Research Article

Staphylococcus aureus: A Review of Antimicrobial Resistance Mechanisms

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Abstract | The emergence of antimicrobial resistance in *Staphylococcus aureus* posed a major veterinary and public challenge worldwide. *S. aureus* being a highly versatile pathogen can quickly acquire resistance genes. The development of resistance in bacteria predates the era of antibiotic use. However, resistance developments in *S. aureus* have been reported since the early 1940-ties, when penicillin resistant *S. aureus* was first reported. Ever since, this pathogen has gain global notoriety as the most common cause of nosocomial, community and livestock associated infection. The mechanism of resistance development in bacteria involved the integration of a complex systems that included the efflux pump, alteration of drug target site, enzymatic inactivation and, mutation in drug target site and gene acquisition of resistance determinants through horizontal gene transfer. This review focused on the mechanisms of antimicrobial resistance in *S. aureus*. Understanding the concept of resistance development and transfer will immensely help in curtailing the global rise in antimicrobial resistance in bacteria.

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Introduction

Staphylococcus aureus is a ubiquitous, versatile and highly adaptive pathogen that colonizes the skin and mucous membrane of the anterior nares, gastrointestinal tracts, perineum, the genitourinary tracts and pharynx (den Heijer et al., 2013). It is the causative agent of a wide range of infections in humans and animals with a significant impact on public health (Luzzago et al., 2014). Host specialization, ability to acquire and loss resistance and virulence genes as well as its zoonotic potential posed a significant public health implication (Holden et al., 2004; Saleha and Zunita, 2010; Luzzago et al., 2014). Clinically, *S. aureus* is the most pathogenic member of the genus staphylococci and the etiologic agent of a wide variety of diseases that ranges from superficial skin abscess, food poisoning and life threatening diseases such bacteremia, necrotic pneumonia in children and endocarditis (Shaw et al., 2004). In animals, it causes mastitis in cow, botryomycosis in horses, dermatitis in dogs, septicemia and arthritis in poultry (Zunita et al., 2008; Luzzago et al., 2014). The severity of the disease is due to the production of several putative virulence factors and possession of antibiotic resistance genes such as *mecA, VanA*, staphylococcal exotoxins and other factors that facilitates the initiation of disease process, immune evasion and host tissue

destruction (Holden et al., 2004; Shaw et al., 2004).

Antibiotics resistance development in *S. aureus* was first reported in the mid-1940-ties when a strain of *S. aureus* developed resistance against penicillin by the production of a hydrolyzing enzyme called penicillinase (Basset et al., 2011). Since then, *S. aureus* strains resistant to penicillin were widely isolated in cases of bacteremia in the UK and United States. Initially, those resistant strains were only isolated from patients and health care personnel where it derives the name nosocomial associated penicillin resistant *S. aureus*. However, resistant strains without apparent identifiable risk factors associated with the hospital strains were later isolated among individuals in the community (Chuang and Huang, 2013). This led to a scenario where increased resistance to penicillin were observed from the late 1940s until the early 1960s when a semi-synthetic homologue of penicillin called methicillin was introduced into the clinics as a strategic drug of choice for the treatment of *S. aureus* infection (Jevon, 1961). However, resistance development to methicillin in *S. aureus* was reported within a year of its introduction as a strategic drug of choice for the treatment of *S. aureus* infection.

Methicillin resistant *S. aureus* (MRSA) arises because of the acquisition of a genomic island carrying methicillin resistance determinant, *mec*A. Ever since its discovery in the early 1960s in the UK, methicillin resistant *S. aureus* have gain global notoriety as the most common cause of human, community and livestock associated infections worldwide. Thus, leading to a reduction in the therapeutic value of many critically important antibiotics and prolonging the length of hospital admission (Purrello et al., 2011). Over the past decades, MRSA has evolved, and this could probably be due to clonal expansion of previously existing clones and from the conversion of methicillin susceptible *S. aureus* (MSSA) to MRSA. This is a sequel to the acquisition of a methicillin resistance determinants coding for an alternative penicillin binding protein with reduced or less susceptibility to all classes of beta lactams antibiotics (Noto et al., 2008). This review focused on the mechanism of antimicrobial resistance in *S. aureus*.

Classification of staphylococcus aureus

Staphylococcus aureus is a gram-positive non-motile, non-spore forming facultative anaerobe that is biochemically catalase and coagulase positive. It occurs as an irregularly grape-like cluster and sometimes singly or in pairs, typical colonies are smooth raised yellow to golden yellow color and hemolytic on blood agar containing 5% sheep or horse blood (Turnidge et al., 2008; Plata et al., 2009).

To date, there are about 40 Staphylococcal species that have been reported, nine of them have two subspecies while one has three subspecies (Doskar et al., 2010). The classification of Staphylococci is not complete yet; new species undergoing validation are still being reported. While some members are important to human medicine, others are relevant to veterinary medicine as they are found in animals or food. Biochemically members of the genus are grouped into two; such as coagulase positive staphylococci and coagulase negative staphylococci. *Staphylococcus aureus* being the most important member of coagulase positive staphylococci causing infection in both humans and animals and are considered as the most pathogenic members of the genus staphylococci (Turnidge et al., 2008; Doskar et al., 2010). Other coagulase positive staphylococcus includes *Staphylococcus intermedius, Staphylococcus hyicus, Staphylococcus pseudintermedius, Staphylococcus lutrae, Staphylococcus schleiferi subspecies coagulans*, and *Staphylococcus delphini* which were mostly isolated in animals (Turnidge et al., 2008; Doskar et al., 2010). Le Loir et al. (2003), reported the classification of *S. aureus* into six different biotypes per their source and biochemical properties these includes; human, non-β-hemolytic human, bovine, ovine, avian and nonspecific.

Morphology and biochemical characteristics of Staphylococcus aureus

The word staphylococci were derived from two Greek words *staphyle* which means "bunch of grapes" and *coccus* which means "spherical bacteria" while *aureus* is a Latin word that stands for "gold" and was given to these bacteria because of yellow to yellowish white colonial appearance on enriched medium (Freeman-cook and Freeman-cook, 2006). *Staphylococcus aureus* is a gram positive non-motile, non-spore forming, facultative anaerobe and pathogenic member of the genus staphylococci approximately 1μM in size (Plata et al., 2009). It forms golden colonies on rich medium and hemolysis on blood agar containing 5% sheep and horse blood due to production of carotenoids and β-hemolysin, on gram staining it appears as bluish grape-like colonies because cell division occurs at different planes (Plata et al., 2009). *Staphylococcus*

aureus is catalase-positive, a unique feature that differentiates it with *Streptococcus* spp., it is oxidase-negative therefore requiring certain important amino acid and B vitamins for growth and can also tolerate high salt concentration. The cell wall is made up of peptidoglycan which contains crosslinks of glycine residue that allows sensitivity towards lysostaphin (Plata et al., 2009; Lindqvist, 2014).

Adaptation of Staphylococcus aureus

Members of the genus Staphylococci are ubiquitous and highly versatile, they are found on the skin, mucous membranes, skin glands, soil, water and air (Freeman-cook and Freeman-cook, 2006). *Staphylococcus aureus* is a very hardy organism and can survive on dry surfaces over a long period; it is resistant to desiccation and can survive high level of salt concentration a basis for selection on growth media from other bacteria (Bremer et al., 2004; Wilkinson et al., 1997). The bacteria can grow on a varying range of temperature from 15 to 45 ºC. Being a facultative anaerobe, they are capable of oxidative fermentation to produce energy and lactic acid. It is one of the most important pathogenic members of the genus Staphylococci and a leading cause of nosocomial, community and livestock associated infection (Bloemendaal et al., 2010).

The stability and worldwide spread of this pathogen is due to its' ability to rapidly acquire and loss resistance and virulence determinants from other members of the genus Staphylococci through horizontal transfer of mobile genetic elements (MGEs) (Bloemendaal et al., 2010; Basset et al., 2011; Bitrus et al., 2017). Studies on whole genome sequence has revealed that the *S. aureus* genome is divided into a relatively stable core genome which is about 75-80% of the entire genome and a relatively less stable mobile genetic element (MGE) consisting of transposons, pathogenicity island, Staphylococcus cassette chromosomes, plasmids, bacteriophage and insertion sequence (Lowy, 2003; Holden et al., 2004). The MGEs in *S. aureus* are lineage specific and freely integrate, recombine and transfer in and out of genome via horizontal transfer (Lindsay, 2014). They encode a wide array of resistance and virulence gene and immune evasion genes, thus facilitating successful adaptation of MRSA and emergence of new and highly resistant and pathogenic clones.

Development of antimicrobial resistance in Staphylococcus aureus

Staphylococcus aureus offers a better and more robust model to understanding the complexity of the adaptive advancement of bacteria in the face selective antibiotic pressure. These pathogens have manifested a novel ability to speedily respond to the challenges posed by new antibiotics via the evolution of new antimicrobial resistance mechanisms. Resistance developments in these pathogens occur via alteration of the drug target site, enzymatic inactivation of the antimicrobial agent, efflux pump and sequestration of the antimicrobial agent (Figure 1). Other resistance mechanisms have developed through acquisition of resistance determinants, position selection and spontaneous mutation (Pantosti et al., 2007; Bitrus et al., 2017).

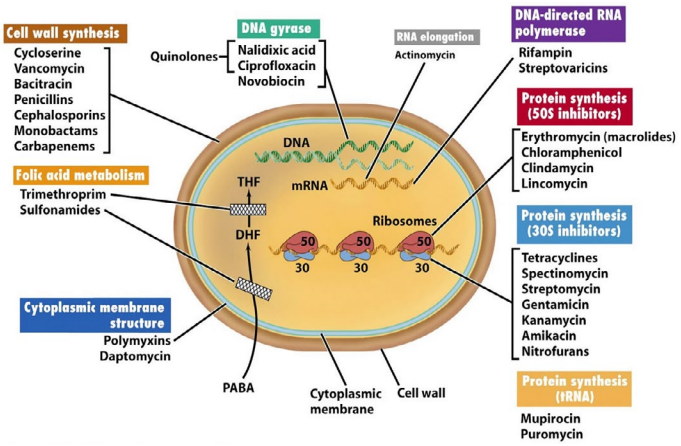

Figure 1: *Schematic representation of antibiotic class and mechanism of antibiotic resistance in bacteria (Adopted from Labnotesweek4, 2013).*

Staphylococcus aureus have a highly clonal core genome that is categorized into lineages characterized by clonal complexes. The pathogens are also categorized based on their epidemiological features as nosocomial, community and livestock associated *S. aureus*. In addition, to the core genome, the pathogen possesses a highly divergent and remarkably variable mobile genetic element. More than 15% of the *S. aureus* genome is made of up mobile genetic elements (MGEs) such as staphylococcus cassette chromosomes (SCCs), bacteriophages, integrons, integrative conjugative plasmids, transposons and pathogenicity island. All these MGEs but, bacteriophages may carry antimicrobial resistance genes. Majority of *S. aureus* clinical isolates possesses a plasmid that ranges from 1 to 60kb in size and these plasmids are known to carry variable numbers of resistance genes. Resistance to tetracycline, chloramphenicol and erythromycin are carried by small plasmids while, large plasmids carry multiple drug resistance genes to aminoglycosides, beta-lactams and macrolides. Additionally, larger plasmids also integrate with other MGEs such as

transposons and confer resistance to spectinomycin, trimethoprim, erythromycin, beta lactams and vancomycin (McCarthy and Lindsay, 2012; Haaber et al., 2017; Bitrus et al., 2017; Planet et al., 2017)

Antibiotic resistance in *S. aureus* predates the era of antibiotics use in clinical practice. Prior to introduction of penicillin, mortality because of invasive *S. aureus* infection was very high. However, penicillin had a significant effect in reducing the rate of mortality because of *S. aureus* infection, not until 1942 when a strain of *S. aureus* resistant to penicillin was identified first in the hospital and then from the community (Oliveira et al., 2002). The use of penicillin as a drug of choice in the treatment of *S. aureus* infection was very effective until the mid-1950s when the number of *S. aureus* resistant to penicillin significantly increased leading to a decrease in the therapeutic value of penicillin (Oliveira et al., 2002). Freeman-cook and Freeman-cook, (2006) reported that about 90% of *S. aureus* are penicillin resistant. Resistance to penicillin was acquired via acquisition of plasmids coding for beta lactam resistance (Deurenberg et al., 2007). The greatest challenge to the treatment of *S. aureus* infection is in the selection of the appropriate therapeutic agent. This is because the pathogens have the potentials of developing resistance to almost all classes of antibiotics (Figure 1). The understanding that antibiotic resistance in *S. aureus* predates the era of antibiotics use in the clinic validates the challenges experienced because of resistance development in recent times. Prior to introduction of penicillin, mortality because of invasive *S. aureus* infection was very high. However, with the introduction of penicillin into clinical practice in the 1940s there was a significant reduction in the rate of mortality because of *S. aureus* infection (Oliveira et al., 2002). This was however short-lived in 1942 when a strain of *S. aureus* resistant to penicillin was identified first in the hospital and then from the community (Basset et al., 2011). Resistance to penicillin is mediated by *bla*Z gene which codes beta lactamase enzymes. Beta lactamase are extracellular enzymes synthesized on exposure to beta lactams class of antibiotics, it hydrolyses the beta lactam ring thereby reducing the therapeutic effect of penicillin (Lowy, 2003).

Methicillin resistant determinant *mec*A is located on large 25-65kb mobile cassette chromosomes called SCC*mec* that facilitates the horizontal transfer of resistance determinants in and out of the bacteria (Chambers, 1997). In addition, it was reported that the acquisition of *mec*A seems to have occurred independently in several *S. aureus* strains, with some clonal lineages having the propensity to colonize specific species and may be adapted to either humans or animals. Other lineages have less host-specificity and can infect a wide variety of species (Bitrus et al., 2018). Moreover, transfer and worldwide dissemination of antibiotic resistance determinants among clinically important bacteria and their mobile genetic element have long been observed to have occurred between bacteria of the same and different clusters (Khan et al., 2000; Wielders et al., 2001; Sabet et al., 2014; Bitrus et al., 2016a). Some studies have also demonstrated the role of horizontal gene transfer in rapid acquisition and dissemination of antibiotics resistance determinants in *S. aureus* (Khan et al., 2000; Barlow, 2009; Sabet et al., 2014; Bitrus et al., 2017). The report of Huddleston, (2014) and Lindsay, (2014) further gives credit to these findings where they reported the role of horizontal gene transfer events in ensuring wide genetic variability as well as successful adaptation between bacteria through high transfer frequency of resistance determinants.

The evolutionary origin as well as detailed mechanism of transfer of *mec*A is not fully understood (Barlow, 2009; Hanssen et al; 2004). However, studies on *Staphylococcus sciuri* and *Staphylococcus hominis* have revealed the presence of methicillin resistant determinant *mec*A with 88% similarity in sequence of amino acid and 80 % DNA sequence identity to the *mec*A gene of MRSA (Wu et al., 1998). In addition, transfer of methicillin resistance has been observed to have occurred both *in vitro* and *in vivo* from *Staphylococcus epidermidis* to *S. aureus* indicating the role of coagulase negative Staphylococci serving as reservoirs of *mec*A (Forbes and Schaberg, 1983; Khan et al., 2000). Furthermore, it has been observed that, the most common pathway of gene transfer events in *S. aureus* is generalized transduction, however transformation and conjugative plasmid transfer have been observed to have occurred too (Lacey, 1975 ; Khan et al., 2000; Huddleston, 2014; Lindsay, 2014). Similarly, only i*n vivo* conjugative plasmid transfer has been reported to be significant (Khan et al., 2000). Conjugative transfer of resistance determinants in *S. aureus* is known to be mediated by conjugative plasmids; however, transfer of resistance determinants in the absence of conjugative plasmids have been reported to have occurred (Forbes and Schaberg, 1983).

Most studies on transfer of antibiotic resistance in human *S. aureus* strains have indicated coagulase negative staphylococci (CoNS) as reservoirs of resistant determinants (Forbes and Schaberg 1983; Wu et al., 1998; Khan et al., 2000). Similarly, studies on antibiotic resistance transfer between human and animal isolates were reported to occur, indicating the importance of resistance transfer in the dissemination and successful adaptation of methicillin resistant S. *aureus* (Khan et al., 2000; Sabet et al., 2014). The rapid spread of resistance between bacteria has been one of the factors limiting the production of new antibiotics to curb the increasing impact of antibiotics resistance on healthcare cost (Barlow, 2009).

Resistance to β-lactams

The common most important inhibitory target site for beta lactams antimicrobials in *S. aureus* is the two-way functional transglycolylase-transpeptidase PBP2. The domain containing the transglycosylase of the enzyme coordinates the transfer of disaccharide pentapeptide raw material of peptidoglycan from membrane-bound lipid II to budding polysaccharide chains. The domain containing the transpeptidase helps to connects to the glycine cross-bridge of the fourth D-alanine of a chain adjacent to it (Walsh, 2016). Members of this class of antibiotics includes, penicillin, oxacillin, methicillin and cephalosporin. They act by inhibiting the transpeptidation step of the peptidoglycan synthesis, which they achieve by binding and inactivation of the penicillin binding proteins in the bacterial cell wall (Page, 2012). Resistance development in *S. aureus* to beta lactams occurs through the acquisition of a genomic island called staphylococcus cassette chromosome (*SCCmec*) carrying methicillin resistance determinant *mec*A (Noto, 2008; Bitrus et al., 2018). This in turn codes for an alternative penicillin binding protein with reduced or less susceptibility to methicillin. In addition, resistance to penicillin was acquired via acquisition of plasmids coding for beta lactam resistance (Noto, 2008). Penicillin resistance is mediated by blaZ gene which codes for beta lactamase enzymes. These genes are regulated by two differently transcribed genes known as *blaI* and *blaRI* (Page, 2012). Beta lactamase are extracellular enzymes synthesized on exposure to beta lactams class of antibiotics, it hydrolyses the beta lactam ring thereby reducing the therapeutic effect of penicillin.

Resistance to vancomycin

Vancomycin is considered as a strategic drug in the treatment of *S. aureus* infection (Bitrus et al., 2016a). It acts by inhibiting the transpeptidation of the peptidoglycan layer in the bacterial cell wall by binding to the C-terminal D-ala-D-ala of the peptidoglycan stem pentapeptide, resulting in the prevention of interaction between the penicillin binding proteins and their substrate. *Staphylococcus aureus* develop resistance to vancomycin through two unique independent mechanisms; this includes: VanA mediated resistance and resistance due to thickened cell wall (Woodford, 2005).

Resistance development mediated by VanA is represented by a high level of inducible resistance to vancomycin and is carried by transposon Tn1546 and closely related elements. This type of resistance development is well established in *Enterococcus* species (Weigel et al., 2003). The role of VanA ligase is to connect the D-ala and D-lac by esterification with resultant replacement of the D-ala-D-ala terminal of the pentapeptide stem by depsipeptide formation. Furthermore, since vancomycin has reduced affinity for the D-ala-D-lac terminal, it does not prevent the incorporation of the substrates into the bacterial cell wall. In either case, the concurrent formation of the D-ala-D-ala and D-ala-D-lac pentapeptide stem is not sufficient enough to initiate resistance development to vancomycin (Weigel et al., 2003). However, resistance development occurs when VanX hydrolyses the D-ala-D-ala dipeptide and VanY removes the C-terminal D-ala residue of the pentapeptide stem when hydrolysis of VanX is incomplete, leading to the formation of a modified less susceptible target molecule with simultaneous cleavage of either of the existing D-ala-D-ala pentapeptide stem in the cell wall *S. aureus* (Reynolds et al., 1994).

On the other hand, the mechanism of resistance development as a result of a thickened bacterial cell wall is mostly associated with *S. aureus* with intermediate resistance to vancomycin (Bugg et al., 1991; Bugg and Brandish, 1994). Vancomycin intermediate resistant *S. aureus* (VISA) do not contain the Van gene or any other known determinants of vancomycin resistance but possesses a common phenotype of a thickened cell wall and a ratio of high cell wall to cell wall volume (Srinivasan et al., 2002; McAleese et al., 2006). These types of phenotypes have a cell wall with a characteristically low level of peptidoglycan cross-link as compared with the normal staphylococcal cell wall (Courvalin, 2006). The formation of a thickened cell wall as well as reduced formation of peptidoglycan cross-

links results in the production of an increased volume of D-ala-D-ala peptide stem outside the cell wall leading to reduced uptake of vancomycin into the cell and subsequently resistance (Reynolds et al., 1994).

Resistance to aminoglycosides

Aminoglycosides are bactericidal antimicrobial agents that act by interfering with protein synthesis when it binds to the 30S ribosomal subunit. Resistance development to aminoglycoside occur through in vitro mutation in the ribosomal subunit. Similarly, acquisition of aminoglycoside modifying enzyme have been reported to serve as a medium for the development of resistance to aminoglycosides (Woodford, 2005; Wilson, 2014; Walsh and Wencewicz, 2016).

Resistant development to fluoroquinolones

Antibiotics under this group act by inhibiting transcription and replication of DNA by targeting DNA gyrase enzymes (Topoisomerase II and IV). Studies have shown that resistance development to quinolone derivatives occurs via two pathways that included mutation of the target Topoisomerase II and IV or through efflux pump system. In addition, it has been established that a single mutation in the target does not confer resistance to quinolones, rather it involves a cascade of mutation associated with increased minimum inhibitory concentration (MIC) of fluoroquinolones (Woodford, 2005; Courvalin, 2006). Findings have it that for resistance development to fluoroquinolones to occur; there must be mutation in the genes regulating DNA gyrase (gyrA and B) and Topoisomerase (ParC and ParE). Similarly, for resistance development mediated by the efflux pump to occur in *S. aureus*, it requires a multidrug efflux pump system coordinated by NorA (Zeng et al., 2016; Foster et al., 2017).

Resistance to chloramphenicol, rifampin and mupirocin

This group of antibiotic drugs, functions by interfering with protein synthesis in bacteria through different pathways. While Rifampin inhibit transcription by binding to RNA polymerase, Chloramphenicol acts by binding to 50S ribosomal subunits and blocking the action of peptidyl transferase. Mupirocin however, functions by inhibiting isoleucine tRNA synthetase (Morton et al., 1995; Woodford, 2005; Wilson, 2009; Schwarz et al., 2016). Resistance development to mupirocin by *S. aureus* occur through acquisition of *mup*A gene which codes for a less sensitive tRNA synthetase while resistance to rifampin and chloramphenicol occurs through mutation in the *rpo*B gene that codes for the Beta subunit of RNA polymerase and action of an inactivating enzyme called chloramphenicol transferases which inactivates the drug (Woodford, 2005).

Resistance to linezolid and tetracycline

Linezolid is a synthetic antimicrobial agent that belongs to the oxazolidinone family and act by interfering with protein synthesis by binding to 50s ribosomal subunits to inhibit the formation of 70s ribosomal initiation complex. It is one of the few antibiotics whose resistance in *S. aureus* is rare and is considered as a strategic drug of choice for the treatment of *S. aureus* infection. Resistance development rarely occur but, when it does it is through mutation of the chromosomal gene coding for the 23s rRNA (Woodford, 2005).

Tetracycline on the other hand, is bacteriostatic in nature and acts by inhibiting the formation of protein by binding to 30s ribosomal subunits and blocking of the tRNA from moving into the acceptor site. Resistance development by *S. aureus* occur via two pathways which includes, ribosomal protection or efflux pump system. The protection of the ribosome is encoded by *tetM*, while *tetK* codes for the efflux pump system (Woodford, 2005; Jenner et al., 2013; Nguyen et al., 2014).

Resistance to macrolide, lincosamides and streptogramins-B

The mechanism of antibiotic resistance development in *S. aureus* to macrolide, lincosamides and Streptogramins-B occur via the methylation of their receptor binding site on the ribosomes. It is important to note that even though these classes of antibiotics have similar receptor binding site, they are structurally unrelated. Furthermore, the methylation that happems at their binding site is catalyzed by a methylases enzymes which is encoded by erythromycin methylases enzyme *erm*A, B and C whose expression is either inducible or constitutive. All the three classes of antibiotics are constitutive but only macrolide can induce expression of gene coding for erythromycin methylases *erm* and is also mediated by an efflux pump system encoded by mrsA. This however, does not lead to resistance development to Streptogramins or lincosamides (Woodford, 2005; Wilson, 2009; Mukhtar et al., 2001).

Methicillin resistant Staphylococcus aureus (MRSA)

The developments of antibiotics resistance in bacteria

were reported even before the era of antibiotic use in the treatment of infection (Cox and Wright, 2013). Antibiotics resistance development in *S. aureus* was first reported in the mid-1940s when a strain of *S. aureus* developed resistance against penicillin by the production of a hydrolyzing enzyme called penicillinase (Basset et al., 2011).

Methicillin resistant *Staphylococcus aureus* (MRSA) is an important human pathogen responsible for hospital, community and livestock acquired infection (Aklilu et al., 2013). It is also a leading cause of skin and soft tissue infections in both humans and animals (Lamy et al., 2012; Nowrouzian et al., 2013) and the second most common cause of blood stream infections in nosocomial associated outbreaks with high mortality and increased or prolonged hospital stay (Purrello et al., 2014).

Resistance to methicillin was first reported in the United Kingdom in 1961 not long after the introduction of methicillin for clinical use (Musser and Kapur, 1992). Within a few years, outbreaks of methicillin resistance *S. aureus* were recorded in the United Kingdom and some part of Europe (Hiramatsu, 2004). In the mid-1970s, MRSA was reported to be a significant problem in health care hospitals in the United States. These resistant organisms are now commonly recovered in virtually every large hospital in the United States and other hospitals worldwide (Musser and Kapur, 1992) and have become a significant infection control problem in nursing homes and other chronic healthcare facilities (Musser and Kapur, 1992).

Staphylococcus aureus acquired methicillin resistance through horizontal transfer of *mec*A which codes for a modified penicillin binding protein (PBP') with low or reduced affinity to beta-lactam antibiotics. Methicillin resistant determinant, *mec*A is located on the staphylococcal cassette chromosome mec (*SCCmec*), a large 20 to 65kb mobile element in *S. aureus* that mediates the horizontal transfer of methicillin resistance (Jansen et al., 2006; Ito et al., 2007; Stojanov et al., 2012). Resistance acquisition in MRSA occurs through mutation of the target gene in the chromosomes, through efflux pump system, horizontal transfer of MGEs or enzymatic action of drugs as in the case of penicillin (Alekshun and Levy, 2007). Emergence of bacterial resistance to multiple antibiotics worldwide have made treatment of MRSA infections difficult, although attributed to mutation on the chromosomes, resistance is most commonly associated with extra-chromosomal elements acquired from other bacteria in the environment. However, intrinsic mechanisms not commonly specified by mobile elements such as efflux pumps that expel multiple classes of antibiotics are now recognized as major contributors to multidrug resistance in bacteria. Once established, multidrug-resistant organisms persist and spread worldwide, resulting in failures to treatment of infection (Alekshun and Levy, 2007). High prevalence of MRSA infection is attributed to toxin production, the ability for rapid spread between humans and animals and its ability to acquire resistance determinants to multiple antibiotics (Lamy et al., 2012) leading to an increased burden on healthcare setting due to a limited treatment options. Because of its frequent association with mobile genetic elements, natural resistance genes can be spread rapidly among pathogenic strains and therefore impedes the clinical value of many drugs (Toh et al., 2007).

MRSA is thought to be restricted to the hospital setting, not until the late 1990s when MRSA infection among healthy individuals in the community with no history of hospitalization, intravenous drug use, prior antimicrobial use, and underlying illnesses such as cardiovascular and pulmonary disease, diabetes, malignancy, and chronic skin diseases was reported (Gorak et al., 1999; Charlebois et al., 2004). This new strain called community acquired MRSA were found to be susceptible to only beta lactams antibiotics, harbor different *SCCmec* class (IV and V *SCCmec*) and a phage-borne pantone valentine leucocidin (PVL) toxin incriminated in skin and soft tissue infection in healthy children and adults (Grundmann et al., 2006). Reported a relatively high incidence of community associated methicillin resistant *S. aureus* with *SCCmec* type IVa or V among healthy carrier patients as in the case with penicillin, methicillin resistance *S. aureus* were identified among individuals in the community and more recently in livestock (Bosch et al., 2015). In addition, *S. aureus* strain showing low level resistance to vancomycin have also been observed (Hiramatsu, 1998).

Conclusion

The number of mechanisms inherent in pathogenic bacteria that makes it resilient or hardy in the presence of extreme conditions and confers it with the ability to resist quite a large compendium of important antibiotics and other toxic compounds are becoming ex-

tremely interesting. Over the past six decades, the use of antibiotics for a long period have been observed to ignite a number of biochemical and genetic mechanism in bacteria that allows it to maneuver the detrimental effect of antibiotics found within their immediate environment. Clones of bacteria with acquired or natural resistance characteristics have been used continuously as a form of evolutionary response to the use of antibiotics. It is a well-established fact that the acquisition of antibiotic resistance mechanism occurred because of genetic events causing changes in the primordial bacterial genome such as deletion or substitution of a single nucleotide base and multiplication of a single number of a gene. However, the most important means of persistence of resistance gene, is the horizontal transfer of mobile genetic elements such as transposons, integrons, and plasmids both within bacteria of the same or different species.

Authors' contribution

AAB and MOP conceived the research review, gathered relevant materials and wrote the first draft of the manuscript, MAA and MDG proof read the manuscript. All authors approved the final draft of this manuscript.

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