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Staphylococcus aureus: Structural biology, virulence determinants, resistance mechanisms, and control strategies

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Abstract

Staphylococcus aureus is considered one of the most clinically important bacterial pathogens worldwide, and contributes substantially to the burden of infectious diseases in both the human and veterinary populations. The pathogenic activity of *S. aureus* is mediated by the coordinated action of multiple virulence-associated factors, including toxins, haemolysins, adhesins, immune-evasion proteins and biofilm-forming determinants that facilitate colonisation, tissue invasion, and persistence or chronic infection. Antimicrobial resistance in *S. aureus* constitutes a substantial challenge, particularly amongst methicillin-resistant (MRSA) strains, in which resistance to β-lactam antibiotics is primarily mediated by the acquisition of the *mecA* gene, present in the staphylococcal chromosomal cassette *mec* (*SCCmec*). This gene encodes an altered penicillin-binding protein (PBP2a), which shows a reduced affinity for β-lactams, allowing for the continued synthesis of peptidoglycan despite exposure to antimicrobials. The widespread dissemination of established MRSA lineages globally highlights the need for coordinated strategies such as the integration of genomic surveillance, the responsible use of antimicrobials, specific infection prevention measures and decolonisation strategies within a One Health framework. The One Health approach recognises the interconnected nature of human, animal, and environmental reservoirs and provides a comprehensive strategy to reduce the emergence and persistence of this pathogen.

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1. Introduction

Staphylococcus aureus, a Gram-positive coccus, generally occurs as a commensal bacterium and also functions as a facultative anaerobe and an opportunistic pathogen (Xu et al. 2025). It is of significant clinical importance because of its highly virulent nature, capable of causing a broad spectrum of diseases ranging from localized skin and soft-tissue infections to severe, life-threatening systemic conditions (Touaitia et al. 2025). Approximately 20-30% of the healthy human population harbour *S. aureus* as part of their normal microflora. When the host-immunity breaks down, colonized individuals serve as reservoirs for transmission and subsequent infection (Piewngam and Otto 2024). Its exceptional capacity to acquire, maintain, and disseminate antimicrobial resistance determinants has further established its clinical relevance. The emergence of resistant strains has complicated the treatment and control of infections that were previously considered readily manageable. The resistant strains of *S. aureus* have significantly increased the morbidity, mortality, and healthcare expenditure, making *S. aureus* a major global public-health concern (Cussolim et al. 2021). Nandhini et al. (2022) reported that, since the emergence of penicillin-resistant strains in the 1940s and the subsequent identification of methicillin-resistant *Staphylococcus aureus* (MRSA) in the 1960s, antimicrobial resistance in this pathogen has expanded both in hospital settings and within the community. Notably, methicillin-resistant strains are associated with a 64% higher risk of mortality than methicillin-susceptible strains. The main molecular mechanism underlying resistance to β-lactam antibiotics in *S. aureus* is the acquisition of the *mecA* gene, which is located within the mobile genetic element known as the staphylococcal cassette chromosome *mec* (SCC*mec*) (Hossain et al. 2024). This gene encodes a modified penicillin-binding protein, PBP2a, which exhibits low affinity for β-lactam antibiotics, thereby preventing effective inhibition of bacterial cell wall synthesis (Nandhini et al. 2022). In addition, *S. aureus* exhibits other resistance strategies, including the production of β-lactamases, modification of efflux pumps, alteration of ribosomal targets and acquisition of resistance genes through plasmids or transposons (Cussolim et al. 2021).

From an epidemiological perspective, MRSA is considered an endemic pathogen worldwide. Genomic studies have revealed considerable clonal diversity, with predominant lineages such as CC239, CC5, and CC59 being particularly relevant; the latter is mainly associated with community-associated MRSA strains (CA-MRSA) (Chen et al. 2022). For instance, in recent years, approximately 40% of *S. aureus* infections reported in China have been attributed to MRSA, with

a marked increase in community-associated cases. Furthermore, the spread of these lineages has been influenced by factors such as the genetic mobility of resistance determinants and the selective pressure exerted by the indiscriminate use of antibiotics (Cussolim et al. 2021). Linz et al. (2023) highlighted that the persistence and expansion of antibiotic-resistant *S. aureus* underscore the need for continuous epidemiological surveillance, as well as for more in-depth studies aimed at understanding its molecular resistance mechanisms. Consequently, this knowledge will contribute to the development of effective therapeutic strategies and antimicrobial stewardship policies aimed at mitigating the spread of multidrug-resistant strains. This review integrates key data from both human and veterinary medicine to provide a comprehensive assessment of *S. aureus* as a pathogen of global significance under a 'One Health' perspective and evaluates the implications for animal health, the use of antimicrobials and food production systems. This review included recent epidemiological data, providing an up-to-date perspective on the global distribution and evolution of *S. aureus* as of 2026. Besides, it examines the genomic plasticity of *S. aureus*, highlighting the selective pressures arising from clinical, veterinary and agricultural environments that have continued to drive the emergence, persistence and spread of virulent and antimicrobial-resistant lineages.

2. Structural characteristics of *S. aureus*

According to Idrees et al. (2021) the genus *Staphylococcus*, currently classified within the family Staphylococcaceae, comprises Gram-positive coccal bacteria that measure approximately 0.5 to 1 μm in diameter (Fig. 1). Generally, these microorganisms are non-motile, do not form spores and, furthermore, lack a prominent capsule under standard culture conditions. Among these species, *S. aureus* is of particular clinical and veterinary importance, and is distinguished by its ability to form yellow colonies on solid media. This pigmentation is largely due to staphyloxanthin, a membrane-associated carotenoid that enhances bacterial resistance to oxidative stress and also contributes to survival during host immune responses (Alkuraythi 2024). According to Sidel et al. (2020), the pathogenic potential of *S. aureus* and its ability to withstand the selective pressure of antibiotics are mediated by bacterial cell wall properties, which is composed mainly of peptidoglycan and teichoic acids, whose primary role is to maintain cellular architecture, regulate interactions between the host and the pathogen, and determine susceptibility to antimicrobials. Teichoic acids and lipoteichoic acids act as negatively charged polymers in the cell wall of *S. aureus* that help regulate the organisation of the cell envelope, viability and ionic homeostasis. These molecules are involved in regulation of bacterial surface charge, thereby influencing the adhesion properties, formation of biofilms, and interactions with antimicrobial compounds. All these factors contribute to the bacterial persistence and adaptation within the host environment (Wang et al. 2018).

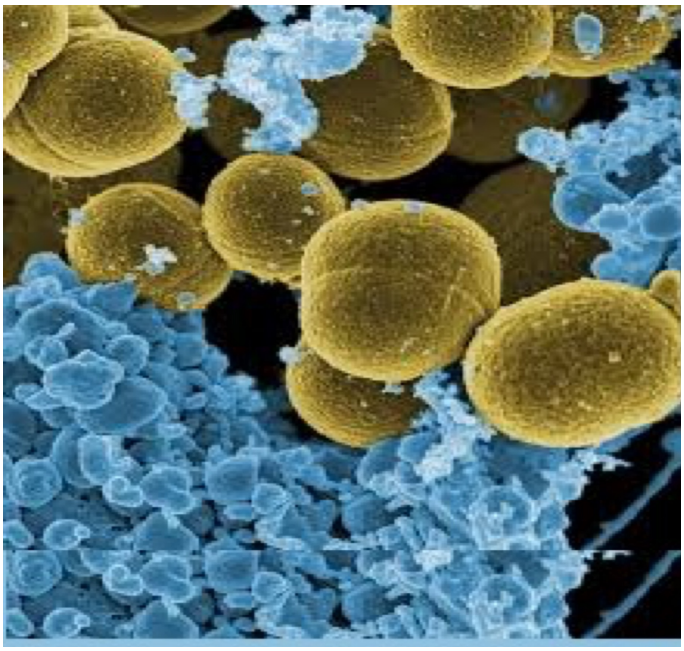


Fig. 1. *Colonial morphology of Staphylococcus aureus on solid culture medium*
Note: *This image is a work of the United States Federal Government (National Institutes of Health/Centers for Disease Control and Prevention), was taken by Janice Haney Carr, and is in the public domain*

In *Staphylococcus*, synthesis of peptidoglycan is mainly mediated by the *mecA* gene, which is located in the staphylococcal cassette chromosome *mec* (SCC*mec*). In the context of β-lactam antibiotic resistance, this gene encodes an altered penicillin-binding protein PBP2a, a low-affinity transpeptidase. This altered transpeptidase maintains the peptidoglycan cross-linking even in presence of β-lactams and allows the cell wall synthesis to continue (Nandhini et al. 2022). On the other hand, vancomycin intermediate susceptibility (VISA) strains of *S. aureus* develop resistance through adaptive chromosomal changes resulting in abnormal architecture of peptidoglycan and the formation of a thicker cell wall. The accumulation of excess peripheral D-Ala-D-Ala residues acts as a molecular trap for vancomycin, reducing its access to the division septum and limiting its inhibitory activity (Blanchevoye et al. 2013). In contrast, vancomycin-resistant *S. aureus* (VRSA) strains acquire the *vanA* operon via horizontal gene transfer, resulting in a modification of the peptidoglycan terminus, which changes from D-Ala-D-Ala to D-Ala-D-Lac. This structural alteration significantly reduces the binding affinity of vancomycin conferring high levels of resistance (Blechman and Wright 2024).

On the other hand, strains of *S. aureus*, particularly those expressing CP5 and CP8 polysaccharide capsules, exhibit strong anti-phagocytic activity, which facilitates immune evasion as these capsules acts as protective layer that conceal surface antigens, reducing opsonisation and limiting recognition and elimination by phagocytic cells. Thus, this mechanism promotes bacterial survival within the host and, furthermore, contributes to systemic dissemination, persistence in the bloodstream and prolonged survival in infected tissues (Visansirikul et al. 2020). The plasma membrane constitutes a dynamic interface that integrates metabolic activity with the defence mechanisms necessary for adaptation to antimicrobial pressure and the host's immune responses. In *S. aureus*, membrane-associated components contribute to pathogenic fitness by regulating stress responses and resistance to host-derived antimicrobial factors. Accordingly, staphyloxanthin, a carotenoid pigment embedded in the bacterial membrane, protects cells against oxidative stress by neutralising the reactive oxygen species generated during neutrophil-mediated destruction, thereby promoting survival within inflammatory foci (Schwartbeck et al. 2024).

Other antimicrobial resistance mechanisms are comprised of membrane-associated efflux pumps, including Tet(K/L) and the *Nor* family (*NorA*, *NorB*, and *NorC*), which reduce intracellular concentrations of tetracyclines and fluoroquinolones, thereby limiting

therapeutic efficacy (Touaitia et al. 2025). Finally, the pathogenesis of *S. aureus* is also driven by its ability to form highly organised, multilayered biofilms, which are enclosed within a self-produced extracellular polymeric matrix. This biofilm acts as both a physical and physiological barrier, limiting the penetration of antimicrobials, altering bacterial metabolic activity and, furthermore, protecting subpopulations of cells from elimination by the immune system. In bovine mastitis, biofilm formation is a key factor in the development of chronic intramammary infection, persistence and recurrence, all of which contribute to poorer treatment responses and long-term bacterial survival (Santesmases 2021; Visansirikul et al. 2020). *Staphylococcus aureus* possesses a wide range of virulence factors, notably coagulase, which promotes the conversion of fibrinogen into fibrin and also facilitates the sequestration of the bacteria within fibrin-rich structures, thereby reducing their exposure to phagocytic elimination (Getahun et al. 2025).

3. Virulence factors of *S. aureus*

Staphylococcus aureus has developed a wide range of mechanisms to evade, modulate and resist the host's immune response (Gordon et al. 2021). The virulence determinants of *S. aureus* are distributed between the core genome and the accessory genome. The core genome comprises highly conserved factors, such as thermostable nuclease (*nuc*), coagulase (*coa*), α-toxin (*hla*), and V8 protease (*sspA*), which are found in more than 95% of clinical strains, while the accessory genome contains horizontally acquired genetic elements, including prophages, plasmids, transposons and staphylococcal pathogenicity islands (*SaPI*); that confer additional virulence traits and help to enhance the bacterium's adaptation to different host environments (Di Bella et al. 2025). This genomic organisation contributes considerably to the variations observed in the clinical outcome of *S. aureus* infections, causing the severity of the disease to evolve in different ways in each patient (Fernandes 2018). *S. aureus* adapts its phenotype according to the stage of infection and the surrounding microenvironment through the coordinated expression of virulence factors controlled by complex regulatory networks. Among these systems is the quorum sensing pathway of the accessory gene regulator (*agr*), which acts as a central regulatory switch. Furthermore, the *agr* locus operates via a positive feedback mechanism mediated by an autoinducer peptide (AIP), which enables the coordinated transition from the expression of surface adhesins involved in early colonisation to the production of toxins and, ultimately, of tissue-damaging factors associated with invasive infection (Idrees et al. 2021).

During the initial phase of exponential growth, the *agr* system remains strongly repressed, favouring the expression of MSCRAMMs (microbial surface components that recognise the adhesive matrix molecules) that mediates initial adhesion to host tissues and, furthermore, promotes colonisation (Gordon et al. 2021). As the bacterial population increases and intercellular communication intensifies, the accumulation of the autoinducer peptide (AIP) activates the *agr* pathway and induces RNAIII expression which suppresses the production of adhesins whilst stimulating the secretion of invasive exoproteins, including toxins, proteases, lipases and leucocidins. Consequently, *S. aureus* shifts from an adhesive colonising phenotype to a more aggressive, invasive and cytolytic state, leading to tissue damage, immune evasion and the establishment of a persistent infection (Powers and Wardenburg 2014).

3.1. Structural components: adhesins and surface-associated molecules

Among the virulence factors of *S. aureus* associated with structural components, a wide range of adhesins and surface-associated molecules have been identified that mediate host colonisation, immune evasion, tissue tropism, and biofilm formation. Among the structural components that contribute to the virulence of *S. aureus*, the cell wall is of particular importance. It is composed primarily of peptidoglycan and teichoic acids and also displays several surface-associated proteins involved in adhesion, immune evasion and host–pathogen interactions. Certain strains additionally produce a polysaccharide capsule that surrounds the bacterial surface (types CP5 and CP8), thereby enhancing resistance to phagocytosis and facilitating systemic dissemination (Table 1) (Visansirikul et al. 2020).

Protein A (*SpA*) is one of the best-characterised immune-evasion determinants of *S. aureus*. This cell-wall-associated protein binds to the Fc region of immunoglobulin G and may also interact with B-cell receptors, thereby disrupting effective opsonisation, impairing phagocytic clearance and modulating the humoral immune response (Bear et al. 2023). In parallel, microbial surface components recognising adhesive matrix molecules (MSCRAMMs) mediate attachment to host extracellular-matrix proteins, including fibronectin, fibrinogen and collagen, as well as epithelial components such as loricrin. Through these interactions, *S. aureus* is able to enhance epithelial adhesion, colonise tissues, and under certain conditions, enter host cells – mechanisms that may promote persistence during subclinical intramammary infection (Speziale and Pietrocola 2020). It is important to note that the clumping factors ClfA and ClfB can mediate fibrinogen-dependent adhesion, and that ClfB also promotes nasal colonisation by binding to loricrin and cytokeratin 10. The collagen adhesin Cna facilitates attachment to collagen-rich extracellular matrices, whereas other cell-wall-anchored proteins, including SdrD and SasG, contribute to epithelial adhesion, skin and nasal colonisation, and biofilm development, collectively supporting niche-specific colonisation by *S. aureus* (Casillas-Ituarte et al. 2021).

Sortase A is a membrane-associated transpeptidase required for the covalent anchoring of LPXTG motif-containing proteins to the peptidoglycan layer. Through this activity, it enables the surface display of MSCRAMMs and other virulence-associated proteins involved in adhesion, colonisation, biofilm development and immune evasion (Wang et al. 2018). Extracellular adherence protein Eap and the MHC class II analogue protein Map are multifunctional adhesins that contribute to host attachment and immune modulation. Eap interacts with multiple extracellular matrix components and has been linked to anti-inflammatory activity, while Map promotes staphylococcal attachment to host tissues, abiotic surfaces, and eukaryotic cells (Alkuraythi 2024; Galindo 2024). The elastin-binding protein of *S. aureus* (*EbpS*) mediates attachment to elastin-rich tissues, supporting colonisation and persistence in host microenvironments such as the skin and vascular tissues (Blanchevoye et al. 2013). The icaADBC operon encodes proteins involved in the synthesis of polysaccharide intercellular adhesin, also known as poly-N-acetylglucosamine, PIA/PNAG, a key component of the biofilm matrix. Biofilm formation promotes *S. aureus* persistence by reducing susceptibility to antimicrobial agents and host immune responses, particularly in chronic or recurrent infections and bovine mastitis (Schwartbeck et al. 2024).

Table 1. Major adhesins, surface-associated virulence factors, and biofilm-related determinants of *Staphylococcus aureus*

Virulence determinant	Gene	Molecular function	Biological consequence	Clinical relevance	References
Protein A	*spa*	A surface-anchored protein that binds to the Fc region of immunoglobulin G (IgG) and interacts with B-cell receptors.	Inhibits opsonisation and subsequent phagocytosis, while inducing apoptosis in susceptible B-cell populations, thereby impairing humoral immune responses.	Contributes to immune evasion and bacterial persistence during invasive and recurrent infections, including bacteraemia. The spa gene is widely conserved across *S. aureus* lineages and forms part of the species' core genome.	(Alkuraythi 2024; Bear et al. 2023)
Polysaccharide capsule	*cap5*, *cap8*	Forms an extracellular polysaccharide layer that masks bacterial surface antigens and interferes with host immune recognition.	Reduces recognition and phagocytic uptake by neutrophils and macrophages, thereby limiting bacterial clearance.	Capsular expression varies among strains and may contribute to immune evasion, bacterial survival in the bloodstream, and the establishment of invasive infections.	(Alkuraythi 2024; Visansirikul et al. 2020)
Clumping factors A and B	*clfA*, *clfB*	Mediate binding to host ligands, with *ClfA* primarily recognising fibrinogen and *ClfB* interacting with fibrinogen, loricrin, and cytokeratin 10.	Promotes fibrinogen-dependent bacterial aggregation and facilitate adhesion to epithelial surfaces, particularly within the nasal mucosa.	Contribute to nasal colonisation, host tissue adhesion, and the establishment of invasive infections, with *ClfA* also implicated in bloodstream-associated pathogenic processes.	(Touaitia et al. 2025)
Fibronectin-binding proteins A and B	*fnbA*, *fnbB*	Mediate bacterial adhesion to fibronectin and promote host cell invasion through fibronectin-dependent engagement of α5β1 integrins.	Promote adhesion to host tissues and internalisation into non-phagocytic cells, including epithelial and endothelial cells.	Facilitate tissue invasion and intracellular persistence, potentially reducing susceptibility to antibiotic-mediated clearance and contributing to recurrent or persistent infections.	(Pasachova et al. 2019; Pietrocola et al. 2017)
Collagen adhesin	*cna*	Mediates bacterial adhesion to collagen-containing extracellular matrices and may contribute to immune evasion through interactions with host complement components.	Facilitates adherence to collagen-rich tissues, including cartilage, bone, and connective tissues associated with cardiac valves.	The *cna* gene is variably distributed among S. aureus lineages and has been associated with invasive infections involving collagen-rich tissues, particularly septic arthritis and osteomyelitis.	(Bhattacharya and Horswill 2024)
Extracellular adherence protein / MHC class II analogue protein	*eap*, *map*	Multifunctional secreted protein that interacts with extracellular matrix components and host immune mediators, thereby modulating adhesion and inflammatory responses.	Promotes bacterial adherence to host tissues and modulates leukocyte recruitment and local inflammatory responses.	May contribute to bacterial persistence and the establishment of invasive infections by interfering with host immune responses and facilitating tissue-associated colonisation.	(Corredor-Rozo et al. 2025; Galindo 2024)
Serine-aspartate repeat proteins (SdrC, SdrD and SdrE)	*sdrC*, *sdrD*, *sdrE*	Mediate adhesion through interactions with distinct host ligands, including epithelial surface proteins and extracellular matrix-associated components, depending on the specific Sdr protein.	Facilitate bacterial attachment to host tissues and may contribute to colonisation, intercellular interactions, and immune evasion.	Have been implicated in host colonisation and the pathogenesis of skin, soft tissue, and invasive infections, although their individual contributions vary according to the protein and strain background.	(Bhattacharya and Horswill 2024)
Elastin-binding protein (EbpS)	*ebpS*	Mediates binding to host elastin and elastin-derived components.	Facilitates bacterial attachment to elastin-rich tissues, including the skin and vascular connective tissues.	May contribute to colonisation of elastin-containing tissues and the pathogenesis of certain skin, soft tissue, and vascular infections, although its specific clinical contribution remains incompletely characterised.	(Bhattacharya and Horswill 2024)
Regulatory operon *icaR*	*icaR*	Encodes a transcriptional repressor that negatively regulates expression of the *icaADBC* operon.	Modulates polysaccharide intercellular adhesin production and biofilm formation; loss-of-function mutations may increase *icaADBC* expression and promote a mucoid biofilm phenotype.	Alterations in *icaR*-mediated regulation have been reported in clinical isolates, including strains associated with chronic respiratory infections in patients with cystic fibrosis.	(González-Hernández et al. 2024; Schwartbeck et al. 2024)
Structural operon *icaADBC*	*icaA*, *icaD*, *icaB*, *icaC*	Encodes proteins involved in the synthesis, modification, and export of polysaccharide intercellular adhesin (PIA), also referred to as poly-N-acetylglucosamine (PNAG).	Promotes intercellular adhesion and the development of a polysaccharide-rich biofilm matrix.	Contributes to biofilm-associated persistence and may facilitate chronic or recurrent infections, including bovine mastitis caused by PIA-producing S. aureus strains.	(González-Hernández et al. 2024; Touaitia et al. 2025)
Sortase A (SrtA)	*srtA*	Membrane-associated transpeptidase that recognises the LPXTG motif and covalently anchors surface proteins to the cell wall peptidoglycan.	Enables the cell wall anchoring of microbial surface components recognising adhesive matrix molecules (MSCRAMMs) and other surface-associated virulence factors involved in host adhesion and colonisation.	Contributes substantially to S. aureus virulence by facilitating the surface display of multiple adhesins. Pharmacological inhibition of SrtA has therefore emerged as a potential antivirulence strategy.	(Wang et al. 2018)

3.2. Virulence enzymes

Staphylococcus aureus is a highly adaptable pathogen that produces a broad range of virulence-associated enzymes involved in tissue invasion, immune evasion, nutrient acquisition and host-cell damage (Table 2). Collectively, these enzymes facilitate bacterial dissemination, degrade extracellular-matrix components, interfere with innate immune defences and promote persistence within infected tissues.

According to Zumba Camila Berenice et al. (2022), the pathogenesis of *S. aureus* involves secreted factors such as coagulase Coa and von Willebrand factor-binding protein. Coa initiates clot formation by promoting fibrin deposition from fibrinogen to generate a fibrin-rich network. This network surrounds the bacterial cells, reducing their exposure to phagocytes and hindering their recognition and elimination by the immune system, while simultaneously blocking opsonophagocytosis and facilitating bacterial aggregation in the bloodstream in collaboration with the clumping factors *ClfA* and *ClfB* (Alkuraythi 2024). Consequently, this entire process is considered a key factor in abscess formation, as it provides a structured and protected microenvironment that enables bacterial survival and persistence within the host tissues (Touaitia et al. 2025). Hyaluronidase degrades hyaluronic acid, which is considered an important component of the extracellular matrix; thus, by altering the integrity of the connective tissue, it acts as a dissemination factor that facilitates tissue penetration, local invasion and bacterial spread within the host microenvironment (Galindo 2024; Gordon et al. 2021; Pasachova et al. 2019).

Staphylococcinase, encoded by the *sak* gene, has been identified as a secreted plasminogen activator that promotes the generation of plasmin and subsequent degradation of fibrin. This activity facilitates bacterial escape from fibrin-containing lesions and also promotes dissemination. Staphylococcinase promotes immune evasion by binding to antimicrobial peptides, including human defensins, and neutralising them, thereby reducing innate antimicrobial activity (Nguyen and Vogel 2016). Lipases significantly enhance the pathogenic potential of *S. aureus* by hydrolysing host lipids and promoting bacterial survival in lipid-rich environments. Enzymes such as SAL1, SAL2 and SAL3

Table 2. Major extracellular enzymes and enzyme-associated virulence factors of *Staphylococcus aureus*

Enzyme	Gene	Function	Pathophysiological effects	References
Coagulase	*coa*	Promotes plasma coagulation by binding to and non-proteolytically activating host prothrombin, forming a catalytically active staphylothrombin complex that converts fibrinogen into fibrin. A related coagulation mechanism is mediated independently by von Willebrand factor-binding protein (vWbp).	Promotes the formation of a fibrin-rich protective layer surrounding bacterial cells, which limits phagocytic uptake and protects bacteria from host immune clearance. This fibrin barrier contributes to abscess formation, bacterial survival, and persistence within infected tissues.	(Touaitia et al. 2025; Zumba Camila Berenice et al. 2022)
Hyaluronidase	*hysA*	Hydrolyses hyaluronic acid, a major component of the host extracellular matrix, thereby disrupting the structural integrity of connective tissues.	Facilitates bacterial dissemination through connective tissues by degrading extracellular matrix components, thereby promoting local tissue invasion and the spread of infection.	(Alkuraythi 2024)
Staphylokinase	*sak*	Acts as a plasminogen activator by forming a complex with plasmin that promotes the conversion of host plasminogen into plasmin, thereby enhancing fibrinolytic activity.	Promotes fibrin degradation and may facilitate bacterial dissemination through infected tissues. Additionally, staphylokinase can bind to and neutralise human α-defensins, thereby contributing to evasion of innate immune defences.	(Touaitia et al. 2025; Zheng et al. 2022)
Lipases	*gehA, gehB*	Hydrolyse host lipid substrates, particularly glycerol esters, releasing free fatty acids and glycerol-derived products that may be utilised for nutrient acquisition and metabolic adaptation.	Facilitate bacterial adaptation to lipid-rich host environments, potentially supporting colonisation and persistence. Depending on the lipid substrate and environmental conditions, lipase activity may also influence bacterial susceptibility to host-derived antimicrobial fatty acids.	(Touaitia et al. 2025)
DNases/Nucleases	*Thermonuclease (Nuc)*	Degrades extracellular DNA released during host immune responses, including DNA scaffolds within neutrophil extracellular traps (NETs).	Facilitates escape from NET-mediated entrapment and contributes to immune evasion. The resulting DNA degradation products can also serve as substrates for adenosine synthase A (AdsA), promoting the generation of cytotoxic deoxyadenosine and impairing macrophage-mediated bacterial clearance.	(Alkuraythi 2024)
Adenosine synthase A	*adsA*	Converts adenosine monophosphate (AMP) into adenosine through its 5′-nucleotidase activity. It can also convert deoxyadenosine monophosphate (dAMP) into deoxyadenosine (dAdo), particularly following extracellular DNA degradation by staphylococcal nuclease.	Generates immunomodulatory adenosine, which can attenuate host inflammatory responses. Additionally, the production of deoxyadenosine induces caspase-3-dependent apoptosis in macrophages, thereby impairing phagocytic clearance and promoting bacterial persistence within infected tissues.	(Alkuraythi 2024)
Proteases (including V8 protease and aureolysin)	*sspA, aur*	Degrade host proteins, including extracellular matrix-associated proteins, immunoglobulins, complement components, and antimicrobial peptides. V8 protease (SspA) is a glutamyl endopeptidase, whereas aureolysin (Aur) is a zinc-dependent metalloprotease that also participates in the proteolytic activation of other staphylococcal enzymes.	Promote tissue damage, disrupt epithelial barrier integrity, and modulate host immune defences through the cleavage of immunoglobulins, complement proteins, and antimicrobial peptides. These activities may facilitate bacterial dissemination and persistence during infection.	(Touaitia et al. 2025)

catalyse the breakdown of triacylglycerols into free fatty acids and glycerol, thereby providing nutrients, facilitating skin colonisation, ensuring persistence and causing tissue damage during infection (Gordon et al. 2021). Nucleases, particularly the secreted thermostable nuclease Nuc, contribute substantially to immune evasion by degrading extracellular DNA and dismantling neutrophil extracellular traps. By altering these DNA-based antimicrobial structures, the *Nuc* gene enables bacteria to evade neutrophil-mediated containment and thereby enhance their persistence and spread within infected tissues. Expression of the *nuc* gene is regulated by the SaeRS two-component regulatory system, a key regulator of virulence gene expression in host–pathogen interactions in *S. aureus* (Olson et al. 2013).

Adenosine synthase A (*AdsA*) is a cell-wall-associated 5′-nucleotidase that plays an important role in immune evasion. It converts adenosine monophosphate into adenosine and aids in the local accumulation of this immunomodulatory metabolite whilst simultaneously suppressing pro-inflammatory signalling and reducing the antimicrobial activity of the host's immune cells. This activity can enhance bacterial survival following phagocytosis, particularly within neutrophils, and also promotes persistence and dissemination via the bloodstream and peripheral tissues (Méndez and Barrera 2016). Finally, *S. aureus* produces proteolytic enzymes essential for virulence, including V8 protease, also known as SspA, and aureolysin, Aur. V8 protease degrades host proteins such as immunoglobulins, reducing antibody-mediated control of infection, whereas aureolysin degrades innate immune factors and modulates the activity of secreted toxins and cell wall-associated proteins (Lehman et al. 2019).

3.3. Toxins: exotoxins and superantigens

Exotoxins are secreted bacterial protein toxins capable of damaging host cells and disrupting host physiological systems, whereas superantigens constitute a particular group of exotoxins that trigger excessive and harmful immune activation by stimulating large populations of T lymphocytes in a non-antigen-specific manner (Table 3). Staphylococcal exotoxins and superantigens are major virulence determinants of *S. aureus* (Bae et al. 2021) and are involved in severe clinical syndromes, including toxic shock syndrome and staphylococcal food poisoning.

Among the virulence factors of *S. aureus*, α-haemolysin, also known as α-toxin, is one of the best-characterised cytotoxins. After binding to the surface of susceptible host cells, α-toxin monomers oligomerise into a homoheptameric prepore, which subsequently undergoes conformational rearrangement to form a mature β-barrel transmembrane pore (Vandenesch et al. 2012). This pore generates an aqueous channel of approximately 14 Å in diameter, allowing the passage of small molecules and ions below approximately 2 kDa, including K^+ and Ca^{2+}. Disruption of membrane integrity triggers cellular dysfunction, promotes necrotic cell death, and compromises endothelial barrier integrity, thereby contributing to vascular damage and tissue injury during *S. aureus* infection (Muñoz Cutillas et al. 2025). Panton–Valentine leucocidin (PVL) is a *S. aureus*-specific bicomponent pore-forming exotoxin with marked pro-inflammatory and cytotoxic effects on neutrophils, monocytes and macrophages. According to Muñoz Cutillas et al. (2025), the presence of this exotoxin in certain strains is associated with severe clinical presentations, such as the formation of abscesses and necrotising pneumonia. The toxic shock syndrome type 1 (TSST-1) toxin, closely linked to the high virulence of *S. aureus*, is a superantigen that binds to class II major histocompatibility complex molecules at a site located outside the conventional peptide-binding groove (Alvarado and Silvia 2020). It subsequently interacts with the Vβ region of the T-cell receptor outside the normal antigen-binding site, resulting in extensive T-cell activation and massive cytokine release. This mechanism can lead to an overwhelming systemic inflammatory response, toxic shock and, in severe cases, multi-organ dysfunction (Bae et al. 2021).

The staphylococcal enterotoxins SEA–SEE are among the most common classical serological types produced by *S. aureus*. These toxins are heat-stable and may resist ordinary cooking conditions, which explains their relevance in foodborne outbreaks. They are considered major contributors to staphylococcal food poisoning, producing clinical manifestations such as vomiting and diarrhoea (Rubio Cieza et al. 2024). More recently, additional staphylococcal enterotoxins and enterotoxin-like proteins, including SEG, SEH and SEI, have also been described. Exfoliative toxins produced by *S. aureus* are proteolytic proteins that disrupt cell–cell adhesion within the epidermis, mainly through cleavage of desmoglein-1 in desmosomes, particularly in the stratum granulosum. According to Meneses Zurita (2022), four exfoliative toxin isoforms produced by *S. aureus* have been identified. Exfoliative toxin A (ETA) is a chromosome-encoded, heat-stable toxin associated with blistering lesions in humans. Exfoliative toxin B (ETB) is a plasmid-encoded, heat-labile toxin that is also pathogenic in humans and is particularly associated with neonatal infections such as staphylococcal scalded skin syndrome, which is characterised by blister formation and superficial epidermal detachment (Tam and Torres 2019). Exfoliative toxin C (ETC) has been described as pathogenic in animals, including horses, mice and birds, where it disrupts epidermal adhesion and promotes detachment of superficial skin layers (Meneses Zurita 2022). Exfoliative toxin D (ETD) has also been associated with animal infections and has been linked to ovine mastitis; its activity is likewise based on the disruption of epidermal cell adhesion, resulting in detachment of the superficial epidermal layer (Tam and Torres 2019).

Delta-toxin is a 26-amino-acid amphipathic α-helical peptide belonging to the phenol-soluble modulin family. This toxin acts in a surfactant-like manner, causing direct damage to cellular membranes and subsequent cell lysis. It has also been implicated in mast cell degranulation and cutaneous inflammation, including inflammatory conditions such as atopic dermatitis (Ahmad-Mansour et al. 2021). Gamma-toxin, also known as γ-haemolysin, is a pore-forming toxin composed of HlgA, HlgB, and HlgC subunits. It belongs to the β-barrel pore-forming toxin family and functions as a leucocidin by damaging the membranes of leucocytes and promoting their lysis. Through these effects, γ-haemolysin enhances the pathogenic potential of *S. aureus* and may act synergistically with other toxins, such as α-toxin, during severe infections including pneumonia and septic arthritis (Di Bella et al. 2025). Beta-toxin, also referred to as sphingomyelinase C or Hlb, hydrolyses sphingomyelin in the plasma membrane, thereby increasing cellular permeability and promoting the lysis of erythrocytes, leucocytes and macrophages. This toxin is considered an important virulence factor in several infections, including those associated with bovine mastitis and biofilm formation in chronic human infections (Tran et al. 2022). In bovine mastitis, these toxins contribute to epithelial damage, neutrophil dysfunction, inflammation, and bacterial persistence within the mammary gland. These effects underscore toxin production as an important component of the pathogenic profile of *S. aureus* strains involved in intramammary infection.

Table 3. Exotoxins and superantigens of *Staphylococcus aureus*

Functional group	Toxin	Gene	Toxin type	Mechanism/ Pathophysiological effect	References
Pore-forming toxins and haemolysins	Alpha-toxin (α-haemolysin)	*hla*	Pore-forming cytotoxin	Binds to host cell membranes, primarily through interactions with the metalloprotease ADAM10, and oligomerises to form homoheptameric transmembrane β-barrel pores with an approximately 14 Å diameter. These pores disrupt ionic homeostasis through K^+ efflux and Ca^{2+} influx, leading to membrane damage, cell death, endothelial barrier dysfunction, and tissue injury.	(Touaitia et al. 2025)
	Beta-toxin (β-haemolysin)	*hlb*	Sphingomyelinase C (enzymatic cytotoxin)	Hydrolyses sphingomyelin in host cell membranes, generating ceramide and phosphocholine. This enzymatic activity alters membrane organisation and integrity, promoting erythrocyte damage and contributing to tissue injury and host cell dysfunction.	(Touaitia et al. 2025; Tran et al. 2022)
	Gamma-haemolysin (γ-haemolysin)	*hlgA*, *hlgB*, *hlgC*	Bicomponent β-barrel pore-forming toxin (haemolysin/ leucocidin)	Gamma-haemolysin comprises three distinct protein components (HlgA, HlgB, and HlgC) that assemble into two functionally active bicomponent toxins, HlgAB and HlgCB. These complexes bind to specific host cell receptors and form transmembrane pores, resulting in leukocyte injury, inflammatory responses, and cell lysis. Their activities contribute to immune evasion and may exacerbate tissue damage during invasive infections.	(Di Bella et al. 2025)
Bicompartmental leucocidins	Panton–Valentine leucocidin (PVL)	*lukS-PV*, *lukF-PV*	Bicomponent β-barrel pore-forming leucocidin	Comprises two synergistically acting subunits, LukS-PV and LukF-PV, which assemble on susceptible host cell membranes to form transmembrane pores. PVL preferentially targets human neutrophils and can also affect monocytes and macrophages through receptor-dependent interactions, leading to cell activation, membrane permeabilisation, and cytolysis. PVL-positive strains have been associated with recurrent skin and soft tissue infections, abscess formation, and severe necrotising pneumonia, although the toxin's independent contribution to clinical severity remains debated.	(Boyle-Vavra and Daum 2007; Muñoz et al. 2017)
Superantigens	Toxic shock syndrome toxin-1 (TSST-1)	*tst*	Superantigen	Binds simultaneously to major histocompatibility complex (MHC) class II molecules on antigen-presenting cells and specific variable β-chain (Vβ) regions of T-cell receptors, independently of conventional antigen-specific recognition. This interaction induces extensive polyclonal T-cell activation and excessive release of pro-inflammatory cytokines, particularly interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumour necrosis factor (TNF), potentially leading to systemic inflammation, hypotension, multiorgan dysfunction, and toxic shock syndrome.	(Alvarado and Silvia 2020; Bae et al. 2021)
	Staphylococcal enterotoxins (SEA–SEE, SEG–SEI)	*sea*, *seb*, *sec*, *sed*, *see*	Heat-stable superantigenic enterotoxins with variable emetic activity.	Staphylococcal enterotoxins are heat-stable, protease-resistant proteins that can retain biological activity following food processing. Enterotoxins with demonstrated emetic activity induce acute gastrointestinal symptoms, particularly nausea, vomiting, abdominal cramps, and occasionally diarrhoea, following ingestion of preformed toxins in contaminated food. Their superantigenic activity additionally promotes non-specific T-cell activation and inflammatory cytokine release.	(Espinosa et al. 2014; Rubio Cieza et al. 2024)
Exfoliative toxins	Exfoliative toxins (ETA, ETB, ETC, ETD)	*eta*, *etb*, *etd*	Glutamate-specific serine proteases	Exfoliative toxins are specialised serine proteases that target desmoglein 1 (Dsg1), a desmosomal cadherin essential for epidermal cell–cell adhesion. Proteolytic cleavage of Dsg1 disrupts desmosomal integrity, leading to superficial epidermal separation and blister formation. ETA and ETB are the principal toxins implicated in staphylococcal scalded skin syndrome and bullous impetigo, whereas other exfoliative toxin variants may exhibit distinct host associations and clinical distributions.	(Tam and Torres 2019)
Phenol-soluble modulins (PSMs)	Delta-toxin (δ-toxin)	*hld*	Amphipathic surfactant-like peptide (PSM)	Acts as an amphipathic, membrane-active peptide that disrupts lipid bilayers and promotes concentration-dependent cytolysis. In addition to its cytotoxic activity, δ-toxin can induce mast cell degranulation and modulate inflammatory signalling, thereby contributing to cutaneous inflammation and potentially exacerbating atopic dermatitis. The hld coding sequence is embedded within RNAIII, the major regulatory RNA of the agr quorum-sensing system.	(Ahmad-Mansour et al. 2021)

3.4. Biofilms

Staphylococcus aureus is characterized by the formation of well-organized, multilayered biofilms, with cells embedded in a self-produced extracellular matrix. The biofilms adhere to biotic as well as abiotic surfaces. Biofilm formation is an adaptive growth strategy that is strongly regulated by genetic as well as environmental factors. Furthermore, biofilm formation is a major virulence factor associated with *S. aureus* and results in chronic infections, antimicrobial tolerance, and evasion of host immune clearance (Visan and Negut 2024). Biofilm formation occurs in four interconnected stages: *viz.* initial adhesion, proliferation and matrix production, maturation, and dispersal (Fig. 2).

Adhesion: It is a stage of bacterial cell attachment to a target surface. The attachment is mediated through an interaction driven by physicochemical forces and specific molecular recognition processes between bacterial adhesins and host or environmental substrates. The microbial surface components capable of recognizing adhesive matrix molecules (MSCRAMM) interact with host extracellular matrix proteins and mediate the adhesion of bacterial cells to biotic surfaces. In contrast, attachment to abiotic surfaces relies heavily on nonspecific physicochemical interactions, such as van der Waals forces, electrostatic

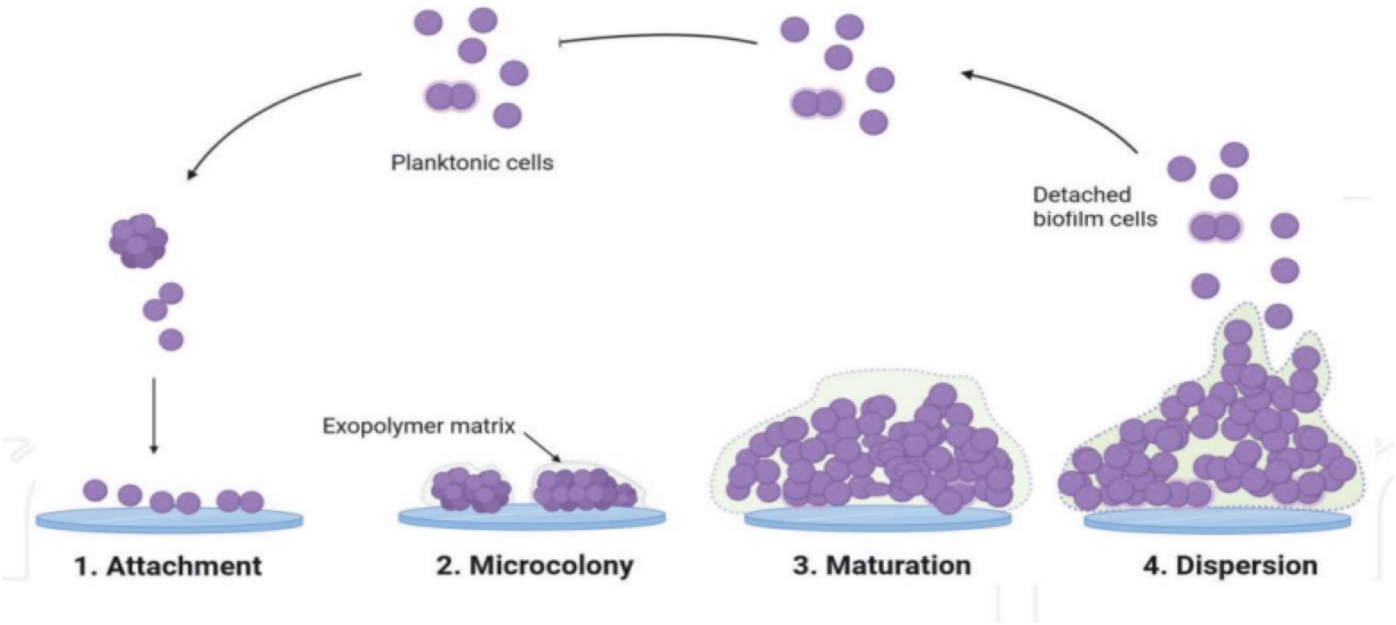


Fig. 2. *Stages of biofilm formation by S. aureus (Alves Carneiro et al. 2020)*

interactions, and steric effects (Aboelnaga et al. 2024). In *S. aureus*, the production of extracellular polymeric substances, including polysaccharide intercellular adhesin (PIA), occurs after initial attachment. PIA, also called as poly-*N*-acetylglucosamine (PNAG), facilitates an irreversible adhesion of cells and provides the structural framework for early biofilm development (Archer et al. 2011).

Proliferation and matrix production: This stage is characterized by an active multiplication of cells to form microcolonies and synthesis of the extracellular polymeric matrix. The matrix is composed primarily of extracellular DNA (eDNA), proteins, and polysaccharides such as PIA/PNAG. The matrix maintains bacterial cohesion and biofilm architecture, and protects bacterial cells against environmental stressors, antimicrobial compounds, and host immunity. According to Visan and Negut (2024), the relative contribution of each matrix component varies according to the different lineages of *S. aureus* and is influenced by specific ecological conditions.

Maturation: In this stage, bacterial cells organize into a complex three-dimensional structure characterized by densely packed microcolonies, matrix-rich regions, and fluid-filled channels. Nutrient transport, waste removal, and chemical communication within the biofilm are facilitated by the internal channels. The structural heterogeneity within the biofilms enables *S. aureus* to adapt to fluctuations in nutrient availability, oxygen limitation, exposure to antimicrobials, and host-derived stress responses (Aboelnaga et al. 2024).

Dispersion: This stage involves the release of bacterial cells or multicellular aggregates from the mature biofilm in a highly regulated manner. The dispersion of the cells or aggregates is triggered by environmental changes, mechanical disturbances, or the enzymatic degradation of matrix components. During this stage, the activities of extracellular proteases, nucleases, phenol-soluble modulins (PSMs), and quorum-sensing regulatory pathways are observed. The released cells can subsequently colonize new niches, contributing to the spread of the infection, its recurrence, and its long-term persistence within the host (Muñoz 2017). Biofilm formation substantially increases antimicrobial tolerance by restricting drug penetration, altering bacterial physiology, and promoting the survival of metabolically distinct subpopulations. Consequently, biofilm formation is a key mechanism contributing to treatment failure, chronic infection, and the persistence of *S. aureus* in host tissues, including the mammary gland (Aboelnaga et al. 2024).

3.4.1. Extracellular matrix as a physical and protective barrier against antimicrobials

During the adhesion and early proliferation stages, bacterial cells release extracellular polymeric substances that progressively establish the biofilm matrix (Muñoz et al. 2017; Schwartbeck et al. 2024). The extracellular matrix consists of an interconnected network of polysaccharides, surface-associated proteins and extracellular DNA (eDNA) and the intercellular polysaccharide adhesin (PIA/PNAG); one of the most important structural components in the development of *S. aureus* biofilms. The biosynthesis of PIA/PNAG is primarily regulated by the icaADBC operon and, together with surface proteins and extracellular DNA, contribute to bacterial cohesion, matrix stability and protection against exposure to antimicrobial agents (Touaitia et al. 2025).

3.4.2. Microstructural heterogeneity and metabolic adaptation during the maturation stage

The stress response to antimicrobial exposure and host-derived pressures is regulated by interconnected global regulatory networks, including the Agr, SaeRS and SigB systems, which coordinate the expression of virulence-associated genes, survival pathways and biofilm-related phenotypes (Di Bella et al. 2025). During the maturation stage, the biofilm develops into a highly complex three-dimensional architecture characterised by the formation of densely clustered microcolonies, embedded in an extracellular matrix and interconnected by fluid-filled channels that facilitate the diffusion of nutrients and the removal of waste products (Visan and Negut 2024). This spatial organisation allows the formation of distinct physicochemical microenvironments, including gradients in oxygen availability, nutrient

concentration and metabolic activity throughout the entire structure of the biofilm. As a result, bacterial populations may enter a state of slow growth or metabolic alteration, which reduces their susceptibility to antimicrobials. Physiological adaptation is a fundamental mechanism by which biofilm-associated cells resist antimicrobial pressure and contributes to persistent infection (Touaitia et al. 2025).

3.4.3. Intracellular persistence and chronicity mediated by adhesins

Key determinants of *S. aureus* persistence include Fibronectin-binding proteins A and B (*fnbA* and *fnbB*). They facilitate bacterial adhesion and internalisation into non-phagocytic cells, including epithelial and endothelial cells. These proteins create protected bacterial reservoirs and contribute to prolonged tissue colonisation. Therefore, intracellular persistence generally complicates bacterial eradication and results in the establishment of chronic infections (Bhattacharya and Horswill 2024). Similarly, the modifications affecting the *icaR* regulatory repressor or the structural *icaADBC* locus potentially enhance PIA/PNAG production, resulting in the emergence of mucoid, matrix-enriched phenotypes associated with increased persistence and recurrence in bovine mastitis and chronic infections in other host systems (Archer et al. 2011; Touaitia et al. 2025).

3.4.4. The dispersal stage contributes to dissemination and therapeutic failure

Dispersion constitutes a critical stage in the developmental cycle of bacterial biofilms, during which individual cells or multicellular aggregates detach from the mature structure and can colonize new niches. This process is regulated by cell-to-cell communication systems (*quorum sensing*), particularly the *Agr* system in *S. aureus*, which modulates the production of proteases, nucleases, and phenol-soluble modulins (PSMs), thereby promoting the breakdown of the extracellular matrix and bacterial release (Baos Muñoz 2017). Dispersion can facilitate the spread of infection, colonization of new tissues, and the emergence of secondary infectious foci, thereby complicating eradication and potentially contributing to therapeutic failure. Together, the process of biofilm formation, maturation, and dispersal create a self-perpetuating cycle, which promotes bacterial persistence, increases the risk of secondary dissemination via the bloodstream, and contributes significantly to treatment failure (Di Bella et al. 2025; Schwartbeck et al. 2024).

4. Molecular mechanisms of antimicrobial resistance in *S. aureus*

Staphylococcus aureus employs a wide range of molecular strategies that enable it to survive antimicrobial pressure and reduce the efficacy of clinically relevant antibiotics (Table 4). These adaptation mechanisms include alterations to antibiotic targets, enzymatic inactivation of antimicrobial compounds, reduction of intracellular drug concentrations mediated by active efflux, and chromosomal changes affecting ribosomal function, metabolic pathways and cell wall biosynthesis. Antimicrobial resistance in *S. aureus* is driven both by horizontal gene transfer and by evolutionary adaptation under selective pressure. Resistance determinants are frequently mobilised via genetic platforms such as plasmids, transposons and the staphylococcal chromosomal *mec* cassette (*SCCmec*). Additional resistance phenotypes may arise through chromosomal mutations selected during repeated exposure to antimicrobials (Baos Muñoz 2017).

4.1. Resistance to β-lactams: Penicillins and cephalosporins

In *S. aureus*, resistance to β-lactam antibiotics is primarily mediated by alteration to antimicrobial targets and enzymatic hydrolysis of these drugs. In methicillin-resistant *S. aureus* (MRSA), this modification is fundamentally associated with the acquisition of the *mecA* gene, carried on the mobile genetic element known as the staphylococcal cassette chromosome *mec* (SCC*mec*). The *mecA* gene encodes penicillin-binding protein 2a (PBP2a), a transpeptidase with markedly reduced affinity for most β-lactam antibiotics. Consequently, PBP2a can sustain peptidoglycan cross-linking and cell-wall biosynthesis even when the native penicillin-binding proteins are inhibited by antimicrobial exposure (Touaitia et al. 2025). Enzymatic resistance is mediated predominantly by β-lactamases, particularly the penicillinase encoded by *blaZ*, which hydrolyses the β-lactam ring before the antibiotic can bind effectively to its target, thereby preventing inhibition of peptidoglycan synthesis (Maldonado Cabrera and Maldonado Cabrera 2024).

4.2. Resistance to glycopeptides: vancomycin

Reduced susceptibility to vancomycin in *S. aureus* is principally associated with vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) phenotypes, which arise through distinct molecular mechanisms. High-level resistance in VRSA is mediated by acquisition of the *vanA* operon, generally through horizontal gene transfer from vancomycin-resistant *Enterococcus* species. The determinant is commonly carried on plasmids or transposon-associated elements and encodes enzymes that replace the terminal D-alanyl-D-alanine residues of peptidoglycan precursors with D-alanyl-D-lactate. This modification markedly reduces the binding affinity of vancomycin for its target and permits continued cell-wall biosynthesis despite antimicrobial exposure (Blechman and Wright 2024). In contrast, VISA generally develops through the cumulative acquisition of chromosomal mutations rather than horizontal acquisition of the *vanA* operon. These adaptive changes alter cell-wall synthesis, turnover and regulation, producing a characteristically thickened and poorly cross-linked peptidoglycan layer. The increased abundance of accessible D-Ala-D-Ala residues acts as a molecular sink that sequesters vancomycin within the peripheral cell wall, thereby limiting its penetration to active sites of peptidoglycan synthesis at the division septum. This mechanism reduces antibacterial activity without directly modifying the canonical vancomycin-binding target (Maldonado Cabrera and Maldonado Cabrera 2024).

4.3. Efflux-mediated antimicrobial resistance

Efflux pumps are membrane-associated transport proteins that reduce intracellular antimicrobial concentrations by actively exporting structurally diverse compounds from the bacterial cell. Depending on the transporter family, efflux is energised either by the proton motive force or by ATP hydrolysis. Increased expression or acquisition of these systems may confer low- to moderate-level resistance and can act synergistically with target-site mutations or other resistance mechanisms (Truong-Bolduc et al. 2024). Resistance to tetracyclines may be mediated by the Tet(K) and Tet(L) efflux pumps, whereas reduced susceptibility to fluoroquinolones is associated with transporters such as NorA, NorB and NorC. Over-expression of these pumps decreases the intracellular accumulation of fluoroquinolones and may increase the likelihood that additional target-site mutations will be selected under antimicrobial pressure (Shao et al. 2025).

4.4. Resistance to linezolid

Table 4. Molecular mechanisms of antimicrobial resistance in *Staphylococcus aureus*

Antimicrobial class	Resistance mechanism	Gene / genetic determinant	Clinical relevance	References
β-lactams (penicillins and cephalosporins)	Resistance is mediated primarily by two distinct mechanisms: the acquisition of the low-affinity penicillin-binding protein PBP2a, which maintains peptidoglycan synthesis despite β-lactam exposure, and the enzymatic hydrolysis of susceptible β-lactam antibiotics by β-lactamases.	*mecA* (carried within *SCCmec*), *blaZ*	The acquisition of *mecA* is a major determinant of methicillin resistance in *S. aureus* (MRSA), conferring resistance to most conventional β-lactams. In contrast, *blaZ*-mediated β-lactamase production primarily confers resistance to penicillinase-susceptible penicillins. MRSA infections can restrict therapeutic options and are associated with substantial morbidity and mortality, particularly in invasive disease.	(Maldonado Cabrera and Maldonado Cabrera 2024; Nandhini et al. 2022)
Glycopeptides (vancomycin)	Resistance develops through distinct molecular mechanisms. In vancomycin-resistant *S. aureus* (VRSA), acquisition of the *vanA* operon leads to replacement of the terminal D-Ala-D-Ala residues of peptidoglycan precursors with D-Ala-D-Lac, markedly reducing vancomycin binding. In vancomycin-intermediate *S. aureus* (VISA), resistance is generally associated with chromosomal adaptations that alter cell wall metabolism, often resulting in cell wall thickening, reduced autolytic activity, and increased vancomycin trapping	*vanA* operon (VRSA); mutations in cell wall regulatory and metabolic pathways, including *walKR*, *vraSR*, and *graRS* (VISA)	Reduced susceptibility or resistance to vancomycin compromises the management of invasive MRSA infections and may increase the risk of persistent bacteraemia and treatment failure, particularly when therapeutic alternatives are limited.	(Blechman and Wright 2024; Maldonado Cabrera and Maldonado Cabrera 2024)
Oxazolidinones (linezolid)	Resistance results from mutations within domain V of 23S rRNA, alterations in ribosomal proteins L3, L4, and L22, methylation of 23S rRNA mediated by Cfr methyltransferase, or acquisition of ABC-F proteins that confer resistance through ribosomal protection. These mechanisms reduce antibiotic binding to the ribosomal peptidyl transferase centre or interfere with its inhibitory activity.	G2576T mutation in 23S rRNA, *cfr*, *optrA*, *poxtA*	Linezolid resistance limits treatment options for serious infections caused by MRSA and other multidrug-resistant Gram-positive pathogens. Transferable determinants such as cfr, optrA, and poxtA are of particular concern because they can facilitate the horizontal dissemination of resistance, while cfr additionally confers resistance to several antimicrobial classes.	(Baos Muñoz 2017; Cussolim et al. 2021)
Tetracyclines	Resistance is primarily mediated by two mechanisms: energy-dependent efflux of tetracyclines through membrane-associated transporters, which reduces intracellular antibiotic accumulation, and ribosomal protection proteins that prevent tetracycline-mediated inhibition of protein synthesis.	*tet(K)*, *tet(L)* (efflux); *tet(M)*, *tet(O)* (ribosomal protection).	These mechanisms reduce susceptibility to tetracyclines and may compromise treatment efficacy. The extent of cross-resistance varies among individual agents, with ribosomal protection generally conferring a broader resistance profile than Tet(K)- or Tet(L)-mediated efflux.	(Shao et al. 2025; Truong-Bolduc et al. 2024)
Fluoroquinolones	Resistance is primarily mediated by point mutations within the quinolone resistance-determining regions (QRDRs) of DNA gyrase and topoisomerase IV, which reduce antibiotic binding to these essential enzymes. Overexpression of multidrug efflux pumps, including NorA, NorB, and NorC, provides an additional mechanism by decreasing intracellular fluoroquinolone accumulation	*grlA*, *grlB* (topoisomerase IV); *gyrA*, *gyrB (DNA gyrase)*; *norA*, *norB*, *norC* (efflux pumps).	The accumulation of target-site mutations, frequently accompanied by increased efflux activity, can progressively increase fluoroquinolone minimum inhibitory concentrations and compromise treatment efficacy. These mechanisms may contribute to multidrug-resistant phenotypes and limit the therapeutic utility of fluoroquinolones against *S. aureus*.	(Shao et al. 2025; Truong-Bolduc et al. 2024)

Linezolid inhibits protein synthesis by binding to domain V of the 23S ribosomal RNA within the 50S ribosomal subunit and interfering with formation of the functional initiation complex. Resistance in *S. aureus* is most frequently associated with mutations in the linezolid-binding region of the 23S rRNA gene, particularly the G2576T substitution. Because *S. aureus* contains several copies of the 23S rRNA gene, resistance levels may increase progressively as the mutation accumulates across multiple ribosomal operons (Baos Muñoz et al. 2017). Additional mechanisms include mutations in genes encoding the ribosomal proteins L3, L4 and L22, which alter the architecture of the linezolid-binding site (Table 4). Resistance may also arise through acquisition of transferable determinants, particularly the *cfr* gene, which encodes a methyltransferase that modifies 23S rRNA and produces cross-resistance to several antimicrobial classes. Other transferable oxazolidinone resistance genes, including *optrA* and *poxtA*, encode ATP-binding cassette F proteins that protect the ribosome from antimicrobial inhibition.

4.5. Active efflux systems: Tetracyclines and fluoroquinolones

Membrane-associated efflux pumps enable *S. aureus* reduce intracellular antimicrobial concentrations and increases survival under antibiotic exposure (Hossain et al. 2024). In tetracycline-resistant strains, this phenotype is primarily mediated by the energy-dependent efflux transporters Tet(K) and Tet(L), which actively remove the antimicrobial compound from the bacterial cytoplasm (Blechman and Wright 2024). Similarly, a link has been established between reduced susceptibility to fluoroquinolones and the increased frequency of multi-drug-resistant efflux systems, in particular *NorA, NorB*, and *NorC* (Truong-Bolduc et al. 2024). Efflux activity on its own may only result in modest changes in antimicrobial susceptibility; however, sustained exposure to selective pressure may favour the emergence of additional chromosomal mutations affecting DNA gyrase and also topoisomerase IV, thereby promoting the progressive development of resistance

(Blechman and Wright 2024; Hossain et al. 2024).

4.6. Ribosomal alteration affecting lincosamides and macrolides

Resistance, particularly to lincosamides such as clindamycin and to macrolides including erythromycin, is mainly due to modifications of the ribosomal target site or to the acquisition of transferable resistance determinants located on mobile genetic elements (Baos Muñoz 2017; Castro Pérez et al. 2020). Beyond their antibacterial activity, protein synthesis inhibitors may influence the pathogenic behaviour of susceptible *S. aureus* strains. In particular, clindamycin can reduce the expression and secretion of extracellular virulence factors, including α-toxin, even at sub-inhibitory concentrations, suggesting an additional antivirulence effect that may contribute to therapeutic benefit in selected clinical contexts (Touaitia et al. 2025).

4.7. Aminoglycoside resistance

The clinical application of aminoglycosides is limited by their toxicity profile; however, resistance among S. aureus populations arises through multiple complementary mechanisms involving enzymatic drug modification, reduced intracellular accumulation, and structural protection within bacterial communities (Baos Muñoz 2017). Tolerance to aminoglycosides in *S. aureus* is linked to its ability to form biofilms, where the extracellular polymeric matrix acts as a physical and chemical barrier that restricts antimicrobial penetration and diffusion. This protected microenvironment allows bacterial subpopulations to persist despite antibiotic exposure, reducing apparent susceptibility and increasing the likelihood of therapeutic failure (Aboelnaga et al. 2024; Touaitia et al. 2025; Visan and Negut 2024).

5. Relationship between virulence and antimicrobial resistance in *S. aureus*

The relationship between antimicrobial resistance and virulence in *S. aureus* is complex and strongly depends on the genetic and environmental context. Resistance mechanisms promote bacterial survival during exposure to antimicrobials, whereas virulence determinants can facilitate adhesion, immune evasion, tissue damage, persistence, and transmission. However, in certain genetic contexts, acquisition of resistance may entail metabolic or regulatory costs that attenuate specific virulence phenotypes (Touaitia et al. 2025) (Fig. 3). Several mechanisms contribute to this interaction. Acquisition of the *mecA* gene within the staphylococcal cassette chromosome *mec* (*SCCmec*) confers methicillin resistance and defines the principal molecular phenotype of methicillin-resistant *S. aureus* (MRSA). The *mecA* gene encodes penicillin-binding protein 2a (PBP2a), which has markedly reduced affinity for most β-lactam antibiotics and allows peptidoglycan synthesis to continue when native penicillin-binding proteins are inhibited (Rasmi et al. 2022). In parallel, virulence factors such as haemolysins, enterotoxins, adhesins and biofilm-associated determinants facilitate host colonisation, immune evasion, tissue injury and bacterial persistence (Touaitia et al. 2025). Global regulatory networks further connect antimicrobial adaptation with virulence expression. The accessory gene regulator (*Agr*) quorum-sensing system coordinates the transition from an adhesive, colonising phenotype to a more invasive phenotype characterised by increased production of secreted toxins and degradative enzymes. *Agr* activity may also be influenced by antimicrobial and host-derived stress signals. Other regulatory systems, including SaeRS, SigB and two-component systems involved in cell-envelope stress responses, contribute to the integration of resistance, persistence and virulence-associated pathways. Nevertheless, the resulting phenotype varies considerably among clonal lineages and environmental conditions (Di Bella et al. 2025).

The coexistence of antimicrobial resistance and an extensive virulence repertoire has important clinical consequences. Certain community-associated MRSA lineages possess strong toxin-producing capacity and have been associated with severe infections, including

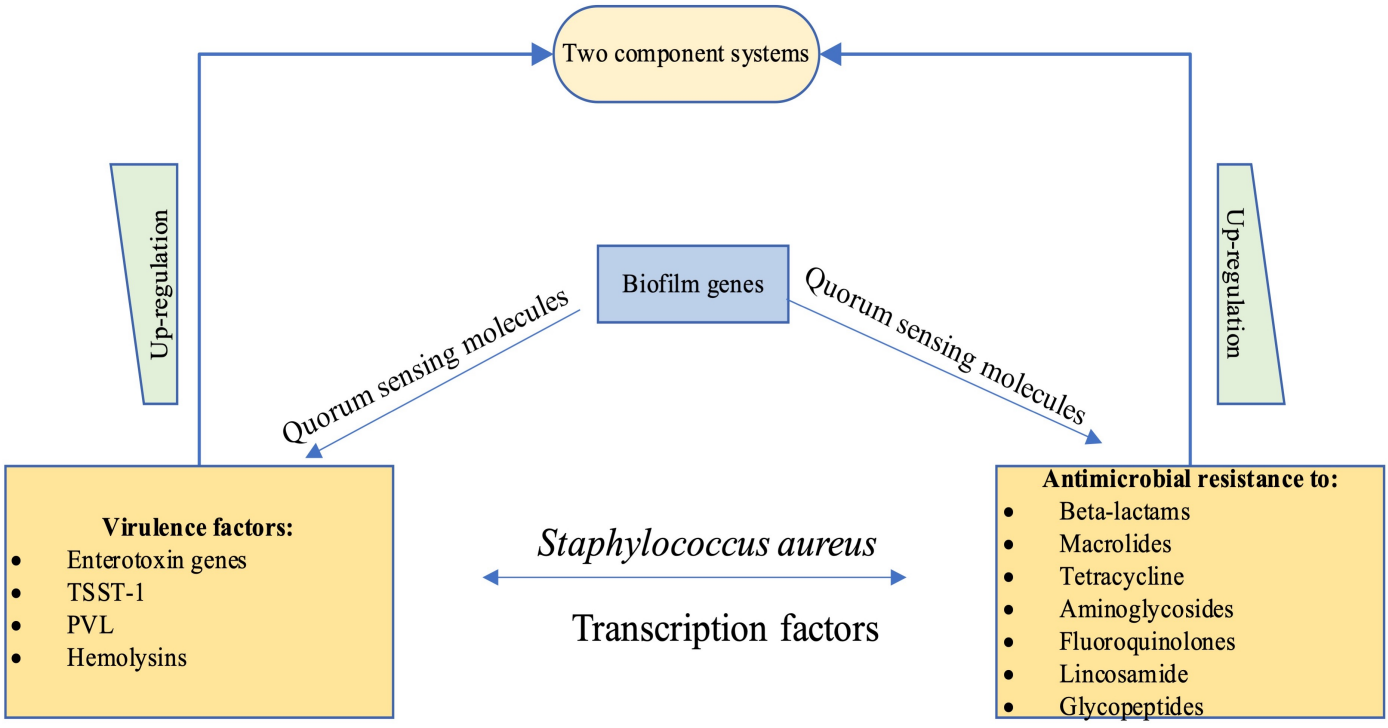


Fig. 3. *Schematic representation of the interplay between antimicrobial-resistance genes and virulence determinants in Staphylococcus aureus (Patel and Rawat 2023)*

bacteraemia, endocarditis, necrotising skin and soft-tissue infections, and other invasive diseases (Di Bella et al. 2025). However, high-level resistance should not automatically be interpreted as evidence of increased virulence, as the pathogenic potential of an isolate depends on the combined effects of its virulence determinants, regulatory state, host susceptibility and site of infection. Antimicrobial exposure may itself modify virulence-gene expression. In some *S. aureus* strains, exposure to subinhibitory or clinically relevant concentrations of selected β-lactams can increase the expression or release of α-toxin, a pore-forming cytotoxin involved in epithelial and endothelial injury, inflammation, disruption of intercellular integrity and immune-cell damage (Nasser et al. 2019; Stevens et al. 2007). This response is dependent on the strain, β-lactam agent, concentration and experimental conditions. Consequently, the finding that some MRSA isolates produce greater quantities of α-toxin following β-lactam exposure than methicillin-susceptible S. aureus should not be generalised to all MRSA lineages (Stevens et al. 2007). By contrast, protein-synthesis inhibitors, particularly clindamycin and linezolid, may suppress α-toxin and other exotoxin production by interfering with bacterial translation, even at concentrations below those required to inhibit growth. Macrolides such as erythromycin may exert a similar effect in susceptible isolates, although their clinical usefulness is limited when resistance is present. Suppression of toxin synthesis may provide an additional therapeutic benefit in severe toxin-mediated *S. aureus* infections, although it does not replace the need for effective bactericidal or source-control measures (Castro Pérez et al. 2020).

6. Epidemiology of *S. aureus*

Over the last decade, the growing global challenge posed by antimicrobial resistance has prompted substantial changes in the epidemiology of *S. aureus*. According to the Global Research on Antimicrobial Resistance (GRAM) project, the global estimates of deaths attributable to methicillin-resistant *S. aureus* (MRSA) increased 57,200 in 1990 to nearly 130,000 in 2021. Furthermore, various modelling studies have forecasted the continuous rise of burden of resistant infections till 2050 (Mestrovic et al. 2025; Naghavi et al. 2024). It demonstrates the potential of *S. aureus* to overcome the effects of sustained antimicrobial pressure and supports the need for surveillance approaches traversing across human, animal, and environmental interfaces. The distribution of MRSA among clinical *S. aureus* isolates varies considerably across regions, with high prevalence in the Americas (22.27%) followed by the Western Pacific region (16.57%) and Europe (10.93%). However, the observed regional differences may be due to variations in population characteristics, sampling frameworks, diagnostic methodologies, and the robustness of regional surveillance systems. In addition, the epidemiology of *S. aureus* is influenced by asymptomatic carriage, which serves as a significant reservoir for subsequent endogenous infections and transmission events. Nasal or cutaneous colonization, present in approximately one-third of certain populations, represents a potential source of invasive disease can emerge, particularly in individuals with heightened susceptibility (Rasquel-Oliveira et al. 2025). Currently, strategies for controlling *S. aureus* infections are increasingly based on a multifaceted approach that combines antimicrobial stewardship, optimization of prescribing practices, implementation of infection prevention measures, and targeted screening and decolonization of high-risk individuals (Lucio López et al. 2026). To track the emergence of successful clones, identify transferable resistance determinants, and reconstruct transmission routes, essential tools such as molecular epidemiology and genomic surveillance are used. Ultimately, reducing the global impact of *S. aureus* will require coordinated interventions that integrate international recommendations with epidemiological realities.

6.1. Global overview and current epidemiology

At the global level, *S. aureus* is considered one of the leading bacterial causes of mortality associated with bloodstream infections (Lucio López et al. 2026). According to Naghavi et al. (2024), approximately 57200 deaths associated with methicillin-resistant *S. aureus* (MRSA) were estimated in 2021, underscoring the critical challenge that this pathogen poses to modern healthcare systems. The geographical distribution of *S. aureus* shows marked variation. According to data reported in relation to the World Health Organization, some of the highest prevalence rates have been described in the United States (23.78%), Great Britain (18.66%) and China (18.07%) (Yuan et al. 2025). Between 2005 and 2 012, MRSA bloodstream infections showed an annual decrease of approximately 12%; however, this decline plateaued after 2013, and renewed increases in hospital prevalence were reported between 2023 and 2024 (Chen and Er 2025; Yuan et al. 2025). The distinction between healthcare-associated and community-associated infections has become increasingly blurred owing to the dissemination of highly virulent clones, such as the USA300 lineage. The spread of such clones has enhanced the capacity of *S. aureus* to persist, circulate and disseminate across different geographical regions and epidemiological settings (Zurita et al. 2022).

6.2. Prevention and control strategies

Staphylococcus aureus is a major pyogenic pathogen of both human and veterinary importance, characterised by remarkable physiological adaptability and ecological versatility that enable colonisation of humans and a wide range of mammalian hosts (Aslam et al. 2025). However, its greatest impact has been observed in veterinary medicine, as it is associated with persistent intramammary infections, particularly in cattle and sheep, contributing to issues that result in reduced milk production, increased somatic cell counts, impaired milk quality, and substantial economic losses at both the individual and herd levels (Lucio López et al. 2026). The One Health approach is an appropriate strategy for an effective control of *S. aureus* infections because it circulates among human, animal, and environmental reservoirs. This strategy combines the rational use of antimicrobials, infection prevention, surveillance, and specific interventions (Septimus 2024). This integrated approach recognizes the ability of *S. aureus* to sustain in diverse ecological niches and acclimate to sustained antimicrobial pressure. In human medical settings, prevention strategies, particularly with respect to multidrug-resistant *S. aureus* (MRSA), rely on the combined implementation of antimicrobial stewardship programs, infection prevention practices, targeted decolonization, and molecular surveillance, rather than on a single intervention. Antimicrobial stewardship programs aim to preserve therapeutic efficacy by ensuring that antibiotics are appropriately selected, administered at effective doses, and prescribed only for clinically justified durations, thereby limiting the selective pressure that accelerates the emergence and spread of resistant strains (Tam and Torres 2019; Touaitia et al. 2025).

On the other hand, preventing transmission in healthcare settings through adherence to hand hygiene protocols, reinforced by continuous training, monitoring programs, and institutional accountability, remains one of the most effective measures for interrupting person-to-

person spread in high-risk environments such as intensive care units and operating rooms (Touaitia et al. 2025; Tran et al. 2022). Colonized individuals, shared medical equipments, and contaminated surfaces help sustain transmission cycles. Both environmental contamination and asymptomatic carriers contribute significantly to MRSA epidemiology (Tam and Torres 2019). The integration of genomic approaches into prevention strategies has helped identify resistant and hypervirulent lineages, reconstruct transmission pathways, and monitored emerging resistance determinants. The information furnished by such advanced approaches helps design certain targeted interventions and formulate control measures suitable for local epidemiological settings (Tran et al. 2022). In dairy cattle and small ruminant production systems, control programmes for mastitis caused by *S. aureus* require effective prevention through interventions aimed at reducing new infections; however, they must also include measures to curb chronic cases, improve treatment outcomes, and maintain herd productivity and milk quality (Septimus 2024). Therefore, the management of infected animals constitutes another key component of mastitis control. It is important to identify infected animals at an early stage to implement appropriate segregation strategies during milking, thereby reducing the likelihood of pathogen spread to other animals in the herd. In cases of recurrent or persistent infections that do not respond to treatment, selective culling can be a practical measure to reduce the infection reservoir within the herd (Septimus 2024).

In dairy farming, maintenance of udder health depends on continuous monitoring rather than reactive intervention after clinical disease sets in. The implementation of timely and precise control measures before the transmission of infection within the herd requires routine somatic cell count assessment and early microbiological identification of intramammary pathogens (Lucio López et al. 2026). Formation of biofilms confers *S. aureus* a greater protection within mammary tissue by resisting exposure to antimicrobials and helps evade the host immune response. Extensive tissue damage and the establishment of chronic infections have been reported in *S. aureus* strains producing PIA/PNAG matrix in greater amounts due to higher activity of the *icaADBC* operon, as well as strains expressing factors such as β-toxin and exfoliative toxin D (ETD) (Schwartbeck et al. 2024). The continuous evolution of *S. aureus* across human, animal, and environmental reservoirs highlights the need to implement integrated surveillance systems that link clinical, veterinary, and food production laboratories (Sangucho et al. 2025). Thus, within the "One Health" framework, combining genomic surveillance with evidence-based prevention strategies offers a comprehensive approach to reducing the burden of *S. aureus* infections, limiting the spread of antimicrobial resistance, protecting animal and human health, and further strengthening food safety systems (Popovich et al. 2023).

7. Conclusions

Staphylococcus aureus infections pose significant health challenges in modern human and veterinary clinical settings because of greater persistence, adaptability, and genetic evolution of the pathogen. *S. aureus* exerts health challenges through a coordinated interplay of multiple virulence mechanisms, including adhesion to host tissues, biofilm formation, toxin production, evasion of the host immune system, and persistence within the host. These challenges are further compounded by the emergence of its antimicrobial resistance, which has significantly limited the therapeutic options. The emergence and spread of resistant lineages carrying both resistance determinants and a broad range of virulence factors highlight the need for coordinated and sustained control measures. Because of its high pathogenic potential, an integrated and effective control of *S. aureus* requires the rational use of antimicrobials, appropriate infection prevention practices, molecular epidemiology, genomic surveillance, and clinical guidelines suitable for local epidemiological conditions. Antimicrobial resistance results from a combination of various mechanisms, including selective pressure exerted by antimicrobials, horizontal gene transfer, chromosomal mutations, and regulatory adaptation. Therefore, the interaction among virulence, resistance, and transmission at the human-animal-environment interface must consider the within a "One Health" framework in the control of *S. aureus* infections. In veterinary clinical settings, particularly in the case of subclinical bovine mastitis, a proper understanding of these interactions is indispensable for reducing the persistence of intramammary infections, preventing treatment failures and herd-level transmission, and maintaining milk quality and productivity. Hence, coordinated surveillance, antimicrobial stewardship, and targeted preventive strategies are essential for reducing the global impact of this highly adaptable pathogen.

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