Zoonotic Aspect of Vancomycin Resistant Staphylococcus Aureus

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ABSTRACT

Staphylococcus aureus is one of the most ubiquitous organisms found all across the globe. They usually colonize the nasal cavity or outer surface of the human body, behaving as a commensal or pathogen according to the conditions. In the past, they were easily fended off by using regularly available antibiotics. This misuse of antibiotics against *S. aureus* soon led to the development of antibiotic resistance in the bacteria. At first, it became resistant to the methicillin group of antibiotics. An alarm was raised among physicians due to the lost effect of methicillin antibiotics and they soon switched to vancomycin. Vancomycin proved effective even in the case of methicillin-resistant bacteria. However, this remedy soon met its end as vancomycin-resistant isolates of *S. aureus* were discovered later on. Although most of the isolates were from animal sources, it still threatened global public health due to the phenomenon of zoonosis leading to the transfer of vancomycin-resistant *Staphylococcus aureus* (VRSA) to the human population. This is a matter of grave concern for the health security of the human population as zoonosis can lead to further aggregation of already rising antibiotic resistance reducing the overall effect of antibiotics. This will in turn produce diseases that will be incurable with the current antibiotics we have available. A forecast of such incurable maladies suggests that humanity will be once again facing the same era of health problems as it faced in medieval times. Commonly curable diseases will become fatal for mankind and life expectancy will begin to reduce considerably. This will halt the progress of humanity pushing us back hundreds of years. Such issues require the implementation of strict rules regarding the prescription and use of antibiotics. Furthermore, stringent regulations should be implemented to prevent the spread of infectious diseases. Reduction in disease prevalence will ultimately lead to less use of antibiotics and hence lower chances of resistance development in bacteria.

Keyword: *Staphylococcus aureus*, VRSA, Vancomycin, Antibiotic, Zoonosis.

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1. INTRODUCTION

Being an opportunistic commensal, *S. aureus* is becoming a significant human pathogen. Life-threatening infections such as endocarditis, osteomyelitis, bloodstream infections, lung abscesses, and sepsis can be brought on by invasive *S. aureus* which is multidrug-resistant. Septic shock can also be produced by *S. aureus*. In contrast to the previously mentioned structural elements, these superantigens can cause a sepsis-like condition by starting a "cytokine storm." According to Ladhani et al. (1999), certain strains also generate exfoliative toxins called epidermolysins, which can result in bullous impetigo or scalded skin conditions. An opportunistic pathogen that may infect both humans and animals, *S. aureus* can cause food poisoning and a wide range of illnesses, from infections of soft and skin tissue to dangerous conditions like pneumonia, endocarditis, osteomyelitis, septicemia, and toxic shock disorders (Chen and Huang 2014). The abuse of antibiotics (e.g., using antibiotics without a prescription, taking antibiotics in excess, and applying medications needlessly) has contributed to a progressive growth in drug resistance in *S. aureus* in recent decades, which has caused bacterial progression (Gharieb et al. 2020; Guo et al. 2020).

2. VANCOMYCIN-RESISTANT *S. AUREUS*

Resistance to vancomycin One of the most frequent germs to colonize human and animal nasal cavities and exterior body surfaces is *Staphylococcus aureus*. *S. aureus* is a type of bacteria that can cause a variety of infectious disorders and can exist as both pathogenic and commensal bacteria (Weese and van Duijkeren 2010). Vancomycin (VAN) is the preferred antibiotic for the treatment of several infections because methicillin-resistant *S. aureus* (MRSA) strains have drawn attention to their public health relevance since they were first identified in 1961 from human patients (Lowy 1998). But when the USA's Centers for Disease Control and Prevention (CDC) reported the first *S. aureus* strain resistant to both methicillin and VAN in July 2002, things took a turn for the worst (CDC 2002). The dromedary camel, also known as the one-humped camel or Camelsus dromedaries, is a significant type of cattle in the Middle East that is adapted to hot, arid climates. In Egypt, camels are regularly killed and their meat is eaten all year round by people. It was previously believed that camels were immune to the majority of diseases that commonly affect cattle. Nevertheless, new research has shown that camels are susceptible to a wide range of pathogens, and as a result, it is now thought that camels serve as a reservoir or carrier for the spread of various zoonoses and transboundary animal diseases (Graveland et al. 2011). For a very long time, vancomycin has been seen as the last option for treating infections of MRSA (Holmes et al. 2015). Overuse of the drug led to the emergence of vancomycin-resistant *S. aureus* (VRSA), vancomycin-intermediate *S. aureus* (VISA), and heterogeneous vancomycin-intermediate *S. aureus* (hVISA) strains (Amberpet et al. 2019). MRSA strains can generate biofilm as a growth and survivability mechanism in addition to their resistance to antibiotics. This capacity is facilitated by the strains' strong compliance, increased drug resistance, and decreased sanitiser efficiency (Brady et al. 2007; Craft et al. 2019). Coagulase negativity With a few rare exceptions, *S. aureus* (CoNS) and *S. aureus* were both susceptible to glycopeptides. These included vancomycin-resistant CoNS, vancomycin-intermediate *S. aureus* (VRSA), and vancomycin-resistant *S. aureus* (VRSA) (Srinivasan et al. 2002; Tenover 2008). The reason for the emergence of vancomycin resistance is the frequent use of antibiotics for infections other than MRSA. The majority of current antibiotics cannot treat VRSA, hence treatment options are limited. The medical

community is concerned about the introduction of VRSA since *S. aureus* can cause potentially fatal infections in both hospitalized and out-of-hospitalized people (Denys and Relich 2014; Limbago et al. 2014). The cell walls of VRSA strains have been seen to be thicker than those of sensitive strains (Daum et al. 1992). Vancomycin is typically sequestered by the bacterium and trapped in the outer layers, which causes resistance (Billot-Klein et al. 1996; Cui et al. 2000).

3. HISTORY OF VRSA

In 1950, Vancomycin, a glycopeptide isolated from *Streptomyces orientalis*, was discovered. In *S. aureus,* there has been an elevated trend in vancomycin resistance. MRSA containing vancomycin resistance and unrestricted use of antibiotic drugs increased the resistance, calling for the need for additional epidemiological studies. Shockingly, the source and spread of VRSA infections are being substantially noticed across the world encompassing the Indian subcontinent. In 2002, the first Vancomycin-resistant variant of *S. aureus* was estimated in the US (CDC 2002). Lately, VRSA strains have also been reported from Brazil (Palazzo et al. 2005) and Jordan (Bataineh 2006). The incidence of MRSA was reported to be 38.7% which was nearly equivalent to the occurrence in different parts of India (Joshi et al. 2013). While VRSA has a low incidence (4.8%), it is threatening that combined MRSA and VRSA will present a greater risk in the treatment of staphylococcal infections (Mendem et al. 2016). Recently, a study (Thati et al. 2011) indicated an increased prevalence of VRSA variants in MRSA that is of greatest concern (Mendem et al. 2016).

4. VRSA GENES TRANSMISSION

It is commonly known that Enterococci and Staphylococci exchange genetic material and that this results in VRSA (Clewell et al. 2002). According to certain theories, people who are susceptible to VRSA get infected or co-colonized with MRSA and vancomycin-resistant Enterococci (VRE), which allows the vanA gene to transfer from VRE to MRSA in a biofilm environment and produce a VRSA strain (Finks et al. 2009). However, an inadequate and unsuitable dosage of vancomycin also plays a role in the development of VRSA (de Vriese and Vandecasteele 2014). While vanY is involved in the transcription of D, Dcarboxypeptidase, which results in greater glycopeptide resistance, the vanH, vanA, and vanX proteins are important in the development of vancomycin-reduced susceptibility. Teicoplanin-like antibiotic resistance is also mediated by another protein, vanZ, albeit the exact mechanism underlying this resistance is yet unknown (Arthur and Quintiliani 2001; Lee et al. 2004; Depardieu et al. 2007). The vanA type revealed decreased susceptibility to vancomycin, which is neutralized by an alternate mechanism that results in the production of a cell wall antecedent terminus in D-Alanyl-D-lactate. This indicates a decline in the attachment of glycopeptides and downshifting of cell wall production via housekeeping enzymes (Arthur and Quintiliani 2001; Lee et al. 2004; Depardieu et al. 2007).

5. ZOONOTIC TRANSMISSION

RTE food is becoming increasingly popular these days, and it can be seen in countless restaurants and on the streets everywhere, most notably in Egypt. Fast food benefits notwithstanding, there is a risk of bacterial disease and a challenge as these RTE products aren't heated anymore *S. aureus*-contaminated raw meat is a major global source of food poisoning (de Boer et al. 2009; Wang et al. 2014; Raji et al. 2016). When the contaminated meat is undercooked or when this bacterium is cross-contaminated with RTE food, the risk of infection increases (Wang et al. 2017). The majority of epidemiological research on

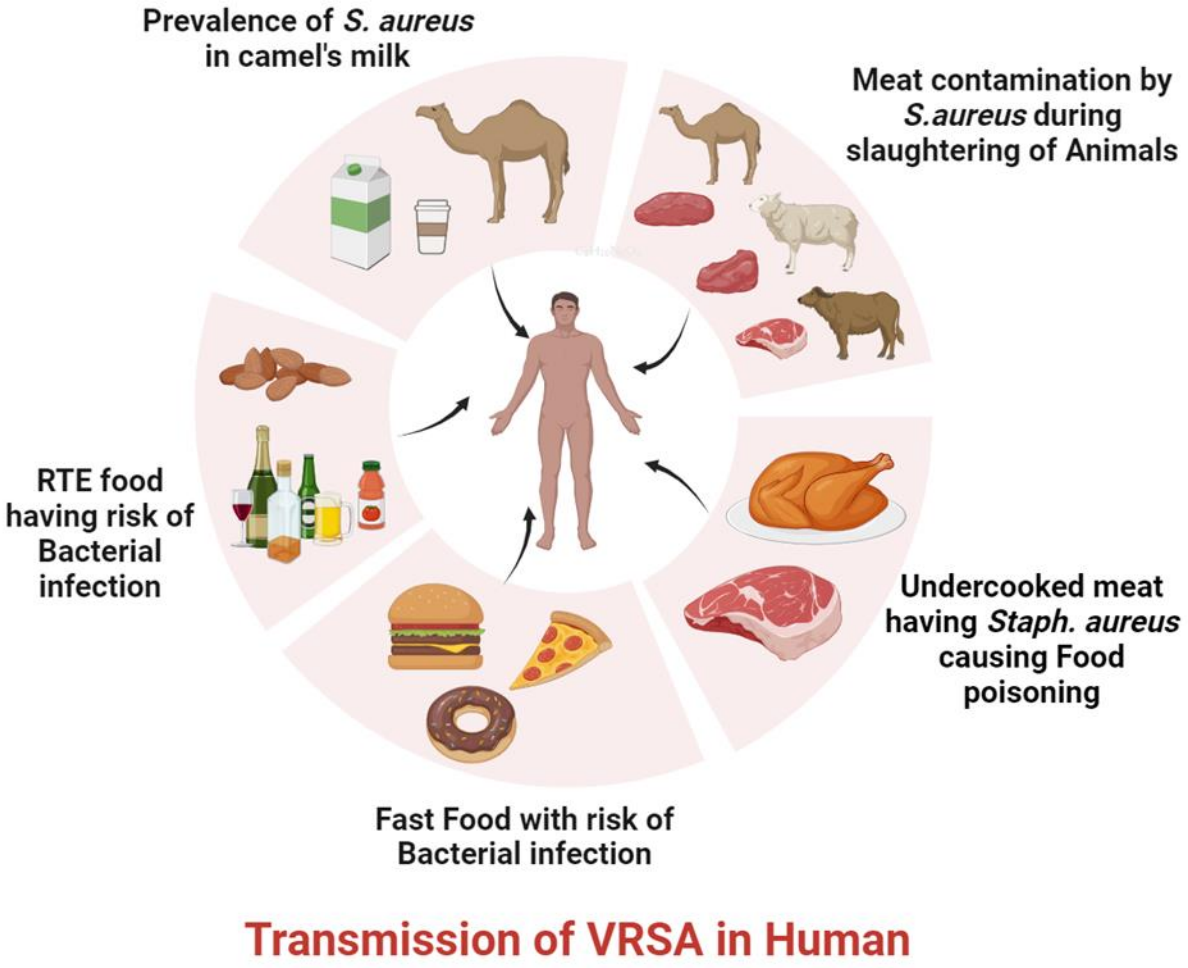

Fig. 2: Zoonotic transmission of Vancomycin-resistant *Staphylococcus aureus*.

resistant *S. aureus* in camels concentrates on the frequency of bacteria in milk (Quddoumi et al. 2006; El Harrak et al. 2011; Mohammad 2011). Few researchers have examined the differences between zoo anthroponotic and anthroponotic transmission resulting from personnel of slaughterhouses or camel breeders getting into contact with camels (Fig. 1). Regarding the distribution, colonization, and transmission of resistant *S. aureus* in camels and their human interactions, there is no data available in Egypt. The purpose of this study was to ascertain whether dromedary camels and abattoir personnel were exposed to VRSA and to investigate the potential zoonotic risk. Generally speaking, VRSA can infect cattle through the ingestion of meat contaminated by viscera during slaughter or by the hands of abattoir workers. Colonization may indicate a potential zoonotic disease risk (Lee 2003; Juhász-Kaszanyitzky et al. 2007). This type of contamination is typically more significant in Asia and Africa than it is in the United States, Canada, or Europe (Pexara et al. 2013).

6. EMERGENCE OF VRSA

When treating multidrug-resistant *S. aureus* and MRSA in healthcare settings, the emergence of vancomycin tolerance has become a major concern (Tiwari and Sen 2006). Assuming the in vitro

exchange of the vanA gene from Enterococcus spp. to *S. aureus*, we estimate the possibility of vancomycin tolerance vanA gene transfer from vancomycin-resistant Enterococci spp. to Staphylococci spp (Whitener et al. 2004). As previous research has shown, the expression of the VanA phenotype depends on the vanA, vanR, vanS, vanH, and vanX genes (Woodford et al. 1998). It has also been found that the cell walls of VRSA isolates are thicker than those of sensitive isolates (Daum et al. 1992). Hetero vancomycin-intermediate *S. aureus* additionally exhibits a thicker cell wall resistance mechanism with a high murein concentration in the cell wall. It has been shown that vancomycin molecules are sequestered by the bacteria and trapped in the outer layers, leading to resistance (Billot-Klein et al. 1996). Transfer of genetic material from one species of bacteria to another is another resistance mechanism for VRSA that has been proposed. According to a theory, people at high risk for VRSA co-colonize and co-infect VRE and VRSA, which facilitates the transfer of the vanA gene from vancomycin-resistant Enterococci to MRSA in a biofilm environment, where it develops into VRSA (Finks et al. 2009). There are only a handful of cases of VRSA found in healthcare environments worldwide, and some of these strains are linked to the population (Whitener et al. 2004). The vanA gene of VRSA was amplified in the current investigation, yet no amplification of the vanA gene suggested that the isolates lacked the gene. It validates the existence of an additional resistance mechanism not dependent on the vanA gene, which requires more research. It is crucial to consider the probability of development and the incidence of VRSA across all populations. Antimicrobial-tolerant microbes like VRSA can be prevented from growing and spreading by using effective contamination control strategies, adequate antimicrobial management, sanitary environments, and increased public knowledge. The reduced susceptibility example of the multi-drug resistant *S. aureus* should be regularly examined. Controlling VRSA infection is crucial because if it isn't, it can cause havoc in both hospital settings and the general community (Riaz et al. 2021).

7. EPIDEMIOLOGY

Recently, human and veterinary medicine have been more interested in the epidemiological distribution of *S. aureus* and its newly discovered strains, mostly due to their potential for zoonosis. Even though the staphylococcal-resistant forms have been known to spread from seemingly healthy pets (Cain 2013) and pigs (Armand-Lefevre et al. 2005), there are no hard data on how common it is in healthy camels or how important a role they play in carrying it. In this investigation, out of 200 dromedary camel meat samples, *S. aureus* was isolated from 14% (29/200); a High isolation rate of 55% (11/20) was also seen in samples obtained from 20 slaughterhouse workers who were directly involved in operations in the investigated facility. Swabs from the carcasses in slaughterhouses in Addis Ababa, Ethiopia yielded comparable rates of isolation of 11.7% (Beyene et al. 2017). However, the incidence of *S. aureus* in the present research was primarily lower than that found in camel nasal samples from Nigeria (20.7%) and higher than that seen in human nasal samples (11.5%) from the same study (Mai-siyama et al. 2014). The issue of antimicrobial resistance has acquired special interest in the African continent over the past decade (Lam et al. 2004). Nonetheless, there's very little information about the actual magnitude of it, as its routine scrutiny is currently being done only in a few countries (WHO 2014).

8. PATTERNS OF MDR IN *S. AUREUS*

In this research, all the isolates of *S. aureus* exhibited distinctive patterns of multi-drug resistance against nine antimicrobial agents. The most dominant resistance patterns were CHL-FOX-OXA-CLI-SXT-ERY-NV for camels and ERY-FOX-OXA-VAN-OFX-SXT for human isolates. The rise of such resistant forms plays a crucial role in therapeutic failure in human and animal diseases. This problem is aggravated by

uncontrolled antibiotic usage, poor diagnostic practices, and improper prescriptions by incompetent physicians (Kimang'a 2012) which creates an enormous hurdle in the prevention and control of the disease agent. Identical resistance patterns were observed by disc diffusion assay in MRSA isolated from emergency care units in Southern India, Hyderabad (Mai-siyama et al. 2014). Furthermore, recently VRSA was reported to be found in a percentage of 16.7 of MRSA forms isolated from skin and nasal samples of buffalo in India using the same method (Kumar et al. 2017). The use of VAN in treating MRSA infections is restricted in both humans and animals due to the issue of antimicrobial resistance, which makes it a last resort (Kumar et al. 2017; Wijesekara et al. 2017). Because of the development of alternative compounds recently, VAN is not the last choice drug anymore; however, it is still the most used antibiotic for the treatment of staphylococcal-related illnesses (David and Daum 2017) In this research, VAN-resistant isolates were also FOX and OXA resistant. MecA gene amplification was performed on all isolates that exhibited resistance to VAN, OXA, and FOX. Consequently, there's a chance that *S. aureus* strains that are more resistant to VAN will arise. Nonetheless, VRSA strains were believed to be rare until recently (Shekarabi et al. 2017).

9. CURRENT TRENDS OF VRSA

The current study on the presence of VRSA in Egypt exposed elevated rates of isolates of VRSA. The prevalence of VRSA was confirmed to be 27.6% (8/29) in dromedary camels and 54.5% (6/11) in human *S. aureus* isolates. Similarly, MRSA was recovered from camel flesh in one study (Quddoumi et al. 2006) and from mastitis female camels in another (Mohammad 2011). Additionally, livestock-associated forms (LAMRSA) have been identified from siblings of the farmers with animal contact (Benito et al. 2014), indicating a possible zoonotic transmission risk to those in contact with animals (Juhász-Kaszanyitzky et al. 2007). Furthermore, previous research in Hong Kong showed that handling meat can result in the acquisition of LA-MRSA (Boost et al. 2013; Ho et al. 2014). It is difficult to compare the findings of our study with previous data from Egypt because, to the best of our knowledge, the incidence of VRSA has never been investigated in camels in the Egyptian region. Five variants of VRSA were identified in our investigation, three of which were human isolates and the other two of which were from camel meat, and all of them demonstrated high-level resistance for VAN (MIC 64 µg/ml). Unsettling evidence of these resistant forms and high VRSA variant prevalence points to a significant public health concern. One mechanism of VAN resistance in *S. aureus* is the conjugation-mediated transfer of a plasmid containing Tn1546 and hence vanA gene cluster from VAN-resistant Enterococcus spp. to *S. aureus* (Saadat et al. 2014). Moreover, vanB has not yet been detected in staphylococci. This study examined the presence of the genes vanA and vanB in *S. aureus* isolates that tested positive for vancomycin (VAN) and discovered that all of the isolates that tested positive for VAN had both genes. According to analyses of VanA gene sequences from camel meat and human samples, the bacteria may have horizontal gene transfer or be of zoonotic relevance (Lee 2003; Juhász-Kaszanyitzky et al. 2007; Boost et al. 2013; Pexara et al. 2013; Ho et al. 2014). VRSA isolates from infected or colonized individuals have been found in Turkey and Asiatic nations (Saha et al. 2008; Cesur et al. 2012; Pahadi et al. 2014). While 4.5% of clinical cases (patients who presented with an evident cutaneous bacterial infection) in Egypt tested positive for VRSA variations, no asymptomatic individuals had these variants detected (ElSayed et al. 2018). Clinical infections may be a major contributor to community-acquired VRSA in Egypt. Even though the front of the nose is commonplace to isolate *S. aureus*, 90% of people also carry the infection on their hands (Wertheim et al. 2005). The lack of nasal swabs from the camels and the workers was a glaring flaw in this investigation; human swabs would have been essential for understanding the colonization and dissemination of VRSA. The requirement to characterize VRSA strains obtained from people and animals

was another deficiency. Additionally, the study hinged on whole genome sequencing, and then core-genome multilocus sequence typing (cg/MLST) was organized with an international laboratory to clarify/assess the zoonotic spread of *S. aureus* in camel butcheries.

10. CONCLUSION

S. aureus is a common bacteria found in commensal or pathogenic relations with its hosts. Recently there has been an emergence of antibiotic resistance among *S. aureus* all across the world. At first *S. aureus* was identified to be resistant to methicillin group antibiotics. At that time Vancomycin was used as the drug of choice against methicillin-resistant *Staphylococcus aureus*. Soon this weapon also became ineffective as *S. aureus* developed resistance against it. These vancomycin-resistant *S. aureus* (VRSA) rendered the antibiotic useless leading to a reduction in the overall effectiveness of antibiotics. This situation was further aggravated as animals became reservoirs of VRSA and its zoonotic transmission prevailed threatening the public health. VRSA was often found colonizing the nasal regions and outer skin surfaces of people who had continuous contact with animals, like pig farmers, veterinarians, etc. These bacteria were also isolated from the family members of such people conclusively proving its secondary prevalence beyond zoonosis.

All of these situations have mainly developed due to the misuse of antibiotics and hence require the implementation of strict policies. Policies should be developed for the use of antibiotics and control of infectious diseases. This will prevent the spread of diseases and simultaneously reduce the usage of antibiotics in turn leading to less misuse of antibiotics. Less misuse of antibiotics will ultimately lower antibiotic resistance among bacteria all over the world hence mitigating the threat of VRSA prevalence among human populations through zoonosis. Such strict control measures have been already implemented in several countries in Europe. In those countries application of control measures was soon followed by a reducing trend of infectious disease prevalence. This trend ultimately led to a pause in the rise of antibiotic resistance among bacteria in those countries. Some of these countries even saw a declining trend of antimicrobial resistance in the bacteria through strict control measures. This proves the importance of control and prevention for disease control which comes before the administration of any kind of antibiotics. It means that if properly implemented, diseases can also be controlled and eradicated through control measures.

REFERENCES

Amberpet R et al., 2019. Detection of heterogeneous vancomycin-intermediate *Staphylococcus aureus*: a preliminary report from south India. The Indian Journal of Medical Research 150(2): 194.

Armand-Lefevre L et al., 2005. Clonal comparison of *Staphylococcus aureus* isolates from healthy pig farmers, human controls, and pigs. Emerging Infectious Diseases 11(5): 711.

Arthur M and Quintiliani R Jr, 2001. Regulation of VanA- and VanB-type glycopeptide resistance in Enterococci. Antimicrobial Agents and Chemotherapy 45(2): 375-381.

Bataineh HA, 2006. Resistance of *Staphylococcus aureus* to vancomycin in Zarqa, Jordan. Pakistan Journal of Medical Sciences 22(2): 144.

Benito D et al., 2014. Characterization of tetracycline and methicillin-resistant *Staphylococcus aureus* strains in a Spanish hospital: is livestock contact a risk factor in infections caused by MRSA CC398?. International Journal of Medical Microbiology 304(8): 1226-1232.

Beyene T et al., 2017. Prevalence and antimicrobial resistance profile of Staphylococcus in dairy farms, abattoir and humans in Addis Ababa, Ethiopia. BMC research notes 10(1): 1-9.

Billot-Klein D et al., 1996. Peptidoglycan synthesis and structure in Staphylococcus haemolyticus expressing increasing levels of resistance to glycopeptide antibiotics. Journal of Bacteriology 178(15): 4696-4703.

Boost M et al., 2013. Colonization of Butchers with Livestock-Associated Methicillin-Resistant *Staphylococcus aureus*. Zoonoses and Public Health 60(8): 572-576.

Brady RA et al., 2007. Immunoglobulins to surface-associated biofilm immunogens provide a novel means of visualization of methicillin-resistant *Staphylococcus aureus* biofilms. Applied and Environmental Microbiology 73(20): 6612-6619.

Cain CL, 2013. Antimicrobial resistance in staphylococci in small animals. Veterinary Clinics: Small Animal Practice 43(1): 19-40.

CDC, 2002. *Staphylococcus aureus* resistant to vancomycin--United States, 2002. MMWR. Morbidity and Mortality Weekly Report 51(26): 565.

Cesur S et al., 2012. Evaluation of antibiotic susceptibilities and VISA-VRSA rates among MRSA strains isolated from hospitalized patients in intensive care units of hospitals in seven provinces of Turkey. Mikrobiyoloji Bulteni 46(3): 352-358.

Chen CJ and Huang YC, 2014. New epidemiology of *Staphylococcus aureus* infection in Asia. Clinical Microbiology and Infection 20(7): 605-623.

Clewell DB et al., 2002. Enterococcal plasmid transfer: sex pheromones, transfer origins, relaxases, and the *Staphylococcus aureus* issue. Plasmid 48(3): 193-201.

Craft KM et al., 2019. Methicillin-resistant *Staphylococcus aureus* (MRSA): antibiotic-resistance and the biofilm phenotype. Medicinal Chemistry Communications 10(8): 1231-1241.

Cui L et al., 2000. Contribution of a thickened cell wall and its glutamine nonamidated component to the vancomycin resistance expressed by *Staphylococcus aureus* Mu50. Antimicrobial Agents and Chemotherapy 44(9): 2276-2285.

Daum RS et al., 1992. Characterization of *Staphylococcus aureus* isolates with decreased susceptibility to vancomycin and teicoplanin: isolation and purification of a constitutively produced protein associated with decreased susceptibility. Journal of Infectious Diseases 166(5): 1066-1072.

David MZ and Daum RS, 2017. Treatment of *Staphylococcus aureus* infections. *Staphylococcus aureus*: Microbiology, Pathology, Immunology, Therapy and Prophylaxis 409: 325-383.

de Boer E et al., 2009. Prevalence of methicillin-resistant *Staphylococcus aureus* in meat. International Journal of Food Microbiology 134(1-2): 52-56.

Denys GA and Relich RF, 2014. Antibiotic Resistance in Nosocomial Respiratory Infections. Clinics in Laboratory Medicine 34(2): 257-270.

Depardieu F et al., 2007. Modes and modulations of antibiotic resistance gene expression. Clinical Microbiology Reviews 20(1): 79-114.

de Vriese AS and Vandecasteele SJ, 2014. Vancomycin: the tale of the vanquisher and the pyrrhic victory. Peritoneal Dialysis International 34(2): 154-161.

El Harrak M et al., 2011. Main pathologies of camels, breeding of camels, constraints, benefits, and perspectives. In Conf. OIE 2011: 1-6.

ElSayed N et al., 2018. Vancomycin resistance among *Staphylococcus aureus* isolates in a rural setting, Egypt. Germs 8(3): 134.

Finks J et al., 2009. Vancomycin-resistant *Staphylococcus aureus*, Michigan, USA, 2007. Emerging Infectious Diseases 15(6): 943-945.

Gharieb RMA et al., 2020. Characterization of two novel lytic bacteriophages for reducing biofilms of zoonotic multidrug-resistant *Staphylococcus aureus* and controlling their growth in milk. Food Science and Technology 124: 109145.

Graveland H et al., 2011. Livestock-associated methicillin-resistant *Staphylococcus aureus* in animals and humans. International Journal of Medical Microbiology 301(8): 630-634.

Guo Y et al., 2020. Prevalence and therapies of antibiotic-resistance in *Staphylococcus aureus*. Frontiers in Cellular and Infection Microbiology 10: 107.

Ho J et al., 2014. Occupational exposure to raw meat: a newly-recognized risk factor for *Staphylococcus aureus* nasal colonization amongst food handlers. International Journal of Hygiene and Environmental Health 217(2-3): 347-353.

Holmes NE et al., 2015. Treatment of methicillin-resistant *Staphylococcus aureus*: vancomycin and beyond. Seminars in Respiratory and Critical Care Medicine 36(1):17-30.

Joshi S et al., 2013. Methicillin-resistant *Staphylococcus aureus* (MRSA) in India: prevalence & susceptibility pattern. The Indian Journal of Medical Research 137(2): 363.

Juhász-Kaszanyitzky É et al., 2007. MRSA transmission between cows and humans. Emerging Infectious Diseases 13(4): 630-632.

Kimang'a AN, 2012. A situational analysis of antimicrobial drug resistance in Africa: are we losing the battle? Ethiopian Journal of Health Sciences 22(2): 135–43.

Kumar A et al., 2017. Prevalence of methicillin-resistant *Staphylococcus aureus* skin and nasal carriage isolates from bovines and its antibiogram. Veterinary World 10(6): 593.

Ladhani S et al., 1999. Clinical, microbial, and biochemical aspects of the exfoliative toxins causing staphylococcal scalded-skin syndrome. Clinical Microbiology Reviews 12(2): 224-242.

Lam MW et al., 2004. Aquatic persistence of eight pharmaceuticals in a microcosm study. Environmental Toxicology and Chemistry 23(6): 1431-1440.

Lee JH, 2003. Methicillin (oxacillin)-resistant *Staphylococcus aureus* strains isolated from major food animals and their potential transmission to humans. Applied and Environmental Microbiology 69(11): 6489-6494.

Lee WG et al., 2004. Reduction in glycopeptide resistance in vancomycin-resistant Enterococci as a result of vanA cluster rearrangements. Antimicrobial Agents and Chemotherapy 48(4): 1379-1381.

Limbago BM et al., 2014. Report of the 13th vancomycin-resistant *Staphylococcus aureus* isolates from the United States. Journal of Clinical Microbiology 52(3): 998-1002.

Lowy FD, 1998. *Staphylococcus aureus* infections. New England Journal of Medicine 339(8): 520-532.

Mai-siyama IB et al., 2014. Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization rate among ruminant animals slaughtered for human consumption and contact persons in Maiduguri, Nigeria. African Journal of Microbiology Research 8: 2643–2649.

Mendem SK et al., 2016. Prevalence of MRSA and VRSA in Kalaburagi region. International Journal of Pharmacy and Biological Sciences 6(3): 81-85.

Mohammad AA, 2011. Colonization and antibiotic susceptibility pattern of methicillin resistance *Staphylococcus aureus* (MRSA) among farm animals in Saudi Arabia. African Journal of Bacteriology Research 3(4): 63-68.

Pahadi PC et al., 2014. Growing resistance to vancomycin among methicillin-resistant *Staphylococcus aureus* isolates from different clinical samples. Journal of Nepal Medical Association 52(196): 977-81.

Palazzo ICV et al., 2005. First report of vancomycin-resistant staphylococci isolated from healthy carriers in Brazil. Journal of Clinical Microbiology 43(1): 179-185.

Pexara A et al., 2013. Prevalence of methicillin-resistant *Staphylococcus aureus* in milk and dairy products. The Journal of the Hellenic Veterinary Medical Society 64(1): 17–34.

Quddoumi SS et al., 2006. Isolation and characterization of methicillin-resistant *Staphylococcus aureus* from livestock and poultry meat. Annals of Microbiology 56: 155-161.

Raji MA et al., 2016. Genetic characterization of *Staphylococcus aureus* isolated from retail meat in Riyadh, Saudi Arabia. Frontiers in Microbiology 7: 911.

Riaz S et al., 2021. Isolation and characterization of Vancomycin-resistant *Staphylococcus aureus* (VRSA) from Intensive Care Units (ICU) of different hospitals in Lahore, Pakistan. Advancements in Life Sciences 8(4): 339-345.

Saadat S et al., 2014. VanA and vanB positive vancomycin-resistant *Staphylococcus aureus* among clinical isolates in Shiraz, South of Iran. Oman Medical Journal 29(5): 335.

Saha B et al., 2008. Identification and characterization of a vancomycin-resistant *Staphylococcus aureus* isolated from Kolkata (South Asia). Journal of Medical Microbiology 57(1): 72-79.

Shekarabi M et al., 2017. Molecular characterization of vancomycin-resistant *Staphylococcus aureus* strains isolated from clinical samples: a three-year study in Tehran, Iran. PLoS One 12(8): e0183607.

Srinivasan A et al., 2002. Vancomycin resistance in Staphylococci. Clinical Microbiology Reviews 15(3): 430-438.

Tenover FC, 2008. Vancomycin-resistant *Staphylococcus aureus*: a perfect but geographically limited storm? Clinical Infectious Diseases 46(5): 675-677.

Thati V et al., 2011. Vancomycin resistance among methicillin-resistant *Staphylococcus aureus* isolates from intensive care units of tertiary care hospitals in Hyderabad. The Indian Journal of Medical Research 134(5): 704.

Tiwari HK and Sen MR, 2006. Emergence of vancomycin-resistant *Staphylococcus aureus* (VRSA) from a tertiary care hospital from northern part of India. BMC Infectious Diseases 6(1): 156.

Wang W et al., 2017. Enterotoxigenicity and antimicrobial resistance of *Staphylococcus aureus* isolated from retail food in China. Frontiers in Microbiology 8: 2256.

Wang X et al., 2014. Antimicrobial susceptibility and molecular typing of methicillin-resistant *Staphylococcus aureus* in retail foods in Shaanxi, China. Foodborne Pathogens and Disease 11(4): 281-286.

Weese JS and van Duijkeren E, 2010. Methicillin-resistant *Staphylococcus aureus* and Staphylococcus pseudintermedius in veterinary medicine. Veterinary Microbiology 140(3-4): 418-429.

Wertheim HF et al., 2005. The role of nasal carriage in *Staphylococcus aureus* infections. The Lancet Infectious Diseases 5(12): 751-762.

Whitener CJ et al., 2004. Vancomycin-resistant *Staphylococcus aureus* in the absence of vancomycin exposure. Clinical Infectious Diseases 38(8): 1049-1055.

WHO, 2014. Antimicrobial Resistance: Global Report on Surveillance. Geneva; 2014.

Wijesekara PNK et al., 2017. Review on usage of vancomycin in livestock and humans: maintaining its efficacy, prevention of resistance and alternative therapy. Veterinary Sciences 4(1): 6.

Woodford N et al., 1998. Diversity of VanA glycopeptide resistance elements in Enterococci from humans and nonhuman sources. Antimicrobial Agents and Chemotherapy 42(3): 502-508.