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Epidemiology, Pathogenicity, Animal Infections, Antibiotic Resistance, Public Health Significance, and Economic Impact of Staphylococcus Aureus: A Comprehensive Review

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Abstract *Staphylococcus aureus* (*S. aureus*) is a gram-positive bacterium that has a greater impact on animal and human health by causing various diseases. *S. aureus* is present as normal flora of the skin and mucous membranes of both humans and animals but can cause disease when it gets the chance to invade either due to trauma or because of impaired immune responses of the host. Different virulence factors are involved in the mechanisms of pathogenesis of *S. aureus* which include surface proteins, enzymes, toxins, and others. These virulence factors play an important role in invasion, colonization, and survival of *S. aureus* in the host to cause staphylococcal diseases. Infections of *S. aureus* pose a major public health threat owing to its ability to cause mild to severe/life-threatening human diseases. Methicillin-resistant *S. aureus* (MRSA) has become a pathogen of increasing importance in hospitals (nosocomial infection) and the community. It can be mainly transmitted to humans by the consumption of food of animal origin. Foods associated with outbreaks of staphylococcal food poisoning include meat and meat products, poultry, and egg products, milk and dairy products, salads, cream-filled bakery products, and sandwich fillings. Additionally, it has great economic importance as it causes different diseases in animals. MRSA shows resistance to different antibiotics including penicillin, methicillin, vancomycin, and others owing to the presence of different antibiotic resistance genes and other resistance mechanisms.

Keywords: *Staphylococcus aureus, virulence factors, methicillin resistant Staphylococcus aureus, vancomycin, animals, public health, antibiotic resistance genes, nosocomial infection, food of animal origin*

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1. Introduction & Background

Staphylococcus aureus (*S. aureus*) is a gram-positive coccus; size ranging from 0.5 to 1.5 µm in diameter [1]. It is a non-motile, non-spore forming, oxidase-negative, hemolytic, catalase-positive, and coagulase-positive bacteria. Staphylococci are categorized in the family of *Staphylococcaceae*, which are facultative anaerobes. *S. aureus* is the most frequent and significant species of the family, because of its potential pathogenicity both in humans and animals [2].

S. aureus is found as normal flora on the skin, anterior nares, nasopharynx, and mucous membranes of animals and humans. It is also found in environmental sites such as soil, water, and air [3,4,5]. *S. aureus* has also been isolated from different foods of animal origin and was reported as the third most common cause of food-borne illnesses around the world [6]. The public health impact of *S. aureus* is interlinked to the animals and their products that are used for food production. Such food from animal origin may be contaminated with one or more preformed staphylococcal enterotoxins (SEs) produced by the organism and cause human diseases [7].

The prevalence of *S. aureus* in milk and dairy products has been reported from many countries as well as different geographical regions of the same country. It was observed that the prevalence rates varied significantly. Increased prevalence of *S. aureus* has been documented in milk and milk products produced from developing countries as compared to the developed countries. Such a difference in

the prevalence rates was attributed to the variations in the management system of dairy cows in the respective countries [8].

S. aureus causes severe animal diseases including clinical and subclinical mastitis in ruminants, suppurative disease, arthritis, omphalitis, urinary tract infections, and others [9]. Its virulence depends on different factors that include extracellular proteins, such as enzymes, and toxins that contribute to the pathogenicity [4,5]. There is now increasing concern about the public health impact of *S. aureus* infections associated with food-producing animals and their products which contain one or more preformed SEs produced by *S. aureus* [7]. In recent years, bacterial drug resistance has been a major concern for scientists. Moreover, the resistance of *S. aureus* to methicillin and vancomycin is well known [10,11].

Therefore, in this review we attempt to highlight the epidemiology, mechanisms of pathogenicity, animal infections, antimicrobial drug resistance, public health significance, and economic impact of *S. aureus*.

2. Review

The physical growth parameters required for the growth and survival of *S. aureus* include an optimum temperature of 35-37ºC, the water activity (aw) of 0.86, an optimum pH of 7-7.5, and the presence of oxygen. These physical growth requirements vary for different *S. aureus* strains. *S. aureus* is a facultative anaerobe that can grow under both aerobic and anaerobic conditions and the growth occurs at a much slower rate under anaerobic conditions. *S. aureus* is an extremely heat sensitive non-spore forming bacteria that can readily be inactivated at a temperature greater than 46°C [12]. These bacteria also show both intrinsic and acquired resistance to different antibacterial drugs [13].

2.1. Epidemiology

2.1.1. The Occurrence of *S. aureus* in Humans, Animals, and Food of Animal Origin

S. aureus is present as normal flora of humans and animals and is an opportunistic pathogen that is widely distributed throughout the world [3,14,15,16,17]. However, it is well recognized as an invasive human pathogen, resulting in significant morbidity and mortality. It has also been frequently isolated from the animals and the food of animal origin [18].

S. aureus is a well-known bacterium that develops antibiotic resistance [19]. Methicillin-resistant Staphylococcus aureus (MRSA) is a strain of *S. aureus*, which has been noted to acquire resistance to different groups of antibiotics and become multi-drug resistant. The MRSA strains can be divided into two different groups, the ones which cause hospital infections (healthcare-associated (HA-MRSA)) and those which cause infections in the community (community-associated (CA-MRSA)). Even though these two groups have similar microbiological characteristics, they differ in the risk factors, genetic structure, virulence determinants, and antibiotic resistance. CA-MRSA strains carry type IV or V Staphylococcus chromosomal cassette mec (SCCmec) element and usually possess the Panton-Valentine toxin/leucocidin (PVL) and are not multi-drug resistant. HA-MRSA species carry type I, II or III SCCmec, do not possess PVL and show multidrug resistance. The PVL is a pore-forming toxin encoded on the genes of bacteriophages and is transmitted to the *S. aureus*, which is associated with increased virulence to humans [20-21]. The CA-MRSA strains are considered more virulent than HA-MRSA strains because they possess specific virulence factors [18].

There are reported cases of MRSA strains linked to livestock, which are classified as livestock-associated MRSA (LA-MRSA). These strains, which are not HA or CA-MRSA, belong mainly to a specific lineage 398 (ST398 or CC398), although other minor sequence types have been described. The emergence of LA-MRSA could be related to a selection and differentiation among the clones/population of methicillin-sensitive *S. aureus* (MSSA) [22].

MRSA CC398 was first isolated from several people and their family members living on a pig farm. Pigs and pig farms are recognized as one of the most important sources of LA-MRSA in farmers, veterinarians, and their families. Subsequent studies on the prevalence of LA-MRSA clones in food-producing animals showed its presence in pigs in several countries of Europe, America, and Asia. The ST398 is the most represented and widely disseminated species of LA-MRSA in pig farms. The prevalence of LA-MRSA in dairy cattle is generally low and is mainly associated with clinical and subclinical mastitis. After the first report of MRSA involved in the cases of cattle mastitis, this pathogen has occasionally been reported in dairy cattle farms [23].

The prevalence of MRSA in poultry flocks is low, although the rates of such resistant pathogens increase among mixed poultry and pig farms. In this case, the source of MRSA contamination to animals and the persistence in the environment is dependent on the farmer. Since their first appearance, LA-MRSA has been considered as an occupational hazard for people who are in continuous contact with animals. Animals are a potential reservoir of LA-MRSA, while people can serve as carriers of these resistant strains into the community. All the farm animals can represent a potential source of MRSA CC398, with some differences in their prevalence [24].

In general, foods from which *S. aureus* was isolated included raw meat (including pork, beef, lamb, chicken, and turkey), dairy products (milk and cheese) and, in one instance, pancakes. Significant differences in prevalence in animal products have been recorded in different countries or even various regions within the same country. These differences may be attributed to different animal production systems practiced among various countries, different national antimicrobial policies and regulations and the presence of multiple animal species in the same area that facilitate the transfer of genetic material between *S. aureus* strains [25,26].

2.1.2. Reservoirs and Sources of Infections

Animals with persistently colonized body sites (udder and teat skin, muzzle, and vagina) represent the primary reservoir of *S. aureus* and sources of infection for others. Animals with subclinical types of inflammatory infections (IMI) are a reservoir of *S. aureus* that serves as a source of

infection in the dairy environment and represents the most common cause of raw milk contamination. Other sources of *S. aureus* include contaminated milking equipment, bedding, and personnel. *S. aureus* infected purchased animals and chronically infected animals are a major source of new staphylococcus infections within a farm. Farms and cheese-making plants can serve as a reservoir of *S. aureus* and can spread the microorganism into the environment. The tonsils and skin of pigs, chickens, and turkeys often harbor *S. aureus* and are also potential sources of *S. aureus* contamination [12]. Coagulase-Negative Staphylococci (CoNS) are found to be the reservoir and a potential source for important resistant elements/genes to *S. aureus* [27].

2.1.3. Modes of Transmission

S. aureus can be transmitted from animal to animal, person to person, as well as from animals to humans and vice-versa. Transmission usually occurs by direct contact, often via the hands, with colonized or infected animals or people and contaminated equipment and surfaces [9]. The most common transmission pathways include the transfer from an infected mammary gland to an uninfected gland via fomites, such as milking equipment, or the milker's hands, un-controlled animal traffic between different farms and handling or eating food contaminated with *S. aureus*. *S. aureus* present in the nose and on the skin is shed into the environment by infected or colonized people and animals, indicating the possibility of airborne transmission as a possible route for infection. Vectors like the housefly (*Musca domestica*) have also been implicated in the transfer of *S. aureus* [23,28].

2.1.4. Predisposing/Risk Factors

The ability of a microorganism to cause disease depends on the host's susceptibility, immune response, internal and external microbial environment (normal flora), previous infection, antibiotic administered, predisposing conditions like accident/trauma, and the age [29]. *S. aureus* carriers could be classified into three different classes: those who always carry a strain (persistent carriers), those who intermittently carry different strains (transient carriers) and those people who never carry *S. aureus* (non-colonizers). The hosts, especially asymptomatic hosts, play an important role in the spread of *S. aureus* into the environment [30].

S. aureus shows wide adaptability to several environmental and host factors, thus permitting colonization of susceptible environments such as hospitals. The prevalence of *S. aureus* strains is high in hospital areas as compared to the other regions. The presence of *S. aureus* in hospitals is a major concern for public health. The ST398 is the most represented and widely disseminated strain of LA-MRSA that is reported from countries with intensive farming. Poor hygienic standards of the farms and increased resistance rates of *S. aureus* species in mixed farms are important predisposing factors for transmission [23].

An essential aspect of LA-MRSA is its remarkable degree of host non-specificity and easy transmissibility between animals and humans. *S. aureus* owes its strong pathogenic capabilities to the presence of a large number of virulence factors. Moreover, an important risk factor for *S. aureus* infections is its tendency to gain resistance to almost all classes of antimicrobial agents. Of particular concern is the acquired resistance that the *S. aureus* develops against the β-lactamase stable β-lactam antibiotics [31].

2.2. Pathogenicity

2.2.1. Virulence Factors of *Staphylococcus aureus*

Bacterial pathogens sense, respond and adapt to harsh environmental conditions present in the mammalian host during the infection. This helps them to invade the host, colonize and survive, despite the host's immune responses and antimicrobial therapy [32]. *S. aureus* produces various enzymes such as coagulase which coagulates the plasma by converting the plasma fibrinogen to fibrin and could coat the bacterial cell and probably prevent phagocytosis. Hyaluronidase, which is also known as a spreading factor, breaks down hyaluronic acid present in the tissues and helps the spread of *S. aureus* within the host. It also produces DNase (deoxyribonuclease) which breaks down the DNA, lipase that digests the lipids, and staphylokinase which dissolves the fibrin. The *S. aureus* is also known to produce β-lactamases for drug resistance, esterase, elastase, and phospholipase enzymes that facilitate colonization and pathogenicity. Other virulence factors of *S. aureus* include leucocidin, which causes cytolytic destruction of phagocytes of some animal species and toxic shock syndrome toxins (TSST) which induces excessive lymphokine production, resulting in tissue damage [2].

Depending on the strain, *S. aureus* is capable of secreting several toxins, which constitute the major virulence factors. These toxins can be categorized into three groups such as superantigens, exfoliative toxins and other toxins that act on cell membranes including alpha toxin, beta toxin, gamma toxin, delta toxin, and several bicomponent toxins, such as Panton-Valentine toxin or leucocidin (PVL) [33,34,35].

Protein A, which plays a key role in the immune-evasive strategies, is anchored to staphylococcal peptidoglycan pentaglycine bridges by the transpeptidase sortase A. Protein A has the ability to bind to the Fragment of crystallization region (Fc) of the IgG (Gamma immunoglobulin) antibody. This phenomenon is used to perform co-agglutination tests, where the protein A can be bound to IgG antibodies produced against the desired microorganism and is then reacted with the corresponding antigen, which is usually present in the patient's sample, to see a visible agglutination reaction. Such reactions are used for the laboratory diagnosis of infections like meningitis caused by *Neisseria meningitidis*. *S. aureus* strains are known to produce pigments like the staphyloxanthin, a golden-yellow colored carotenoid pigment. This pigment acts as a virulence factor, primarily by acting as a bacterial antioxidant, that helps the microbe evade the reactive oxygen species which the host immune system uses to kill the pathogens [36].

The production of virulence factors is a result of the phenotypic changes caused by lysogenic conversion which plays an important role in the pathobiology of *S. aureus* species. The temperate phage types of *S. aureus* that are involved in human diseases are classified into six categories including the SGA, SGB, SGD, SGL, and 2SGF (SGFa and SGFb). [17].

2.2.2. Mechanism of Pathogenicity

Although *S. aureus* is a normal flora of the skin and mucous membranes, any break in the skin or colonization of individuals with compromised immune systems can give an opportunity for this bacterium to invade and cause infection. The disease process can be mediated via two possible mechanisms; the production of toxins and the colonization that causes tissue invasion and destruction [37].

Adhesion and colonization: *S. aureus* can up-regulate a variety of virulence factors, enabling it to adhere to and colonize the nares and damage the skin or the surfaces of the infected area and to cause serious bloodstream infections. The teichoic acid, a polymer present on the surface of *S. aureus*, facilitates this process as observed by a previous study [38].

Invasion: *S. aureus* disrupts the skin barrier by secreting exfoliative toxins, hemolysins, which form pores in the skin cell membranes, and produces various enzymes that destroy tissue. The invasion may be triggered when the immune system is compromised and when there is a break in the physical integument, and/or when localized inflammation occurs [39].

Evasion: *S. aureus* causes immune evasion by secreting anti-opsonizing proteins (chemotaxis inhibitory protein), which prevent phagocytosis by neutrophils. Protein A, located on the surface of *S. aureus* cells, also has antiphagocytic properties. Moreover, *S. aureus* secretes PVL, which lyses the leukocytes, and expresses superantigens (enterotoxin and TSST1), which subvert the normal immune response by inducing strong, polyclonal stimulation and expansion of T cells (receptor β-variable specific T cells). This results in the deletion or suppression of these T cells to an anergic state [40]. The PVL genes can be transmitted by means of bacteriophages, which allow them to be transmitted from one organism to the other [13].

Biofilms: The development of a biofilm is a two-step process involving an initial attachment and a subsequent maturation phase, which are physiologically different from each other and require phase-specific factors. A final detachment (or dispersal) phase involves the detachment of single cells or cell clusters by various mechanisms and is believed to be crucial for the dissemination of the bacteria [41]. *S. aureus* quorum sensing may regulate gene expression to form slimy biofilms on damaged skin or body sites. The depletion of nutrients and oxygen causes bacteria to enter a non-growing (dormant) state in which they are less susceptible to some antibiotics. In particular, small-colony variants of *S. aureus*, when adherent and in the stationary phase, demonstrate almost complete resistance to antimicrobial agents. The biofilm matrix protects the bacterial cells by restricting the entry of some antibiotics [21,42].

2.3. Diseases Caused by *S. aureus* in the Farm Animals

Small Ruminants: *S. aureus* causes both clinical, mainly gangrenous mastitis, and subclinical mastitis in small ruminants. In dairy sheep and goats, subclinical mastitis is frequently caused by CoNS. Staphylococcal septicemia of the newborn lambs (2-12 weeks old), results in a high mortality rate attributed to the myocardial lesions. The tick pyemia of lambs which is caused by the ticks *Ixodes ricinus*, and *Anaplasma phagocytophilum*, predisposes them to serious staphylococcal infections [43].

Cattle: *S. aureus* causes simple abscesses to severe mastitis and toxic shock syndrome in cattle. It is the major pathogen causing both clinical and subclinical mastitis in dairy farms, with a majority of infections being subclinical [44]. *S. aureus* also causes other diseases such as dermatitis, furunculosis, gastroenteritis, osteomyelitis, meningitis, pneumonia, endocarditis, and wound infections [6,9,11,45]. Staphylococcal per-acute and gangrenous infections are associated with severe systemic reactions and can be life-threatening. In gangrenous mastitis, the affected tissue, which becomes cold and blue-black, eventually sloughs-off. Tissue necrosis is attributed to the alpha-toxin which causes contraction and necrosis of smooth muscle in blood vessel walls, impeding blood flow in the affected regions. In addition, this toxin releases lysosomal enzymes from leukocytes [2].

Pigs: *S. aureus* species are known to cause exudative dermatitis (greasy pig disease) in pigs. Entire litters of suckling pigs and young weaned piglets are usually affected. Skin necrosis and facial dermatitis are also common in suckling pigs [46]. Pigs have been shown to be a major reservoir for MRSA multilocus sequence type 398 (ST398) [47].

Poultry: In birds, *S. aureus* is often associated with bumblefoot, omphalitis (yolk sac infection), arthritis, tenosynovitis (inflammation of tendon sheath), necrotic dermatitis, necrotic skin lesions or abscesses and osteomyelitis. An epidemic of systemic staphylococcosis in White Leghorn chicks has been reported previously by Pal (1992) [48]. The occurrence of MRSA in both chickens and farmworkers from poultry farms has also been reported [47,49,50]. Poultry may pose a higher risk than either cattle or swine because the skin is left intact on many cuts of the poultry but is eliminated from cattle and swine [51].

Fish: *S. aureus* is the most important fish pathogen and its prevalence has been observed in seafood including different species of fishes. This affects fish and fish product food marketing systems in different countries as noted by previous research reports [52,53].

2.4. Antibiotic Susceptibility and Resistance Mechanisms

Antibiotics (depending on their class/group/type) act on bacteria by inhibition of cell wall synthesis, protein synthesis, nucleic acid synthesis, and metabolic pathways. Antibiotic-resistant bacteria prevent the action of antibiotics by both the innate and acquired resistance mechanisms. Methods of acquired resistance include transformation (the exchange of nucleic acid), transduction (bacteriophage mediated resistance gene incorporation into bacteria), conjugation with plasmids or transposons and mutation [54]. Among the microorganisms showing resistance to antibiotics *S. aureus* represents a major public health concern. In contrast to other microorganisms, such as some species of *Enterococcus* that show intrinsic resistance to several antibiotics due to their natural

metabolism, *S. aureus* can be defined as a microorganism with increased potential to develop acquired antimicrobial resistance [55]. To minimize the antibiotic resistance problems, a helper compound called thioridazine, which potentiates the effect of the β-lactam antibiotic dicloxacillin is used against MRSA [56].

S. aureus strains have acquired resistance against multiple antibiotics such as penicillin, methicillin, and vancomycin. MRSA has become a major problem worldwide and is increasingly being detected in both hospitals and communities [27].

2.4.1. Resistance Genes

Antibiotic resistance genes of S. aureus include the common ERY resistance genes (ermA, ermB, ermC), and the TET resistance genes (tetL, tetK, tetM, tetO). These genes can be detected by applying the polymerase chain reaction (PCR) assays [5]. The recent emergence of highly virulent CA-MRSA strains and vancomycin-resistant, vancomycin intermediate-resistant, or hetero-resistant *S. aureus* strains further heightens public health concerns [57]. Quinolone resistance determining region, mecA and chloramphenicol-florfenicol resistance (cfr) genes of MRSA are some important aspects that determine antibiotic resistance which can be identified by PCR assays [11,58,59].

A recent report had identified 32 antibiotic-resistant genes in various *S. aureus* strains that included AAC(6')-ie-APH(2")-ia, ANT(4')-ib, ANT(9)-ia, antibiotic resistant fabl, APH(3)-iiia, arlR, arlS, bcrA, dfrC, dfrG, ErmA, ImrB, mecA, mecl, mecR1, mepA, mepR, mfd, mgrA, mphC, norA, norB, PC1 beta-lactamase (blaZ), SAT-4, sav1866, *S. aureus* gyrA conferring resistance to fluoroquinolones, TaeA, tet(38), tet(K), tetM, vgaALC and FosB3 [60]. Antibiotic resistance in the MRSA strains isolated from hospital Cockroaches (*Periplaneta americana* and *Blattella germanica*) has been evaluated phenotypically by disk diffusion and genotypically by PCR amplification methods [37,61]. It was noted that the MRSA strains have acquired the mecA gene which encodes for an alternative penicillin-binding protein 2α with reduced affinity for methicillin. This gene complex also allows cross resistance to non-beta lactam antibiotics such as clindamycin, ciprofloxacin, cotrimoxazole, erythromycin and gentamycin because of the presence of insertion sites for plasmids and transposons [62].

2.4.2. Mechanisms of Antibiotic Resistance in *S. aureus*

Glycopeptide Resistance: Vancomycin resistance in *S. aureus* strains is a global issue [63]. Vancomycin has been used for many years and is the most preferred drug to treat MRSA infections. Vancomycin intermediate sensitive *S. aureus* (VISA) was first reported from a Japanese patient in 1997. Vancomycin resistance was described for the first time in the *Enterococcus* species. In the past, it was demonstrated that the genes coding for vancomycin resistance could be transferred from vancomycin-resistant *Enterococcus* (VRE) to MRSA by conjugation [54].

β-lactam Resistance: *S. aureus* acquires resistance to β-lactam by two major resistance mechanisms that include the production of penicillinase and the production of modified penicillin-binding proteins (PBP). Methicillin resistance is caused by the expression of an alternative penicillin-binding protein, called PBP2a or PBP2', where such species are encoded by the mecA gene. PBP2a shows a very low affinity for β-lactam antibiotics, resulting in an enduring bacterial cell wall construction and, hence, increases the survival of the bacterium. The mecA gene is localized in a mobile genetic element, named the SCCmec, which is found, integrated into the chromosome at a specific open reading frame (orf) of unknown function, orfX. The penicillinase blaZ, inactivate β-lactam antibiotics by hydrolysis of the β-lactam ring. Based on the differences in β-lactam ring hydrolysis, penicillinase can be classified into four different classes: A, B, C and D. The BlaZ genes, coding for penicillinase A, C and D are usually located on plasmids, while blaZ encoding penicillinase B is located on the chromosome. The expression of blaZ structural gene is controlled by blaI repression gene and by blaR1, a signal transducer sensor protein, which is clustered together. In the same manner of blaZ, mecA gene expression is regulated by a two-component system, mecA repression gene, and mecR1, a signal transducer-sensor protein [64].

Vancomycin Resistance: It is associated with van genes that code for different resistance phenotypes, carrying the same name of the correspondent genes. VanA, gene encodes for high-level resistance to both vancomycin and teicoplanin; vanB, gene encodes for resistance only to vancomycin; vanC1, vanC2 and vanC3 genes encode for a low-level resistance to vancomycin; vanD, is a novel gene, found in *Enterococcus* (*E*) *faecium*, that codes for vancomycin resistance; vanE, is another novel gene, found in *E. fecalis*, coding for low-level resistance to vancomycin. Genes coding for vancomycin resistance are carried on mobile genetic elements such as transposons and plasmids. VanA and VanB are the most prevalent phenotypes in nature. VanA is the phenotype usually associated with VRSA. Similar to the methicillin resistance, *S. aureus* strains acquire vancomycin resistance (VRSA) by a mutation in the PBP structure. Expression of the van genes is controlled by a two-component system, vans (sensor) and vanr (response regulator), regulating the transcription of vanHAX gene cluster. Resistance rates of *S. aureus* to vancomycin are extremely high as noted by previous reports [10,65].

Aminoglycoside Resistance: *S. aureus* strains show resistance to aminoglycosides and epidemiological analyses showed that the resistance to aminoglycosides is generally associated with methicillin resistance. MRSA strains often carry a plasmid with aacA or aphD genes which code for resistance to gentamycin, tobramycin, and kanamycin. The product of the expression of aacA or aphD genes is a bifunctional aminoglycoside modifying enzyme (AAC6 or APH2) that inactivates the aminoglycoside drugs [66].

Macrolides and Lincosamides Resistance: Three different mechanisms are involved in the acquisition of resistance to Macrolides and Lincosamides in *S. aureus* strains that includes modification of the target site by mutation or methylation of 23s rRNA subunit encoded by one or more erm genes, mainly ermA, ermB and ermC genes located on plasmids or the chromosome (ermC), and activation of an efflux pump encoded by mrsA and mrsB genes. The latter is more prevalent in CoNS than in *S. aureus*. The enzymatic inactivation of the antibiotic via

activation of phosphotransferase C encoded by mphC gene for Macrolide resistance was also observed. Moreover, inactivation of Lincosamide drugs is mediated by the activation of a Lincosamide nucleotide transferase encoded by lnuA gene. In *S. aureus* strains, the Macrolide resistance is brought about by the methylation of the 23s rRNA encoded by ermA gene [67,68].

Tetracycline Resistance: The mechanisms involved in *S. aureus* resistance to tetracyclines are the ribosomal protection by elongation of proteins, and activation of the efflux pump. Ribosomal protection is coded by tetM and tetO genes carried on the chromosome, while the efflux pump is coded by tetK and tetL genes located on plasmids. Recently the tet38 gene was noted to contribute to tetracycline resistance in *S. aureus* strains. The activation of this efflux pump is controlled by mgrA regulator gene. The mgrA protein is an indirect repressor of the pump tet38. Therefore, the inactivation of mgrA leads to the activation of the efflux pump as noted by a previous research report [64].

2.5. Public Health Importance of *S. aureus*

S. aureus is a major pathogen of public health concern throughout the world. MRSA has become a pathogen of increasing importance in hospitals (nosocomial infection), the community, and also in the livestock. Staphylococcal food poisoning is an intoxication that is caused by the ingestion of food contaminated with pre-formed staphylococcal enterotoxins (SEs). There are several different types of SEs that include enterotoxin A, D, E and H, and to a lesser extent B, G and I, of which the enterotoxin A is most commonly associated with staphylococcal food poisoning in humans. SEs are resistant to the heat and low pH conditions that easily destroy *S. aureus* bacteria. The SEs are also resistant to proteolytic enzymes; hence SEs remain unaffected in the gastrointestinal tract after the ingestion [69]. The presence of antibiotic-resistant strains has become an emerging zoonotic issue of public health concern. Although extensive researches have been conducted, many people still suffer from staphylococcal infections associated with livestock [6,37,59].

Foods associated with the outbreaks of staphylococcal food poisoning include meat and meat products, poultry and poultry products, egg, milk, and dairy products, salads, cream-filled bakery products, and sandwich fillings [26,69,70]. Common symptoms of staphylococcal food poisoning include nausea, vomiting, abdominal cramps and diarrhea which are usually rapid in onset. In severe cases, headache, muscle cramping and transient changes in blood pressure and pulse rate may occur. *S. aureus* can cause various non-food related health issues such as respiratory infections, skin inflammations, wound sepsis, and toxic shock syndrome [9,12,70]. This bacterium continues to pose major public health challenges because of the problems with antibiotic resistance [71].

2.6. Economic Impact of *S. aureus*

Bovine mastitis is a significant infectious disease with an impact on the economy of milk production. Besides health disorders of the mammary gland, mastitis can also cause significant losses in the milk yield, alterations in its quality (impaired nutritive value of milk), fertility disorders, and even systemic diseases accounting for increased health care and production costs [44,72].

Although clinical mastitis may cause serious damage to the udder and even systemic disorders leading to the culling of affected animals, the subclinical mastitis is, in general, a more insidious form of the disease because it is invisible to the farmer, leading to delayed diagnosis and also spreads widely among the dairy herds. This results in reduced milk quality and yield, which in turn leads to a reduction in the farmer's income as well as that of the dairy industry. Like dairy cows, mastitis in dairy sheep and goats can cause economic losses as a consequence of a decrease in milk production, undervaluation of milk with high somatic cell counts, mortality and treatment costs. In poultry economic losses may result from decreased weight gain, decreased egg production, lameness, mortality, and condemnation at slaughter [73].

3. Conclusions

S. aureus has been recognized as an important pathogen that causes both human and animal diseases. Increased prevalence of *S. aureus* is more likely to occur in animals that were poorly managed and frequently treated with antibiotics. The primary reservoirs of the bacteria in different countries are food-producing/farm animals that include pigs, veal calves, ruminants, and poultry. An essential aspect of *S. aureus* is its remarkable degree of host un-specificity and due to its immense zoonotic implications. *S. aureus* strains are resistant to penicillin, vancomycin, β-lactam antibiotics, and others mediated by various genetic and enzymatic mechanisms. As a result, the diseases caused by *S. aureus* have a great economic impact on the animals, and the quality of foods of animal origin. It can be transmitted to humans by the consumption of food of animal origins such as milk, meat, egg, and other animal products. Because *S. aureus* is present as a normal flora of healthy humans which facilitates easy human-human transmission, hospital and community acquired infections with MRSA, VISA, VRSA, and multi-drug resistant *S. aureus* strains cause significant morbidity, mortality, and increased healthcare-related costs.

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