Dissemination of Resistance and Virulence Determinants in Methicillin-Resistant *Staphylococcus aureus* During Colonization and Disease: A Review

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Abstract | The successful in vivo horizontal transfer of mobile genetic elements carrying resistance and virulence determinants have contributed immensely to a global dissemination of virulent and multi-drug resistant pathogens. The pathogenesis of MRSA infection is enhanced via initial colonization of the skin through the component of the microbial surface antigen recognizing adhesive matrix molecules and by their ability to evade host immune response. Furthermore, it was also observed that the genetic diversity of pathogenic MRSA is due to its’ ability to rapidly acquire resistance and virulence determinants. A characteristic feature that made it one of the most important nosocomial pathogen worldwide. Similarly, the expression of virulence gene in MRSA has been observed to be regulated by the accessory gene regulator system (*agr*). These system is made up of a series of genes whose product build up quorum-sensing regulatory mechanisms that is growth dependent. At a certain growth stage, the *agr* systems triggers pronounced changes in the expression of genes called the quorum sensing. The findings of this review affirmed the importance of horizontal gene transfer in the dissemination of resistance and virulence determinants and as well as the genetic diversity of MRSA.

Keywords | Accessory gene regulators, Colonization, Horizontal gene transfer, Resistance, Virulence

**INTRODUCTION**

The emergence and worldwide spread of methicillin resistant *S. aureus* strains is largely due to horizontal transfer of mobile genetic elements carrying resistance and virulence determinants (Haaber et al., 2017; San et al., 2017). Horizontal gene transfer (HGT) provided the basis for the expansion of previously unsuccessful clones (Kelly et al., 2009; Haaber et al., 2017). Interspecies transfer of Staphylococcal cassette chromosome mec (SCCmec) have been reported to contribute to the spread of resistance and virulence gene (Bloemendaal et al., 2010). The clinical importance of MRSA is due to its’ ability to rapidly acquire and loss resistance and virulence determinants (Lamy et al., 2012). Thus, leading to an increased burden on health care 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).

The emergence of methicillin- resistant *S. aureus* (MRSA)
Nasal colonization is the most important means of disseminating MRSA to other body parts (Al-Talib et al., 2013). This is because evidence abounds that after topical treatment of nasal colonization, corresponding decrease in colonization of other body parts was also observed (Liu, 2009; Klyutmans et al., 1997). Furthermore, Klyutmans et al. (1997) described three types of nasal colonization and these include; persistent carriers which carry a particular strain of MRSA and are observed in about 20–25% of the human population, the intermittent carriers which were found in about 60% of the population and the strains change at varying degree and finally the non-carriers or non-colonised which were observed in 20% of the population. Similarly, it was also observed that persistent carriage was more common in children than adults and the pattern of carriage was observed to change in most individuals between the ages of 10 and 20 years. A number of studies have revealed that quite a large number of the human populations are at great risk of S. aureus infection with some persistently colonized while others intermittently colonized (Oliveira et al., 2002; Sakwinska et al., 2009). For instance, investigation of pig farm dominated areas for nasal colonization of MRSA between farm owners, veterinarians and their non-exposed families as well as 462 pupils revealed that 86% of farmers sampled where exposed and only 4.3% of their family members were observed to carry MRSA with similar spa types belonging to that of clonal complex CC398 found in Pigs. The authors further reported that nasal colonization was observed in 45% of the veterinarians who had contact with pig farms and in 9% of their family who had no history of exposure to pigs. Similarly, 3 pupils out of the 462 pupils sampled were observed to be colonized by CC398 and all were observed to have had history of contact with pigs or living on pig farms. The health implication of this finding is that, CC398 can serve as a potential reservoir for MRSA infection to humans (Cuny et al., 2016).

Higher carriage rates of about 25% to 50% MRSA were reported in persons with skin conditions, patients with the history of prolong hospital admission and indwelling intravascular devices, health-care workers, young children and injection drug users (Chambers, 2001).

It is difficult to ascertain the primary source of infection and the role of a particular virulence factor in the pathogenesis of disease caused by MRSA. This is because virulence determinants present in MRSA have been shown to spread across different patients, health care settings and personnel. In addition, virulence determinants have been observed to work synergistically in initiating a disease process (Mainous et al., 2006). The spectrum of infection associated with MRSA ranges from mild uncomplicated superficial abscess to a more life-threatening conditions such as central nervous disease, necrotic pneumonia, necrotic fasciitis, meningitis, cerebritis, osteomyelitis, pericarditis, myocarditis, urinary tract infections and infection associated with the use of an invasive device (Lindqvist, 2014). Furthermore, MRSA is frequently implicated in cases of skin and subcutaneous infections such as Furunculosis, bo-lus impetigo, cellulitis, mastitis, and folliculitis. Similarly, it is also associated with post-operative wound infection, toxic shock syndrome, scalded skin syndrome and staphyloccocal food poisoning (Cuny and Witte, 2017). The overall mortality as a result of MRSA blood stream infection was 30%. However, the severity of the infection was observed more in children and adults or individuals with immune-related diseases (Liu, 2009). Individuals at risk of infection with hospital acquired-MRSA includes, persons in contact with health care setting, prolong admission, persons with invasive surgical devices and intensive care unit, indiscriminate and prolong use of antibiotics and patients with weak immune system (Salgado et al., 2003). However, a new strain of MRSA without known identifiable risk factors associated with the hospital associated MRSA was found causing severe infection in healthy individuals in the community (Leiber et al., 2017). In the United states, studies have shown that these strains were replacing the hospital acquired MRSA (Chua et al., 2014). Community-acquired MRSA (CA-MRSA) is the cause of skin and soft tissue infection in children and adults (Maree et al., 2007). In addition, CA-MRSA infection was observed in individuals in overcrowded place, army recruits in training facilities, athletes, and prisoners and in men sleeping with men (Maree et al., 2007). Methicillin resistant Staphylococcus aureus is a highly versatile human pathogen than is also emerging as a potential zoonosis with an incredible adaptive powers (Bitrus et al., 2017). Transfer of resistance and virulence determinants occurs through the horizontal...
transfer of mobile genetic elements (MGEs). That is commonly shared between isolates from same clonal lineage. These have resulted in rapid changes seen in the epidemiology of MRSA strains (Bitrus et al., 2016). Recent reports have also shown that, MRSA is no longer restricted to the hospital setting. Additionally, evidence of clonal replacement at a higher frequency is reported, this is because, community acquired MRSA are now been reported as the major cause of hospital acquired infections and in some cases evidence of human colonization with livestock associated MRSA have been reported (Bitrus et al., 2017; Haaber et al., 2017). This wouldn't have been possible without the active role of horizontal gene transfer. Thus, the need for a review on the dissemination of resistance and virulence determinants in MRSA during colonization and disease.

MATERIALS AND METHODS

This review employed the collection of published articles on the “the transfer of resistance determinants and the evolution of new MRSA clones”. The articles were retrieved from Thompson Reuter’s web of science, Springer, Lancet, Scopus, Science direct, Pub Med and Wiley. The search was also conducted on other scientifically relevant database. Words and phrases such as Methicillin resistant Staphylococcus aureus, Clonal evolution of MRSA, Pathogenesis of MRSA and gene acquisition in MRSA were used. All articles used in this review were appropriately cited in the bibliography.

ACQUISITION OF RESISTANCES DETERMINANTS AND THE EVOLUTION OF NEW MRSA CLONES

Proliferation of bacterial pathogens from a previously unexploited habitat leading to emergence of new strains and diversification of the natural population was made possible through Horizontal gene transfer (HGT) (Kelly et al., 2009; Haaber et al., 2017). The concept of horizontal gene transfer was first demonstrated by Griffiths in 1928 where he transferred virulent determinants between pneumococci in mice (Kelly et al., 2009). The emergence of MRSA from MSSA through horizontal acquisition of SCCmec carrying methicillin resistance determinants mecA has greatly increase research interest in the study of MSSA (Lindqvist, 2014; Bitrus et al., 2017). Horizontal transfer of mobile genetic elements carrying resistance and virulence gene occurs at a higher frequency between strains of the same cluster while limited between strains of different clusters (Rapacka-Zdonczyk et al., 2014). In addition, successful in vivo horizontal transfer of mobile genetic elements carrying resistance and virulence determinants have contributed immensely to a global dissemination of virulent and multi-drug resistant pathogens (Bloemendaal et al., 2010; Corvaglia et al., 2010).

In *S. aureus*, generalized transduction, conjugation and transformation are the processes involved in the transfer of bacterial DNA from one cell to another. However, generalized transduction is likely to be the main medium of transfer of DNA between strains of *S. aureus* as it possess many phage required for transfer and it is very efficient in the laboratory (Lee, 1995; Corvaglia et al., 2010; Lindsay et al., 2014; Bitrus et al., 2017; Haaber et al., 2017; Rahimzadeh et al., 2017). Host specificity have been reported in the bacteriophage of *S. aureus* and this explains why *S. aureus* mobile genetic elements are rarely found in other species or genera. The phage genomes is 45kb in size and are known to code for bacterial virulence determinants such as enterotoxins A and Panton valentine leucocidin while others encode chemotaxis inhibitory protein or complement inhibition proteins a strategy that helps the bacteria escape host immunity (Lindsay, 2014; Stanczak-Mrozek et al., 2017; Cafini et al., 2017; Rahimzadeh et al., 2017). Central to evolution of virulent strain, is the transfer of toxin genes phage conversion or lysogenic bacteriophage (Kelly et al., 2009). Restriction and modification system most especially type I are the barriers to gene transfer in MRSA, even though CRISPR (clustered, regularly interspaced palindromic repeats) also played a role but at a lower frequency (Lindsay, 2014). New clones of MRSA will continue to evolve because of selective pressure exerted upon them by the environment and horizontal gene transfer. Methicillin resistant *Staphylococcus aureus* is constantly evolving and increasingly becoming a global threat, the pathogen is no longer restricted to the hospital setting as previously reported Aires-de-Sousa, (2017). This is because, MRSA has been isolated among individuals without the apparent identifiable risk factors of MRSA acquisition. Additionally, colonization with Livestock Associated MRSA (LA-MRSA) have been reported among Veterinarians, farmers and personnel working in close contacts with animals (Kwoji et al., 2017). The reservoir of MRSA is also expanding and cases of colonization of animals and other food sources from animals have also been reported (Ge et al., 2017). Recently, there is an increasing report of human colonization and infection with LA-MRSA. Even though this is commonly reported among veterinarians and other personnel working in close contact with animals, LA-MRSA colonization of individuals without prior contact with animals have been reported (Doulgeraki et al., 2017). The major clonal complex commonly shared between animals and humans is the CC 398 which was predominantly reported in pigs. However, Poultry and other animals have been reported to serve as reservoirs of colonization and infection with CC 398. In a study conducted by Tang et al. (2017) using n= 145 meat samples consisting of n= 102 from chickens, n=23 from turkey and n= 20 from pork meat showed that 13% (19/145) of the isolates were MRSA which corresponds to the prevalence of 52% in Turkey, 15 % in pork and 4 % in chickens. Genetic profiling of the isolates showed that 68%
of the MRSA belongs to CC 398, 1% of which were from chickens. Spa typing also showed that 16% of samples collected from Turkey belong to t1430 CC9. Additionally, 16% of the samples collected from chickens are associated with spa type t008 belonging to clonal complex CC8. The isolation of MRSA from food animals poses a serious health risk. This also indicated how horizontal transfer of mobile genetic element and transposon between bacterial cells contribute to the spread of MRSA. In addition, recent findings also indicate a link between MRSA carriage in livestock and infection in individuals who have close contact with animals (Springer et al., 2009). Similarly, Petersen et al. (2013) reported that inter-specie transmission of MRSA between human and animal reservoirs may have been achieved by host adaptation as well as to selective pressure to antibiotics. Isolation of MRSA have also been reported in variety of domestic animals such as cats, dogs, pigs, sheep, chickens and horses leading to a sudden increase in reports and interest in colonization with MRSA and infection in animals (Leonard and Markey, 2008; Saleha and Zunita, 2010; Aires-de-Sousa, 2017). Luzzago et al. (2014) reported that t1328 and ST22 isolates obtained from the liver of the chamois kid was a methicillin-resistant S. aureus (MRSA) harbouring SCCmec cassette type IV. Furthermore, Price et al. (2012) reported that MRSA ST398 initially originated as methicillin susceptible S. aureus in humans which was later transmitted to pigs where it acquires methicillin resistance and is now seen re-infecting humans. In 2011, García-Álvarez et al. (2011) reported the isolation of S. aureus in cattle and humans with a new homologue of SCCmec designed as SCCmecC. Subsequently, increasing numbers of reports have been published on MRSA infection and colonization in both companion and food-chain animals showing MRSA as an important veterinary and zoonotic pathogen (Obaidat et al., 2017). Molecular typing showed that some animal lineages are host specific while others are able to colonize or infect a wide variety of animals including humans. Studies on the clonal evolution of MRSA has shown that some MRSA lineages are host specific while others are not (Bitrus et al., 2016; Aires-de-Sousa, 2017). The isolation of MRSA from pets in the late 1990s provided sufficient evidences in the clonal dissemination of the pathogen, this is because, prior to this, MRSA is hardly isolated from pets. However, cases of human to pet transmission at a high frequency have been reported. In Australia, Malik et al. (2006) reported the isolation of HA-MRSA (ST239-III) in dogs. In another studies conducted in UK and Portugal, the authors reported the occurrence of EMRSA-15, ST22-IV isolates that is commonly associated with human nosocomial infection. This is suggestive of human to animal transmission. (Coelho et al., 2011; Wedley et al., 2014). Interestingly, Lin et al. (2011) reported that more than 50% of the MRSA strains isolated from pets in the North-eastern and Midwestern states of the United States of American

Host Colonization, Disease Pathogenesis and Gene Regulation in MRSA

Methicillin resistant S. aureus being an important pathogen of veterinary and public health significance and regarded as one of the most frequent causes of hospital, community and livestock associated infection. The pathogen is highly versatile and is considered as a potential emerging zoonosis (Saleha and Zunita, 2010; Obaidat et al., 2017). The diversity and emergence of pathogenic methicillin resistant S. aureus is due to its’ ability to rapidly acquire resistance and virulence determinants. This characteristic feature, is what gives MRSA the potentials of causing a wide range of infections in the host in different habitats worldwide (Bitrus et al., 2016). The successful adaptation and difference in pathogenic potentials is largely due to the presence of a variety of coordinated virulence gene (Shaw et al., 2004). To establish or initiate a disease process the virulence of S. aureus functions basically to promote adherence and invasion of host tissue, evasion of the host immune systems and direct damage and induction of inflammatory process by the actions of the toxins they elicit (Lindqvist, 2014). Survival and multiplication inside the hosts is enhanced through formation of small colony variants, biofilm and production of antiphagocytic microcapsule which prevent opsonisation (Liu, 2009). Furthermore, bacterial surface proteins are produced at the early growth stage while secretion of toxins and enzymes is at the late phase of growth mostly when the growth rate declines due to depletion of resources (Lindqvist, 2014). In most cases, it is difficult to ascertain the role of single virulence determinants in disease pathogenesis, their effect were however cumulative indicating the possibility of the virulence determinants working synergistically (Peacock et al., 2002).

Host colonization provides the basis for initiation of disease process, MRSA are frequent colonizers of the nostrils (Gordon and Lowy, 2008; Doulgeraki et al., 2017). Nasal carriage contributes to dissemination of MRSA to other body parts, this was evident when topical mupirocin was used to treat nasal colonization of MRSA which was followed by a subsequent decolonization of other body parts. Similarly, studies on bacteraemia revealed that 82% of S. aureus isolated from blood samples were identical to those
In MRSA, invasion and adherence to nasal epithelium is mediated by an aggregation of bacterial protein molecules called the Microbial surface component recognizing adhesins macromolecules (MSCRAM) clumping factor B and cell wall associated teichoic acid (Liu, 2009). Furthermore, it is important to note that colonization does not necessarily mean infection. Previous studies have shown that colonization of the epithelium leads to the activation of a quorum sensing system called the accessory gene regulator (agr) which regulates the expression of the virulence gene (Liu, 2009). Methicillin-resistant S. aureus can evade neutrophilic-killing by secreting two molecules, Chemotaxis Inhibitory Protein (CHP) and Extracellular adherence protein (Eap). These molecules help to block neutrophil recognition of chemotactic factors and neutrophil binding to endothelial adhesion molecule ICAM-1 which subsequently leads to leukocyte adhesion, diapedesis, and extravasation from the bloodstream to the site of infection (Liu, 2009). Other virulence factors involved in disease pathogenesis includes the exotoxins such as the Panton valentine leucocidin toxin, alpha and beta hemolysin, superantigens and enzymes (Plata et al., 2009).

The pathogenesis of infection with MRSA begins with an initial colonization of host skin and mucosal surfaces. It involves bacterial attachment to host cells often through components of the extracellular matrix MSCRAMMS (microbial surface components recognizing adhesive matrix molecules) and the ability of the organism to evade the host immune response (Gordon and Lowy, 2008). The pathogenesis is mostly associated with expression of several virulence determinants such as the Panton–valentine leukocidin (PVL) a bi–component cytolytic toxin of the synergomenotropic family whose lytic activity is restricted to polymorph nuclear cells, monocytes and macrophages in humans and animals and multiple resistances to antimicrobials, mostly carried on a carried on a mobile genetic element (MGEs) on the MRSA genome (Pantosti et al., 2007). The past decades have witnessed an intense research activity in the aspect of molecular studies of MRSA virulence. This is due to the emergence of a highly pathogenic community associated MRSA strain with an exceptionally high rate of resistance spread and virulence. Similarly, the past decade also witnessed the identification of another unrecognized virulence factor the phenol soluble modulins (Psm) peptide and the presence or absence of accessory gene regulator (agr). Thus, indicating the persistent nature of the HA-MRSA in the health care setting. The formation of biofilms by some strains of MRSA deficient in agr was also observed to have exacerbated the magnitude of infection within the biofilm matrix; MRSA can withstand the therapeutic effect of some antibiotics and also evade the host defence system by adhering to indwelling catheters, implants, and prosthetic heart devices through the formation of biofilm (Liu, 2009; Doulgeraki et al., 2017). Virulent species of MRSA causes severe disease, which can be fatal (DeLeo FR et al., 2010) with a high morbidity and mortality.

The accessory gene regulator forms the basis for the expression of genes inMRSA (Balaban et al., 2000). The agr locus is made up of two divergently distinct transcribed operon identified as RNAII and RNAIII. However, it is the RNAII operon which contains the agr BDCA gene coding for signal transducers (AgrC) and response regulator (AgrA), AgrB and AgrD that are involved in the generating signal molecules that initiates Quorum sensing (Balaban et al., 2003). In addition, the survival of S. aureus has been observed to be dependent upon the agr system regulating quorum sensing and promotes initiation of cellular adhesion necessary for the formation of biofilm. The expression of these virulence determinants are under the control of a quorum sensing system called the accessory gene regulator (agr) (Booth et al., 1997; Cheung et al., 2011). The accessory gene regulator system (agr) of S. aureus is made up of a series of genes whose product build up quorum-sensing regulatory mechanisms that is growth dependent. At a certain stage of growth, the agr systems triggers a pronounced changes in the expression of genes called the quorum sensing (Balaban et al., 2001). In addition, the agr system also helps in the upregulation of virulent determinants such as the protease, nucleases and lipases and down regulate the expression of surface binding protein (Liu, 2009; Cheung et al., 2011) specific to certain set of virulence determinants. The use of animal models have enhanced the knowledge on the role of agr system in the pathogenesis of disease. For example, agr mutant strains of MRSA have been demonstrated to produce an attenuated virulence. The authors also reported that, rapid burst in the agr within 3 hours of S. aureus infection in the

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In another development, since agr quorum sensing has been shown to be responsible for the initiation of biofilm formation. Studies have reported the role of biofilm in facilitating the spread of antibiotic resistance and virulence determinants through horizontal gene transfer (Fux et al., 2005). This finding was however argued by some school of thoughts whose assertions were that the resistance characteristics of *S. aureus* in biofilm is independent of antibiotics resistances acquisition due to plasmids, transposons and insertion sequence or efflux pump system. But rather due to the nature of the metabolites they elicit and the heterogenic nature of the pathogens that made up the biofilm. This they were able to prove by harvesting the organisms in the biofilm and testing them with the same antibiotics they were resistant to in the biofilm. Furthermore, in another study, down-regulation of the agr locus or agr mutant strains of *S. aureus* have also been reported to persist in their resistance characteristics (Fux et al., 2005). A possibility that the loss or down regulation of the agr locus compensate for resistance development. Other authors were of the opinion that since agr is known to regulate gene expression, it is likely that it also helps to regulate the spread of resistance. While others believed that since the whole concept of quorum sensing is to initiate cell to cell contact that will ultimately lead to the creation of a multicellular niche. It can be argued out that this close association will enhance gene transfer processes like transformation and conjugation.

It has been established that majority of severe diseases caused by biofilm-associated *S. aureus* infection were under the of agr quorum sensing system (Balaban et al., 2003). In addition, studies have also revealed the relationship between persistent bacteremia and resistance to methicillin (Raffa et al., 2005). Furthermore, loss of agr activity has been linked to resistance to methicillin and vancomycin indicating a kind of compensatory mechanism between loss of virulence and resistance (Balaban et al., 1998; Raffa et al., 2005). Similarly, studies carried out in MRSA with type II SCCmec type have been shown to have decreased expression of cytolytic toxins as compared to MRSA with type IV SCCmec (Stewart et al., 2001). Hence the indication that specific SCCmec elements regulates the expression of toxins. In addition, other studies carried out indicate that expression of penicillin binding protein results in decrease expression of agr operon. Furthermore, deletion of mecA in a strain of MRSA leads to restoration of the agr activity (Tseng and Stewart, 2005). Even though the above studies did not directly portrays the role of agr operon in the dissemination of antibiotic resistance. It can be inferred that the trade-off between loss of agr locus and gain of resistance and virulence determinants is as a result of the transfer and loss of resistance initiated by the quorum sensing mechanism.

**MRSA IN ANIMALS AND ITS PUBLIC HEALTH AND ECONOMIC IMPLICATIONS**

Methicillin resistant *S. aureus* (MRSA) is an important aetiology of a wide range of infections in humans and animals. Recently higher rate of colonization with MRSA in animals have been reported (Kwon et al., 2006; Lee, 2003). Although the first report of MRSA isolation in animals dates back to the early 1970s when MRSA was isolated from a case of mastitis in cows (O’Mahony et al., 2005). Since then, MRSA colonization has been reported in various species of animals such as dogs and cats, pigs and rabbits, chicken, cattle, sheep and horses (De Boer et al., 2009; Larsen et al., 2012; Lee, 2003, Bitrus et al., 2016; Bitrus et al., 2017). Depending on the study design, the estimated carriage rate of *S. aureus* in chickens is about 90%, while 42% in pigs, 29% in sheep, 14% to 23% in cows and up to 35% in heifers with the teats and the muzzle being the most colonized site (Peton and Le Loir, 2014). The spectrum of infections caused by MRSA in animals includes; mastitis in cows, pyaemic dermatitis in dogs, cats and rabbits, arthritis and septicemia in chickens, botryomycosis in mares, cows and dogs and urinary tract infection associated with the production of extracellular toxins and enzymes (Lee, 2003; Zunita et al., 2008; Peton and Le Loir, 2014). The colonization of animals by MRSA have severe clinical consequence. This is because studies have revealed colonized animals are serving as potential carriers of MRSA infection to humans. In addition, low milk yield is reported in cows and sheep with clinical mastitis. Furthermore, *S. aureus* mastitis have been reported to be of great public health significance. This is because studies have revealed colonized animals are serving as potential carriers of MRSA infection to humans. In addition, low milk yield is reported in cows and sheep with clinical mastitis. Furthermore, *S. aureus* mastitis have been reported to be of great public health significance. This is because studies have revealed colonized animals are serving as potential carriers of MRSA infection to humans. In addition, low milk yield is reported in cows and sheep with clinical mastitis. Furthermore, *S. aureus* mastitis have been reported to be of great public health significance. This is because studies have revealed colonized animals are serving as potential carriers of MRSA infection to humans. In addition, low milk yield is reported in cows and sheep with clinical mastitis. Furthermore, *S. aureus* mastitis have been reported to be of great public health significance. This is because studies have revealed colonized animals are serving as potential carriers of MRSA infection to humans. In addition, low milk yield is reported in cows and sheep with clinical mastitis. Furthermore, *S. aureus* mastitis have been reported to be of great public health significance. This is because studies have revealed colonized animals are serving as potential carriers of MRSA infection to humans. In addition, low milk yield is reported in cows and sheep with clinical mastitis. Furthermore, *S. aureus* mastitis have been reported to be of great public health significance. This is because studies have revealed colonized animals are serving as potential carriers of MRSA infection to humans. In addition, low milk yield is reported in cows and sheep with clinical mastitis.
The isolation of MRSA on animal origin have changed the narrative on the epidemiology and clonal spread of MRSA. The emergence of MRSA clone belonging to sequence type 398 in 2005 from healthy pigs and farmers in Netherlands and France stimulated a renewed interest in the study of MRSA of animal origin (Armand-Lefevre et al., 2005; Voss et al., 2005; Bitrus et al., 2016; Ge et al., 2017). Since then, a number of studies have reported the occurrence of livestock-associated MRSA (LA-MRSA) in food animals such as calves, pigs and broilers and in people with frequent contact with animal (Fitzgerald, 2012; Kwoji et al., 2017). For instance, LA-MRSA-398 accounted for more than 20% of the cases of human infection in the Netherlands, this is however, considered as low (Van Rijen et al., 2008). Molecular typing of MRSA have showed that LA-MRSA 398 actually originated from humans as S. aureus strain that is susceptible to methicillin. The report further showed that due to sustained usage of antibiotics in an intensively reared livestock farm, this strain later acquired resistance determinants for methicillin and tetracycline (Price et al., 2012). Thus, indicating the role of frequent and indiscriminate use of antibiotics in the transfer of resistance determinants. Additionally, since this strain was isolated from human cases, revealed the potentials of this pathogen as a zoonotic pathogen. The most predominant MRSA clone isolated in Asia among pigs is the ST 9 (Cui et al., 2009). Other lineage related to livestock associated MRSA included ST1, ST5, ST97, ST130 and ST425 and more recently ST 177 in horse (Fitzgerald, 2012; Zunita et al., 2017). Similarly, a number of studies have revealed the occurrence of ST398, ST5 and ST 9 in the United States of America, this could be attributed to movement of people and meat products especially those coming to Asia as tourist (Molla et al., 2012; Smith et al., 2009; Frana et al., 2013). Livestock associated MRSA is now a major public health issue, stakeholders are becoming increasingly worried because of its potential as a zoonotic pathogen that can be transmitted through the food chain.

Methicillin-resistant S. aureus is a major cause of severe life-threatening infection in animals (Bosch et al., 2015; El-Gendy et al., 2017). The economic implication of disease caused by MRSA is hinged on its ability to rapidly acquire resistance and virulence determinants, cost of treatment, prevention and control and production of antibiotics (Bitrus et al., 2016). Currently, MRSA is the leading cause of death among infants and adult individuals in the United States (Chua et al., 2014). The development of antibiotic resistance occurred immediately after the introduction of antibiotics, this is classically exemplified in resistance development to penicillin and methicillin in 1940s and 1960s respectively (Chambers and De Leo, 2009; Bitrus et al., 2017). Over the years, antibiotic resistance development represented a relatively less challenging situation, since newer classes of effective antibiotics were developed to counteract the threat posed by antibiotic resistant bacteria. However, the recent years saw a significant decrease in the development of new antibiotics with regards to the emergence of multidrug resistant strains of bacteria (Silver, 2011). The gap created, coupled with the absence or lack of improvement of new and effective antibiotics lead to the emergence of highly resistant strains and ultimately increase the rate of spread of antibiotic resistance globally (WHO, 2012). Recently in 2013, the World Economic Forum identified antimicrobial resistance as one of the greatest risk to human health worldwide. The economic implication of disease caused by MRSA result in drastic reduction in productivity and mortality in humans and animals, a classic case of mastitis caused by MRSA in cows will result in severe reduction in milk yield.

CONCLUSION

Horizontal transfer of resistance and virulence determinants forms the basis for the successful expansion of several clones of MRSA. Colonization of the nasal epithelium enhances the dissemination of MRSA to other body parts. Furthermore, it was also observed that colonization of the skin and mucous membrane is the first line of events in the initiation of a disease. Similarly, successful adaptation and difference in pathogenic potentials of MRSA was largely observed to be due to the presence of a variety of coordinated virulence determinants and toxins. Finally, it was also observed that the survival of MRSA is dependent upon the agr system regulating quorum sensing and promoting the initiation of cellular adhesion necessary for the formation of biofilm. Expression of these virulence determinants are under the control of a quorum sensing system called the accessory gene regulator (agr).

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.
AUTHOR’S CONTRIBUTION

The design and execution of this research study is a collective effort of all the authors. All authors were also involved in the critical analysis and review of the manuscript.

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