistance (AMR) in MRSA. Particularly pigs seem to be significant MRSA reservoirs and ideal breeding grounds for advancing the transmission of AMR from animals to people. Therefore, it is crucial to comprehend the processes of AMR in MRSA from a clinical and epidemiological standpoint (Watkins et al., 2019).

Staphylococcal cassette chromosome *mec* (SCCmec) is a distinct mobile genetic element that carries the *mecA* gene, which codes for PBP2a. The expression of the *mecA* gene is controlled by a proteolytic signal transduction pathway consisting of a sensor protein (MecR1) and a repressor (MecI) (Peacock and Paterson, 2015). It was recently shown that a novel genetic determinant called *mecC* encodes a transpeptidase enzyme that is only 63% similar to *mecA*-encoded PBP2a. (Vestergaard et al., 2019).

- 8. Novel Therapy on MRSA:** Novel antimicrobial medications are desperately needed, as seen by the rise in multidrug resistance brought on by MRSA. *S. aureus* infections were initially treated with penicillin, also Vancomycin used for over 50 years, inhibits MRSA bacteremia by inhibiting peptidoglycan synthesis. Daptomycin, a cyclic lipopeptide, was approved in 2003 for soft tissue infections, with concentration-dependent killing and high

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bacterial activity. Bacterial skin infections are treated with mupirocin. It stops the action of isoleucyl t-RNA synthase, which inhibits the synthesis of proteins by Gram-positive bacteria. The recently licensed drug linezolid is a treatment for MRSA infections. Linezolid has broad-spectrum efficacy against MRSA, methicillin-resistant *S. aureus* (VRSA), vancomycin-resistant *S. aureus* (VRSA), and other Gram-positive bacteria such as *Bacillus fragilis* and penicillin-resistant streptococci. Semisynthetic medications such as tigecycline, oritavancin, dalbavancin, iclaprim, cethromycin, and delafloxacin exhibit superior efficacy against MRSA by impeding the production of proteins or peptidoglycans (Nandhini et al., 2022).

- 9. Antimicrobial Peptides:** Antimicrobial peptides (AMPs) are emerging as a powerful weapon against MRSA due to their capability to directly target as well as disrupt the bacterial cell membrane. Unlike traditional antibiotics, this unique mechanism reduces the risk of resistance development by MRSA. While challenges like enzyme degradation and human cell toxicity remain, researchers are actively developing new AMPs, with some like cathelicidin-BF derivatives showing promising results in combating this antibiotic-resistant pathogen (Yuan et al., 2022).

Amphiphilic 2-phenyl-1H-phenanthro [9, 10-d] imidazole-antimicrobial peptide (AMP) mimic conjugates (III1-30) produced; compound III13 exhibits significant antibacterial activity against MRSA isolates and gram-positive bacteria. It showed quick bactericidal action and was less vulnerable to resistance in bacteria. III13 causes cell death by generating intracellular ROS and targeting phosphatidylglycerol on bacterial membranes (Xu et al., 2024).

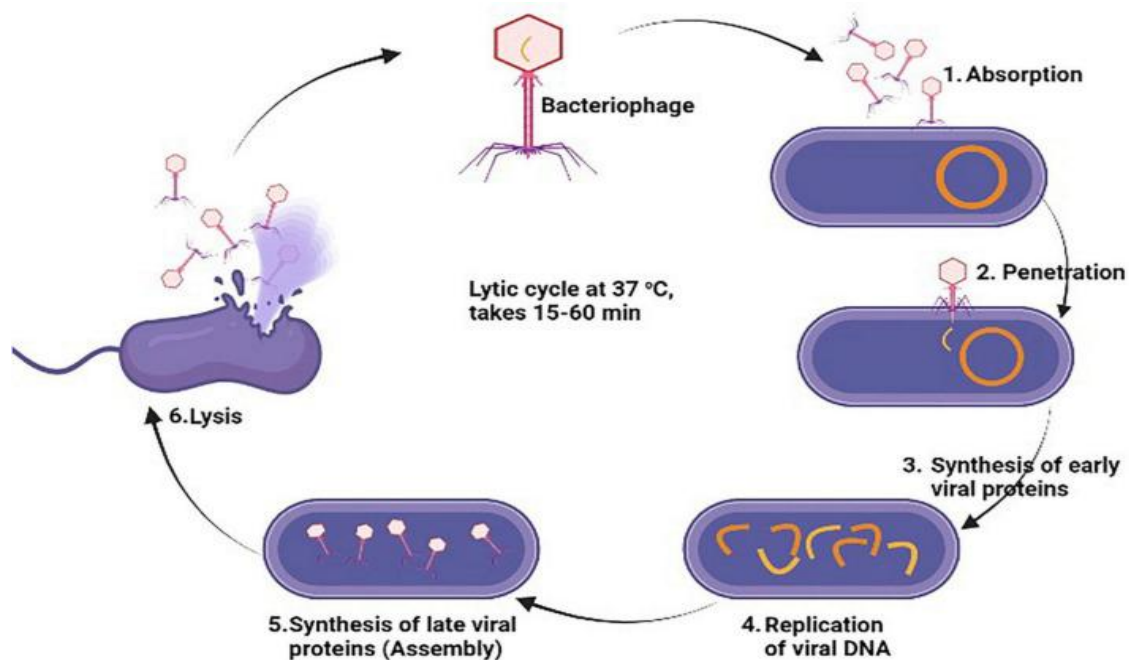
Novel isoxanthohumol-amine conjugates were produced and tested for antibacterial activity. Compound E2 demonstrated better antibacterial action than vancomycin against isolates of *S. aureus* and MRSA, along with little hemolysis, good membrane selectivity, quick bacterial death, and acceptable plasma stability (Yang et al., 2024).

- 10. Probiotic Therapy:** In humans colonized by *S. aureus* from the Songkhla region of Thailand, a Phase 2, double-blind, randomized, placebo-controlled trial revealed that the *B. subtilis* probiotic destroyed over 95% of all *S. aureus* colonies in the human body without changing the microbiota. Concerning current decontamination procedures, this probiotic approach has several significant advantages that make it a better option for individuals who are at long-term or chronic risk of *S. aureus* infection (Piewngam et al., 2023).

- 11. Phage Therapy:** Phage therapy, sometimes referred to as bacteriophage therapy, is a low-cost therapeutic strategy that treats bacterial diseases with viruses (Figure 3). Bacteria are susceptible to phages but do not pose a threat to people, animals, or plants. Phage therapy has demonstrated efficacy in treating infections caused by *P. aeruginosa*, surgical wounds, staphylococcal lung infections, and eye infections. Researchers looked into kayviruses' lytic ability against multidrug-resistant *S. aureus* using three different phages: vB\_SauM-A, vB\_SauM-C, and vB\_SauM-D. Myovirion morphology is revealed by the morphological investigations of the phages, and the phage vB\_SauM-A exhibited

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quick adsorption, a brief latent time, and a sizable burst size. According to genomic research, the phages resemble phage K and have big genomes with low G+C concentration (Łubowska et al., 2019).



**Figure 3:** The wide antibacterial action of bacteriophages against methicillin-resistant *S. aureus* strains (MRSA). Image Courtesy of (Shoaib et al., 2023a).

**12. Bacteriophage-Antibiotic Therapy:** Bacterial infections that are resistant to numerous medications can be treated with antibiotic-treated phages. During therapy, phages can multiply and cause the bacteria to die by rupturing their cell wall and membrane. Grygorcewicz et al. investigated the use of bacteriophage-antibiotic therapy to treat *Acinetobacter baumannii* biofilm in a human urine model (Grygorcewicz et al., 2021).

They used a combination of antibiotics and bacteriophages infected with Multi-Drug Resistant (MDR) *Acinetobacter baumannii* to eradicate the bacterial biofilm present in human urine. This work showed that bacteriophage-antibiotic therapy could reduce biofilm biomass in a human urine model. Phage mixes showed an excellent synergistic effect with the antibiotics used in the treatment.

**Prevention Strategies for MRSA:** The three main strategies for preventing and managing MRSA are patient isolation, staff decolonization, and hand and environmental hygiene (as part of routine precautions). Enhancing hand hygiene practices is particularly crucial in settings where infection risk is highest, such as critical care. Two benefits of physical separation are that it disrupts transmission and highlights the need for safety measures. Risk assessment should be done to determine which patients, given the limited isolation facilities, should be isolated. Despite its importance, environmental hygiene is

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not as vital as routine precautions. The patient's best interests should come first when a patient is prepared for transfer (to another healthcare institution) or discharge (home). As soon as feasible, all patients should be made aware of their MRSA-positive status. Decolonization should be done selectively due to the rise of mupirocin resistance. Depending on the nature of their work, restricting the professional activity of MRSA-positive staff members will vary. Lastly, to optimize MRSA prevention and control, lawmakers and other stakeholders must pledge to provide the required funding (Humphreys et al., 2009).

**Vaccines:** The rise in antibiotic-resistant bacteria in *S. aureus* has complicated the treatment of infections worldwide. As a result, vaccinations can be useful interventions. *S. aureus* monoclonal and polyclonal vaccines targeting key toxins ( $\alpha$ -hemolysin (Hla), Panton-Valentine leukocidin (PVL), and phenol-soluble modulins (PSM) have failed in clinical trials despite promising preclinical results, suggesting that specific antibodies were not sufficient to prevent pathogen escape (Raafat et al., 2019). Currently, StaphVAX (divalent polysaccharide and protein conjugate vaccine) developed by Nabi Biopharm, V710, a vaccine being tested by Merck (McNeely et al., 2014), and SA4ag, a vaccine candidate: four capsular polysaccharide antigens are formed was withdrawn by Combination with recombinant proteins from Pfizer (Begier et al., 2017). The development of other candidate vaccines, including the SpA virulence factor and the pore-forming toxin leukocidin, is urgently required, along with new components from the former (Micoli et al., 2021). In addition, several companies are testing attempts to develop an effective vaccine against MRSA. The development of vaccines that are effective against multiple strains of MRSA requires the use of multiple antigens to create effective immunity against different strains (Shoab et al., 2023b).

## IV. CHALLENGES AND CURRENT OPPORTUNITIES

### 1. Challenges

- The emergence of new, even more resistant strains of MRSA, often termed VRSA (vancomycin-resistant Staphylococcus aureus), poses a significant challenge. These strains are resistant to many of the last-resort antibiotics, making infections extremely difficult to treat.
- MRSA remains a serious problem in hospitals and other healthcare settings. Adherence to infection control measures is important, but this can be difficult to maintain.
- The rise of CA-MRSA, which spreads outside of healthcare settings, is another concern.

### 2. Current Opportunities

- Research into novel antibiotic classes with unique mechanisms of action offers hope for combating resistant strains of MRSA.
- Exploring alternative therapies like bacteriophages (viruses that specifically target bacteria) and antimicrobial peptides holds promise for future treatment options.

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- The development of effective vaccines against MRSA is an ongoing area of research. A successful vaccine could significantly reduce the burden of MRSA infections.
- Implementing stricter hygiene protocols in healthcare settings and promoting good hygiene habits in the community can significantly reduce transmission rates.

## V. CONCLUSION AND RECOMMENDATIONS

**Conclusion:** *S. aureus* is resistant to antibiotics, especially methicillin, a semi-synthetic penicillin. Methicillin-resistant *S. aureus*, characterized by the *mecA* gene, is resistant to most  $\beta$ -lactam antibiotics. The presence of resistance to antibiotics is a significant concern. This is particularly problematic. The high pathogenicity of antibiotic- and methicillin-resistant *S. aureus* can compromise host health and cause serious infections, including skin and soft tissue infections, bacteremia, sepsis, and toxic shock. HA-MRSA spreads in hospitals and health care facilities, among people whose immune systems have been weakened by medical or medical conditions. Especially for MRSA, the epidemiology of *S. aureus* has changed rapidly in recent years. A global outlook indicates that MRSA is a problem in all countries and study countries, given the high cost of drug use and an increasing number of patients. *S. aureus* tends to quickly develop resistance to antibiotics, and MRSA is known for its resistance to many drugs. The distribution of MRSA strains varies over time around the world, with some regions having a high prevalence influenced by factors such as medical practice and contact with animals. MRSA is screened using clinical and molecular testing, and antibiotic resistance is evaluated through diagnostic tests that employ disk immunoassays and PCR for the *mecA* gene. To fight MRSA infections, scientists are using new non-antibiotic methods, such as combination therapy, immunotherapy and probiotics, nanoparticles, bacteriophages, and bacteriophage antibiotic therapy.

A MRSA vaccine is being trialed by a few companies at present. The development of vaccines that are effective against multiple strains of MRSA requires the use of multiple antigens to create effective immunity against different strains

### Recommendations

- It is important to pay close attention to infection control procedures in hospitals and other healthcare facilities. This includes proper hand hygiene, appropriate use of antibiotics, and isolation of infected patients.
- Raising awareness about MRSA transmission and prevention strategies in the community and healthcare facilities can empower individuals to protect themselves and others.
- Careful use of antibiotics in human and veterinary medicine is important to delay the emergence of antibiotic-resistant bacteria.
- Continuous research into new diagnostic tools, effective antibiotics against resistant strains, and potential vaccines for MRSA is essential for future control.

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## ABBREVIATION AND ACRONYMS

AMR	Antimicrobial resistance
CA-MRSA	Community-associated methicillin-resistant <i>Staphylococcus aureus</i>
GLASS	Global antimicrobial resistance and use surveillance system
HA-MRSA	Hospital-associated methicillin-resistant <i>Staphylococcus aureus</i>
HCWs	Health care workers
LA-MRSA	Livestock-associated methicillin-resistant <i>Staphylococcus aureus</i>
MRSA	Methicillin resistance staphylococcus <i>aureus</i>
MSCRAMMs	Microbial surface components recognizing adhesive matrix molecules
MSSA	Methicillin-sensitive staphylococcus aureus
PBP2	Penicillin-binding protein2
PVL	Panton-Valentine leukocidin
QS	Quorum sensing
SDG	Sustainable development goals
SSC-mec	Staphylococcal cassette chromosome

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