

REVIEW ARTICLE

Staphylococcus aureus, ESKAPE Bacteria Challenging Current Health Care and Community Settings: a Literature Review

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SUMMARY

Background: *Staphylococcus aureus* is a gram-positive coccus forming grape like clusters performing both aerobic and anaerobic respiration. Most strains of *S. aureus* ferment mannitol and they form characteristic golden yellow colonies. They produce catalase, coagulase, and extracellular cell clumping factor. Some strains can also produce capsules. It is a major commensal bacterium and a human pathogen that causes a wide range of clinical infections including abscesses of various organs, pneumonia, osteomyelitis, endocarditis, arthritis, and sepsis. *S. aureus* is the key organism for food poisoning and it is the third most important cause of food borne disorders in the world.

Methods: We reviewed all the relevant literature available on PubMed, Web of Science, and Google Scholar. We selected different scientific studies and reports published in English language which addressed prevalence, pathogenesis, burden and laboratory diagnosis methods of *S. aureus* to compile the current review.

Results: *Staphylococcus aureus* has an outstanding ability to acquire resistance to most classes of antimicrobial agents. This successful and adaptable resistance has made treatment and control of staphylococcal infections increasingly difficult. Expression of virulence factors of *S. aureus* is controlled by bacterial cell density and many environmental factors such as pH, oxygen, and carbon dioxide. There are different mechanisms that microorganisms use to prevent attack by antimicrobial agents. These include limiting uptake of the drug, modification of the drug target, inactivation of the drug, and active efflux of the drug. Specimens collected for diagnosis of *S. aureus* infection depend on the type of infection. The samples for diagnosis are pus, sputum, blood, feces, vomit and the remains of suspected food, and nasal swab for the detection of carriers. Gram stain, culture, biochemical tests, serological tests and molecular techniques are the common laboratory diagnosis methods.

Conclusions and Recommendations: Multidrug resistant *S. aureus* strains are emerging and current antibiotics are not efficacious against such strains. Both active and passive immunization strategies have thus far failed to show efficacy in humans. Therefore, infection preventive measures, and further research is required to develop vaccines and antibiotics to target this pathogen.

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KEY WORDS

Staphylococcus aureus, ESKAPE, health care, community

LIST OF ABBREVIATIONS

CA-MRSA - Community Acquired Methicillin Resistant *Staphylococcus aureus*
eDNA - Extracellular Deoxy Nucleic Acid
ESKAPE - *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*,

Pseudomonas aeruginosa and *Enterococcus* species
 HA-MRSA - Hospital Acquired Methicillin Resistant *Staphylococcus aureus*
 HVISA - Heterogeneous Vancomycin Intermediate *Staphylococcus aureus*
 MHC - Major Histocompatibility Complex
 MIC - Minimum Inhibitory Concentration
 MRSA - Methicillin Resistance *Staphylococcus aureus*
 PSM - Phenol Soluble Modulins
 PVL - Panton Valentine Leucocidin
 ROS - Reactive Oxygen Species
 SAIE - *Staphylococcus aureus* Infective Endocarditis
 TLR - Toll-Like Receptor
 SAB - *Staphylococcus aureus* Bacteremia
 SCCmec - Staphylococcal Cassete Chromosome mec
 USA - United States of America
 VISA - Vancomycin Intermediate *Staphylococcus aureus*
 VRSA - Vancomycin Resistant *Staphylococcus aureus*

INTRODUCTION

Staphylococcus aureus is a gram positive extracellular growing bacterium. It is a major source of mortality in medical facilities. It causes a wide range of infections from skin infection to life threatening diseases such as abscesses of various organs, skin and soft tissue, urinary tract infections, central nervous system infections, pulmonary infection, device related infections, pneumonia, osteomyelitis, endocarditis, arthritis, sepsis, chronic lung infections associated with cystic fibrosis, and several syndromes caused by exotoxins and enterotoxins including food poisoning, scalded skin, and toxic shock syndromes [1,2]. It is surrounded by a cell wall envelope containing attached polypeptides and polysaccharides. Surface proteins of *S. aureus* have long been characterized as adhesins for human tissues [3]. Most strains of *S. aureus* ferment mannitol anaerobically and they form characteristic golden yellow colonies on blood agar. They produce catalase, coagulase, extracellular cell clumping factor, and some strains produce capsules [4]. It is the key organism for food poisoning due to production of heat stable exotoxins. It is the third most important cause of food borne disorders [5]. Antibiotic resistant bacteria such as *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter species* are called the ESKAPE pathogens due to their ability of escaping the biocidal action of antibiotics [6]. The increase in the resistance of these virulent pathogens to antibacterial agents with their increasing prevalence as nosocomial pathogens is a major concern [4]. *Staphylococcus aureus* has an outstanding ability to acquire resistance to most classes of antimicrobial agents such as penicillins, macrolides, aminoglycosides, chloramphenicol, and tetracycline. The widespread use of methicillin and other semisynthetic penicillins in the late 1960s led to the emergence of methicillin resistant

Staphylococcus aureus (MRSA) which continues to persist in both the health care and community environments [7]. The glycopeptide antibiotic, vancomycin is effective therapy against most strains of multidrug resistant *Staphylococci* including MRSA. However, the emergence of *S. aureus* with intermediate levels of resistance to vancomycin in 1997 and the most recent emergence of *S. aureus* with high levels of resistance to vancomycin has limited its effectiveness [3,7].

Burden of *Staphylococcus aureus*

Despite constant improvement in patient care, *S. aureus* infections remain associated with considerable morbidity and mortality both in hospitals and in the community [8,9]. *S. aureus* increase the incidence of *S. aureus* bacteremia (SAB) which is associated with advancements in medicine that require more frequent use of catheters and implanted devices. The incidence of *S. aureus* bacteremia and its complications has increased sharply in recent years because of the increased frequency of invasive procedures, increased numbers of immunocompromised patients, and increased resistance of *S. aureus* strains to available antibiotics [10]. The incidence of SAB, particularly bacteremia, caused by methicillin resistant *S. aureus* strains has increased dramatically in recent years. SAB is associated with a high mortality rate and places a substantial cost and resource burden on health care systems [11].

Staphylococcus aureus is one of the only causes of endocarditis in structurally normal heart valves and it is the leading cause of infective endocarditis in several countries. *Staphylococcus aureus* infective endocarditis (SAIE) occurs frequently among injection drug users, in patients with prosthetic heart valves, and other intravascular devices [12-14]. Patients with type I diabetes mellitus, receiving renal hemodialysis, received vancomycin treatment. Those with intravascular devices, MRSA infection or persistent bacteremia are at increased risk of developing SAIE [15-18].

Virulence factors of *Staphylococcus aureus*

Staphylococcus aureus has numerous surface proteins that promote attachment to host proteins such as laminin and fibronectin that form part of the extracellular matrix. The virulence factors of *S. aureus* include antigens (capsule, adhesins), enzymes (coagulase, lipase, hyaluronidase, staphylokinase, nuclease), and toxins (β -Toxin, δ -Toxin, P-V Leukocidins, Enterotoxin, Exfoliative Toxin, Toxic Shock Syndrome Toxin) [19-21]. Production of an extracellular mixture of sugar polymers called exopolysaccharide is characteristic and critical for biofilm formation which is involved in the protection of bacteria from the host immune response by interfering with phagocytosis and neutrophils [22]. Cytotoxins (α -toxin, β -toxin, γ -toxin, and leukocidins) are a group of toxins that can lyse host cells and alter the host immune response. Enterotoxins cause food poisoning whereas toxic shock toxin is responsible for toxic shock syndrome. Exfoliative toxin can change the con-

formation of desmoglein-1, a cell-cell adhesin in the epidermis and causing degradation and exfoliation. Proteases are involved in tissue invasion and immunomodulation [23].

Protein A is a cell wall anchored protein of *S. aureus* which has the ability to interact with several host components. It interferes with the host immune response by sensitizing B cells or depleting innate-like B cells. Protein A can enhance platelet aggregation and undermine phagocytosis by binding to antibodies and also contributes to the adherence to damaged endothelial surfaces by binding to von-Willebrand factor and induces local inflammation by binding to tumor-necrosis factor receptor-1 [24]. Biofilms serve as an important virulence factor in *S. aureus* infections [25]. Extracellular genomic DNA (eDNA) and teichoic acids from lysed cells facilitate aggregation *S. aureus* due to their polyanionic nature [26]. *S. aureus* has the capability to switch on selective sets of genes to enhance its chances for survival. This switching process is precisely controlled by global regulatory elements [27,28]. There are two major groups of global regulatory elements in *S. aureus*: the two-component regulatory systems and the SarA protein family. The sensor proteins of the 16 TCRSs provide external sensing while the members of the SarA protein family function as effectors within the intricate regulatory network to respond to environmental stimuli [29, 30].

Transmission of *Staphylococcus aureus*

Transmission of *S. aureus* occurs by direct contact with infected patients, colonized subjects or a contaminated environment, person-to-person transmission from persons with lesions, and sharing of personal items appear to be important factors, spread via the hands, sneezing, fomites, surgical wounds, and lungs of cystic fibrosis patients. Transmission also occurs through foods associated with food poisoning, airborne droplets, and recently heterosexual transmission was described [31,32].

Pathogenesis of *Staphylococcus aureus*

Both structural and secreted products of *S. aureus* play a major role in the pathogenesis of infection. Different microbial surface components recognizing adhesive matrix molecules may adhere to the same host-tissue component and appear to play a key role in initiation of endovascular infections, bone infections, joint infections and prosthetic device infections [18]. Once *S. aureus* adheres to host tissues or prosthetic materials, it is able to invade and survive inside epithelial cells including endothelial cells. During infection, *S. aureus* produces numerous enzymes such as proteases, lipases, and elastases that enable it to invade and destroy host tissues and metastasize to other sites [33]. Encapsulated *S. aureus* can induce abscess formation, and protein A binds the Fc portion of immunoglobulin and prevents opsonization. Chemotaxis inhibitory protein of Staphylococci or the extracellular adherence protein interfere with neutrophil extravasation and chemotaxis to the site of

infection. Leukocidins cause leukocyte destruction by the formation of pores in the cell membrane [34].

Staphylococcus aureus interacts with and activates the host immune system and coagulation pathways. These superantigens can produce a sepsis-like syndrome by initiating a cytokine storm. Some strains also produce epidermolysins or exfoliative toxins capable of causing scalded skin syndrome or bullous impetigo. *S. aureus* can disrupt the skin barrier by secreting exfoliate toxins, hemolysins (α -hemolysin, which forms pores in skin cell membranes), and various enzymes can destroy tissue [35,36]. Capsule and Protein A are surface factors that inhibit phagocytic engulfment whereas carotenoids and catalase production are biochemical properties that enhance their survival in phagocytes [34,37-39]. Neutrophils release antimicrobial substances including antimicrobial peptides, reactive oxygen species (ROS), reactive nitrogen species, proteases, and lysozyme. Defense against ROS is mediated in *S. aureus* by deployment of a large number of antioxidant enzymes (e.g., catalase, pigment, superoxide dismutase) that neutralize ROS and reactive nitrogen species. The recently identified phenol soluble modulins (PSM) is a group of bacterial peptides which induce inflammation and neutrophil cytolysis [35,40].

Disease caused by *Staphylococcus aureus*

There are many types of disease caused by *S. aureus*: skin and soft tissue (impetigo) is a small area of erythema that progresses into bullae (filled with cloudy fluid) that rupture and heal with the formation of a honey-colored crust [41]; Scalded skin syndrome (Ritter disease) a toxin-mediated disorder with superficial fragile blisters that burst and leaving a tender base often accompanied by fever and mucopurulent eye discharge [42]; Folliculitis is a tender pustule that involves the hair follicle which is caused by Panton-Valentine leukocidins (PVL) is a cytotoxin that causes leukocyte destruction and tissue necrosis [43]; Furuncle is a small abscesses characterized by exuding purulent material from a single opening which involves both the skin and the subcutaneous tissues in areas with hair follicles. Furuncles are acute, usually necrotic infections of hair follicles [44]; carbuncle is an aggregate of connected furuncles with several pustular openings. *Staphylococcus aureus* is the almost-universal cause of carbuncles worldwide [45]; and bone infections (osteomyelitis) common in children with sudden onset of fever and bony tenderness or a limp by Panton-Valentine leukocidins is a necrotizing toxin secreted by *S. aureus* [46].

In addition, septic arthritis is an increase in the incidence and severity of acute osteoarticular infections in children resulting in decreased range of motion, warmth, erythema and tenderness of the joint with constitutional symptoms and fever [47]. *S. aureus* is the leading cause of infectious endocarditis. It initially presents as fever and malaise which involves healthy valves [48]. Toxic shock syndrome is a diffuse macular erythema and hypotension with involvement of 3 or more or-

gan systems [49]. Necrotizing pneumonia, due to PVL producing strains of *S. aureus*, is associated with a high mortality rate which is common in infants, young children, and debilitated patients. A short prodrome of fever is followed by rapid onset of respiratory distress [50]. Thrombophlebitis presents as fever, pain, and erythema at the insertion site of an intravenous catheter, usually affecting hospitalized patients [51]. Deep tissue abscess and infection are muscles and organs that can become infected, including the parotid gland, eyes, liver, spleen, kidneys, and central nervous system [52]. In Ethiopia also, *S. aureus* was shown to be a bacterium that causes very serious clinical infections and an important public health threat. Previous regional research findings reflect a summary about the rates of the distribution of this bacterium in different clinical source.

Immunological response for *Staphylococcus aureus* infection

During bacterial infection the first thing that happens is tissue injury which leads to inflammation. Inflammation is a consequence of the activation of different cell types including macrophages that reside in the infected tissue by bacterial components that act as ligands to different receptors on the immune cells. Activated macrophages secrete different cytokines and chemokines that induce the activation of the vascular endothelium [64]. Dendritic cells residing in host tissues take up antigen in the infected tissues, and they are activated through innate immune receptors such as toll like receptors (TLRs) and nucleotide oligomerization domain proteins which respond to common constituents of pathogens. Activated dendritic cells increase their synthesis of MHC-II and begin to express the co-stimulatory molecules B7.1 and B7.2 on their surface [65,66].

Neutrophils play a central part in protecting humans against *S. aureus* infection. Staphylococcal entry and replication in host tissues leads to the release of bacterial products (formyl-peptides, lipoproteins or peptidoglycan) and to damaged tissues that produce inflammatory signals, i.e., chemo attractants and cytokines. Neutrophils extravasate from blood vessels and migrate towards the site of infection to phagocytose and kill bacteria [64,67]. *S. aureus* is capable of manipulating B cell survival and function, especially via the activity of SpA which is a sortase-anchored surface protein with high affinity for vertebrate immunoglobulin including human IgA, IgD, IgG, IgM, and IgE. *S. aureus* can also manipulate T cell responses by promoting T cell lysis. For example, δ -toxin, a member of the PSM α family, can lyse T cells and has also been reported to trigger mast cell degranulation [68].

Drug resistance mechanisms of *Staphylococcus aureus*

Staphylococcus aureus is well known due to its ability to become resistant to many antibiotics. Its resistance is often acquired by horizontal transfer to genes from outside sources, chromosomal mutation, and antibiotic se-

lection [69]. Resistance mechanisms include enzymatic inactivation of the antibiotic (penicillinase and aminoglycoside-modification enzymes), alteration of the target with decreased affinity for the antibiotic (penicillin-binding protein 2a of MRSA and D-Ala-D-Lac of peptidoglycan precursors of vancomycin-resistant strains), trapping of the antibiotic (for vancomycin and possibly daptomycin), and efflux pumps (fluoroquinolones and tetracycline). Complex genetic arrays (staphylococcal chromosomal cassette mec elements or the vanA operon) have been acquired by *S. aureus* through horizontal gene transfer, while resistance to other antibiotics including some of the most recent ones (fluoroquinolones, linezolid and daptomycin) have developed through spontaneous mutations and positive selection [70].

Drug resistant strains of *Staphylococcus aureus* Methicillin resistant *Staphylococcus aureus* (MRSA)

MRSA continues to be a major issue in hospitals and has emerged as a problem in the community. Methicillin resistance in *S. aureus* is encoded by the *mecA* gene which is embedded within a mobile staphylococcal cassette chromosome element known as SCCmec. MRSA can emerge from methicillin susceptible *S. aureus* upon site specific integration of SCCmec into the *orfX* locus in the chromosome. To date, nine major types of SCCmec have been recognized in *S. aureus* [71].

Hospital acquired methicillin resistant *Staphylococcus aureus* (HA-MRSA)

Hospital acquired MRSA (HA-MRSA) is prevalent in nearly all healthcare facilities and constitutes a huge infectious disease burden in the world. Health care associated MRSA cases are defined as patients with MRSA infection identified after 48 hours of admission to a hospital with a history of hospitalization, surgery, dialysis, residence in a long-term health care facility, a permanent indwelling catheter or percutaneous medical device present at the time of culture or a known positive culture for MRSA prior to the study period. It is resistant to many antibiotic classes, and often they are resistant to the common beta lactam and non-beta lactam antibiotics [72]. Community-associated and health care-associated MRSA cases differ demographically, clinically, and microbiologically distinct. MRSA has become a major nosocomial pathogen in community hospitals, long-term-care facilities, and tertiary care hospitals. The incidence of nosocomial MRSA has increased greatly in recent years in both developing and developed countries [73].

Community acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA)

CA-MRSA infection is an infection diagnosed in an outpatient or within 48 hours of hospitalization if the patient lacks hemodialysis, surgery, residence in a long-term-care facility or hospitalization, the presence of an indwelling catheter or percutaneous device at the time of culture. The lack or loss of resistance to multiple an-

tibiotics suggests a community origin because antibiotic selective pressure is much lower within the community than in hospitals and the survival advantage of multiple-drug resistance is lower [74]. Outbreaks of CA-MRSA infection are typically associated with skin diseases, and they can also result in invasive infections. It is more virulent and transmissible than hospital-associated MRSA strains. The restricted treatment options for CA-MRSA infections compound the effect of enhanced virulence and transmission [75].

CA-MRSA strains are more susceptible to non-beta lactam antimicrobials. They frequently contain the staphylococcal chromosome cassette mec type IV which contains mecA, the resistance gene against beta lactam agents. SCCmec type IV is smaller than the cassettes usually found in hospital strains of MRSA because of the omission of non-beta lactam resistance genes. CA-MRSA strains are also associated with greater toxin production compared with nosocomial MRSA strains. Many CA-MRSA strains carry the Panton-Valentine leucocidin genes which encode cytotoxins that can cause tissue necrosis and leukocyte destruction [76]. CA-MRSA is a growing concern in patients with no health care contact or apparent risk factors and primarily described as a cause of skin and soft-tissue infections, but it has also been associated with sepsis and necrotizing pneumonia [77].

Vancomycin resistant *Staphylococcus aureus*

Vancomycin resistance in *S. aureus* (VRSA) is maintained by the acquisition of the vanA gene. Reduced vancomycin susceptibility in vancomycin-intermediate *S. aureus* and hetero resistant vancomycin-intermediate *S. aureus* has been linked to mutations in structure or regulatory genes associated with the accessory gene regulator pathway. Vancomycin intermediate *S. aureus* (VISA) strains were first reported in Japan in 1996 and now identified more commonly in many countries including the United States [78]. Heterogeneous VISA (hVISA) strains are susceptible to vancomycin when tested with routine methods (≤ 2 mg/L) but contain subpopulations with MICs in the vancomycin-intermediate range (4 - 8 mg/L). The hVISA phenotype has been considered to be an essential step during the conversion of vancomycin-susceptible *S. aureus* and VISA phenotypes and is associated with poor clinical outcome in patients with invasive staphylococcal infections [79].

Laboratory diagnosis of *Staphylococcus aureus* infection

Various tests can be used to identify *S. aureus* including production of protein A, cell-bound clumping factor, extracellular coagulase and heat-stable nuclease. Specimens collected for diagnosis of *S. aureus* infection depend on the type of infection, and samples collected for diagnosis of *S. aureus* infection are pus (suppurative lesion), sputum (respiratory infection), blood (bacteremia & septicemia), feces, vomit & the remains of suspected food (food poisoning), and nasal swabs for the detection

of carriers [80]. Recent molecular genotyping methods to identify *S. aureus* include multilocus sequence typing, pulsed-field gel electrophoresis, Spa typing, Staphylococcal Chromosome Cassette mec, DNA Microarray-Based Identification, PCR/electrospray ionization-mass spectrometry, Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry, and Raman spectroscopy [81-88]. However, there are traditional (routine) methods used to identify *S. aureus* including gram stain, culture, biochemical tests, molecular technique, serological technique, antimicrobial susceptibility testing, and automated methods [89-95].

Treatment of *Staphylococcus aureus* infection

Methicillin/Nafcillin/Oxacillin/Cloxacillin are recommended for MRSA but due to changes in major penicillin-binding proteins it is commonly resistant to all antibiotics except vancomycin and fusidic acid. Topical mupirocin reduces nasal colonization. However, guidelines suggest that antibiotics should be used prophylactically when patients undergo medical procedures associated with bacteremia. Incision, drainage, and empirical therapy is of critical importance in the treatment of *S. aureus* bacteremia because delaying antibiotic treatment increases the risk of infection-related mortality and the duration of hospitalization [96]. Surgical drainage is crucial for the cure of furuncles and soft-tissue abscesses. Antibiotic therapy of vancomycin, linezolid, daptomycin, and tigecycline are US Food and Drug Administration approved and investigational agents for complicated skin and soft-tissue infection due to MRSA [92].

Prevention and control

The following are common strategies to prevent and control *S. aureus* infection and include decolonization of MRSA carriers, application of basic hospital infection control, washing hands, keeping wounds covered, reducing tampon risks, avoiding sharing of personal care items, cooking and storing food properly. Prevention of *S. aureus* infections relies on implementation of adequate principles of infection control (e.g., hand hygiene, contact precautions, and environmental control), and antimicrobial prophylaxis is recommended for all other surgical procedures [97].

Vaccine for *Staphylococcus aureus*

A vaccine targeting antibiotic resistant *S. aureus* prevents infection by targeting several secreted bacterial toxins. These toxoid vaccine candidates provide 100% immunity in separate rabbit models of endocarditis and pneumonia, highly relevant surrogates for the human condition. A recent discovery revealed that the superantigens have an additional host cell receptor that mediates antibody production. Studies evaluate antibody production in response to the superantigens, and cytolysin toxoid vaccine candidates show a synergistic effect when administered in combination. [98]. There are several potential reasons behind the disappointing results of

Table 1. Virulence factors of *Staphylococcus aureus*.

Virulence factors	Examples
Cell wall-associated factors	adhesins, exopolysaccharides, peptidoglycan and teichoic acid
Toxins	hemolysins, leucocidins, cytotoxins, enterotoxins, toxic shock toxin-1 and exfoliative toxins
Enzymes	hyaluronidase, proteases, lipase and coagulase
Biofilm formation	exopolysaccharides (fibronectin binding protein, biofilm associated protein)

Table 2. The rates of the distribution of *S. aureus* and MRSA in different clinical sources in Ethiopia.

Study area	Study period	Study design	Sample source	Sample size	<i>S. aureus</i>	MRSA n (%)	Ref.
Addis Ababa	2013 - 2014	Cs	blood, body fluids, nose, throat, eye, ear, abscess, vagina, urethra, urine, stool, sputum	1,360	194 (14.3)	34 (17.5)	[53]
Tikur Anbessa, Addis Ababa	2013 - 2014	Cs	wound, ear, nose	188	79 (42.02)	54 (68.4)	[54]
Adigrat and Wukro hospitals, Tigray	2016	Cs	nose	242	29 (2)	14 (48.3)	[55]
Gondar	2018	Cs	nose	622	143 (23)	14 (9.79)	[56]
Felege Hiwot, Dessie and Debera tabor	2013 - 2014	Cs	anterior nares, skin and perineum	1,200	281 (23.4)	73 (26)	[57]
Ethiopia	2003 - 2018	Ma	nose	2,495	721 (28.9)	186 (25.8)	[58]
Jimma	2010 - 2011	Cs	nose	354	169 (47.7)	39 (23.08)	[59]
Debre Markos	2010 - 2012	Cs	surgical site	184	73 (39.7)	36 (49.7)	[60]
Gondar	2011	Cs	nose	200	41 (20.5)	4 (9.8)	[61]
Gondar	2016	Cs	ear	312	96 (30.8)	23 (23.9)	[62]
Gondar	2010	Cs	surgical site, vagina	1,627	26 (91.6)	9 (34.6)	[63]
				8,784	1,852 (21)	486 (26.2)	

Cs - cross-sectional, Ma - meta-analysis, Ref - References.

clinical trials such as *S. aureus* having a wide array of virulence factors that allow it to evade the host immune responses, *S. aureus* strains are geographically diverse and very versatile in their antigenic repertoire, current animal models for staphylococcal disease do not have good predictive value, assays that can reflect physiological endpoints are needed to evaluate the host's potential to identify and eliminate *S. aureus*, certain types of antigens should be used to induce protective immunity, lack of a validated clinically-relevant correlate of protection, and we currently do not know whether a vaccine that

protects against soft-tissue infection can also protect against other forms of *S. aureus* [99].

CONCLUSION AND RECOMMENDATION

Multidrug resistant *S. aureus* strains are emerging and current antibiotics are not efficacious against such strains. Both active and passive immunization strategies have thus far failed to show efficacy in humans. Therefore, infection preventive measures and further research

Table 3. Antimicrobial resistance genes and mechanisms of resistance in *Staphylococcus aureus*.

Antimicrobial agents	Mechanisms of resistance	Genetic basis
β-lactams ✓ Penicillins ✓ Cephalosporins ✓ Monobactams ✓ Carbapenems	β-lactamases - inactivate drugs altered penicillin-binding protein (PBP2a) targets	blasZ - plasmid mecA - acquired from?
Glycopeptides ✓ Vancomycin	VISA - cell wall thickens VRSA - modified target	gene unknown vanA - from enterococci
Lipopeptides ✓ Daptomycin	change in cell membrane charge decreased drug binding	mprF gene mutation
Aminoglycosides ✓ Amikacin ✓ Gentamicin ✓ Tobramycin	aminoglycoside modifying enzymes modify target	aac - plasmid ant - plasmid aph - plasmid
Tetracyclines ✓ Tetracycline ✓ Minocycline ✓ Tigecycline	active efflux ribosomal protection - competitive binding	tetK - plasmid tetM - plasmid
Chloramphenicol	acetylation of drug - inactivation	cat - plasmid
Macrolide and Lincosamides ✓ Erythromycin ✓ Clindamycin	methylation of ribosome - decreased binding	ermA, ermB, ermC - plasmid
Oxazolidinones ✓ Linezolid	mutation of ribosome methylation of ribosome	Rrn cfr - plasmid
Streptogramins ✓ Quinupristin/Dalfopristin	methylation of ribosome	ermA, ermB, ermC
Fluoroquinolones ✓ Ciprofloxacin ✓ Norfloxacin ✓ Levofloxacin ✓ Gatifloxacin ✓ Moxifloxacin	modified target - gyrase modified target - topoisomerase IV active efflux	gyrA grlA norA
Metabolic Pathway Inhibitors ✓ Trimethoprim/Sulfamethoxazole	target enzyme modification	TMP - dhfr SMZ - dhps

Table 4. Comparisons between HA-MRSA and CA-MRSA.

Variables	HA-MRSA	CA-MRSA
Patient population	acquired after staying more than 48 hours in the hospital	community without exposure to the hospital environment
Pre-disposing factors	surgery, intubation, catheter, dialysis, prior MRSA infection, long term care facility	members of military, IVDU, homosexual males, children, athletes, inmates, Pregnant women, children and infants
Virulent factors	SCCmec type I to III	SCCmec type IV or V, Panton-Valentine leucocidin & other toxins
Clinical presentations	systemic infection such as UTI and pneumonia	most common soft tissue and skin infection
Antibiotic resistance profile	resistant to most antibiotics except few (e.g., vancomycin, linezolid)	resistant to beta-lactam group of antibiotics but susceptible to quinolones and trimethoprim. Topical fusidic acid and mupirocin. Some are susceptible to clindamycin
SCCmec element	carry a large SCCmec elements	carry smaller SCCmec element
Lineages	predominantly of USA100 or USA200 lineage. CA-MRSA	predominantly of USA300 or USA400 lineage

are required to reduce the burden of *S. aureus*. Moreover, there is an urgent need to develop vaccines and antibiotics to target this pathogen.

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We declare that this review paper is our original work.

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