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ARTICLE

A Review of Emerging Methicillin-Resistant *Staphylococcus Aureus* (MRSA): A growing Threat to Veterinarians

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SUMMARY

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a gram-positive bacterium that is resistant to methicillin and many other β-lactam antimicrobials. It was discovered in 1961 in the United Kingdom soon after the discovery of methicillin, and often referred to in the press a "Superbug". Since that time, MRSA has emerged as a significant problem world wide, and the term has evolved to include resistance to additional β-lactam antimicrobials. Currently, the term MRSA is often used to describe multi-drug resistant *Staphylococcus aureus*. MRSA infections occur mostly in hospitals and health care facilities, with a higher incidence rate in nursing home or long-term care facilities, and transmission is thought to occur primarily from colonized or infected persons to other persons. The organism is often sub-categorized as Community-acquired MRSA (CA-MRSA) or hospital-associated MRSA (HA-MRSA). Transmission of MRSA was solely from human to animals, with MRSA colonization and infection typically occurring with contact between the hands of the human and anterior nares (nostrils) of the animal. There is now increasing evidence that MRSA can be transmitted in both directions, from animal to human (zoonotic) and human to animal (reverse zoonotic). MRSA was considered only a human pathogen, until a report of MRSA mastitis in a dairy cow 'surfaced in 1972. It has now become an increasing urgent problem in veterinary medicine, with MRSA infections reported in horses, dogs, cats, pet birds, cattle and pigs, and recently food products like bovine milk and retailed meat. Treatment of the infections involves the use of drugs such as vancomycin, teicoplanin, mupuricin, linezolid, clindamycin etc, and prevention is mainly by hand hygiene, hand sanitizers and the use of protective clothing and devices in the clinics.

KEY WORDS: Emerging, Methicillin-resistant *Staphylococcus aureus* (MRSA), Growing, Threat, Veterinarians.

INTRODUCTION

Staphylococcus aureus is one of the species of the genus Staphylococcus. It is a gram positive, non-motile, catalase positive, coagulase positive, facultative anaerobe, involved in causing a number of diseases including boils, pustules, impetigo, osteomyelitis, mastitis, septicemia, meningitis, pneumonia and toxic shock syndrome (Cheesbrough, 2002; Talaro and Talaro, 2002). For humans, this organism is an important cause of food borne intoxication, pneumonia, post operative wound infections, and nosocomial bacteremias (Horan *et al*., 1988; Mansouri and Khleghi, 1997). *S. aureus* is considered the most resistant of all non-spore forming pathogens, with well developed capacities to withstand high salt concentrations (7.5 – 10%), extremes in pH and high temperatures (up to 60^{0}C for 60minutes). It also remains viable after months of air–drying and resists the effects of many disinfectants and antibiotics (Talaro and Talaro, 2002).

S. aureus is known to be notorious in their acquisition of resistance to new drugs and continues to defy control measures (Talaro and Talaro, 2002). Many strains of *S. aureus* carry a wide variety of multi-drug resistant genes on plasmids (Ikeagwu *et al*., 2008). Human isolates of *S. aureus*, unlike animal's isolates, are frequently resistant to penicillinase-reistant penicillins (Kloos and Bannerman, 1995; Tenover and Gaynes, 2005). An organism exhibiting this type of resistance is referred to as Methicillin (oxacillin)-resistant *S. aureus* (MRSA). Such organisms are also frequently resistant to most of the commonly used antimicrobial agents, including the amino glycosides, macrolides, chloramphenicol, tetracycline and fluoroquinolones (Ikeagwu *et al*., 2008).

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a gram-positive bacterium that is resistant to methicillin (a member of the

penicillin family) and many other β-lactam antimicrobials (β-lactam antimicrobials include penicillins and cephalosporins), and are resistant to macrolides and aminoglycosides. The description "methicillin-resistant" was first used in 1961, based on the discovery of a human *Staphylococcus aureus* infection in the United Kingdom that was resistant to methicillin (Barber, 1961). Since that time, MRSA has emerged as a significant problem world wide, and the term has evolved to include resistance to other β-lactam antimicrobials. Currently, the term MRSA is often used to describe multi-drug resistant *Staphylococcus aureus.*

DISCOVERY AND HISTORY OF METHICILLIN - RESISTANT *STAPHALLOCOCCUS AUREUS* (MRSA)

Methicillin-resistant *Staphylococcus aureus* was discovered in 1961 in the United Kingdom. It made its first major appearance in the United States in 1981 among intravenous drug users. MRSA is often referred to by the press as **"**Superbug**"** (CDC, 2007). In the past decade or so the number of MRSA infections in the United States has increased significantly. The Centers for Disease Control and Prevention (CDC) estimated that the number of MRSA infections in hospitals doubled nationwide, from approximately 127, 000 in 1999 to 278,000 in 2005, while annual deaths toll increased from 11,000 to more than 17,000 (CDC, 2007; Klein *et al.,* 2007; Labondeira-ray *et al*., 2007). Another study by the CDC estimated that MRSA was responsible for 94,360 serious infections and associated with 18,650 hospital stay-related deaths in the United states in 2005 (Klevens *et al*., 2007; CDC, 2007). These figures suggest that MRSA infections are responsible for more deaths in the US each year than AIDS (Stein, 2007). However, there are "associated" deaths, that is, people who died with, but not primarily due to MRSA.

STRAINS OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

Several strains of MRSA have been identified based on genetic analysis of the organism. In the UK, the most common strains of MRSA are EMRSA15 and EMRSA16 (Johnson *et al*., 2001). EMRSA16 has been found to be identical to the ST36:USA200, which circulates in the United States, and carry the (Staphylococcal Cassette Chromosome) SCC<i>mec type II, enterotoxin A and toxic shock syndrome toxin I genes (Diep *et al.*, 2006). Under new international typing system, this strain is now called MRSA252. It is not entirely certain why this strain has become so successful, whereas previous strains have failed to persist. One explanation is the characteristic pattern of antibiotic susceptibility exhibited by these strains. Both EMRSA15 and EMRSA16 strains are resistant to erythromycin and ciprofloxacin. It is known that *S. aureus* can survive intracellulary (Von Eiff *et al*., 2001), and these strains of *S. aureus* are therefore able to exploit an intracellular niche.

In the United States, most cases of Community-associated MRSA (CA-MRSA) are caused by a Clonal Complex (CC)8 strain designated Sequence Type (ST)8:USA300, which carries (Staphylococcal Cassette Chromosome) SCC<i> mec type IV, Panton-Valentine Leukocidin, PSM-alpha and enterotoxin Q and K (Diep *et al*., 2006) and ST1:USA400 (Wang, 2007). Other community-acquired strains of MRSA are ST8:USA500 and ST59:USA1000. In many nations of to world, MRSA strains with different predominant genetic background types have come to predominate among CA-MRSA strains; USA300 easily tops the list in the US and is becoming more common in Canada. For example, in Australia ST93 strains are common, while in continental Europe, ST93 strains predominate. In Taiwan, ST59 strains, some of which are resistant to many non-bete-lactam antibiotics, have arisen as common causes of skin and soft tissue infections in the community (David *et al*., 2008).

Nomenclature of MRSA strains

MRSA nomenclature varies worldwide, and a standard method for typing and naming MRSA strains has not yet been adopted; therefore, one genetic strain of MRSA may be referred to by several different names. The organism is often sub-categorized as community-acquired (Community-associated) MRSA (CA-MRSA) or hospital-associated (Health care-associated) MRSA (HA-MRSA) although this distinction is complex (Leonard and Markey, 2008).

Community-Associated MRSA (CA-MRSA)

Some have defined CA-MRSA by criteria related to the patients suffering from an MRSA infection

while other authors have defined CA-MRSA by genetic characteristics of the bacteria themselves (Okuma I *et al*., 2002). CA-MRSA strains were first reported in the late 1990s; these cases were defined by a lack of exposure to the health care setting. In the next several years, it became clear that CA-MRSA infections were caused by strains of MRSA that differed from the older and better studied health care-associated strains (Okuma I *et al*., 2002). CA-MRSA infections occur in otherwise healthy people without a recent history of hospitalization or clinical presentation, and are usually associated with skin and soft tissue infection. Risk factors for CA-MRSA include crowding, frequent contact, compromised skin, contaminated surfaces and shared items, and poor hygiene. To date the commonest human associated MRSA is USA300 (Naimi *et al*., 2003).

Hospital-associated MRSA (HA-MRSA)

HA-MRSA infections occur most commonly in immunocompromised individuals in hospitals and health care centers. Risk factors for HA-MRSA include hospitalization, surgery, dialysis, long-term care, indwelling devices, and history of previous MRSA infection. The bulk of MRSA related clinical infections are caused by HA-MRSA, which are considered "nosocomial"), while strains USA 100 are the commonest **(**Hanselman *et al*., 2006; Klevens *et al.*, 2007).

RESISTANCE AND VIRULENCE FACTORS ASSOCIATED WITH MRSA

MRSA has emerged because there are countless different strains of a single type, and each has subtle natural genetic mutations which make it different from another (Weese, 2005). Some strains' genetic makeup accords them a slight advantage in fighting off antibiotic attack unlike the weaker strains that are eliminated. Strains that manage to carry two or three resistance genes will have extraordinary powers of resistance to antibiotics (Weese, 2005; Voyich *et al*., 2006; Labandeira-ray *et al*., 2007). Resistance is mediated by a gene (*mec* A) that encodes the production of an altered penicillin-binding protein (PB2a), which does not allow for the binding of β-lactams to the bacterial cell wall (Weese, 2005). Because β-lactams exert antibacterial activity by binding and inhibiting enzymes necessary for bacterial cell wall synthesis, these antimicrobials are not effective against MRSA.

Novel MRSA isolates that are less likely to be resistant to antimicrobial drugs other than β-lactams have been identified and association with epidemic CA-MRSA infections. Such strains are commonly susceptible to drugs such as clindamycin, gentamycin, tetracycline, and rifampin. They are reported to encode the virulence genes of the pore-forming, bicomponent cytotoxin, Panton-Valentine Leukocidin (PVL) (Li-Zhong *et al*., 2004). However, evidence from animal studies has been contradictory in assessing the importance of PVL in the virulence of these isolates (Voyich *et al*., 2006; Labandara-ray *et al*., 2007). In addition to PVL genes, strains that cause CA-MRSA infections typically carry Staphylococcal chromosomal cassette *mec* (SCC *mec*) types IV and V which are small genetic resistance elements that are presumably mobile (Li-Zhong *et al*., 2004). A single CA-MRSA strain USA 300 with genetic background corresponding to sequence type (ST) 8 by multilocus sequence typing (MLST), and defined by pulse-field gel electrophoresis has become predominant among CA-MRSA isolates in many health centers in the United States (Pan *et al*, 2005; Diep *et al*., 2006; Moran *et al*., 2006). The reason for the dominance of USA300 is unknown.

HUMAN AND ANIMAL CROSS INFECTION WITH MRSA

For many years, MRSA was considered only a human pathogen, until a report of MRSA mastitis (udder infection) in a dairy cow surfaced in 1972 (Devriese *et al*., 1972). It has now become an increasing urgent problem in veterinary medicine, with MRSA infections reported in horses, dogs, cats, pet birds, cattle and pigs (Lee, 2003; Baptise *et al*., 2005; Voss *et al*., 2005., Weese, 2005; 2006; Abbort *et al*., 2006; Khanna *et al*., 2008; Smith *et al*., 2009; George *et al.,* 2010).

It was first thought that the transmission of M RSA was solely from human to animals, with MRSA colonization and infection typically occurring with contact between the hands of the human and anterior nares (nostrils) of the animal. There is now increasing evidence that MRSA can be transmitted in both directions, from animal to human (zoonotic) and human to

animal (reverse zoonotic). Once exposed to MRSA, animals can become colonized, and may serve as reservoirs for transmitting the infection to other animals and their human handlers (Baptise *et al*., 2005; Klevens *et al*., 2007; Leonard and Markey, 2008; Weese *et al*., 2006). It has been shown that even apparently healthy animals may be MRSA reservoirs, and could therefore pose a risk to their handlers (Klevens *et al*., 2007, Smith *et al*., 2009). This has been documented in the general community, and is becoming increasingly documented in health-care settings and in animal environments among which are veterinary clinics, hospitals, farms, and slaughterhouse (Voss and Doebbeling, 1995; Lee, 2003; Weese *et al*., 2006; De Neeling *et al*., 2007). Data have indicated that owners and veterinary personnel who come into contact with MRSA-colonized or MRSA-infected animals may become colonized by MRSA (AVMA, 2009).

With human-to-animal transmission of MRSA, there is a possibility that until the animal is free of infection, re-transmission from the animal to man and subsequently human-to-human might occur ((Baptise *et al*., 2005; Voss *et al.,* 2005; Leonard and Markey, 2008). In one reported case of possible dog-to-human transmission, a diabetes mellitus patient and his wife experienced recurring MRSA infections and difficulty in elimination (decolonization) the MRSA. Nares culture of the family dog revealed colonization with MRSA, and long-term decolonization of the man and his wife were feasible after the dog was treated (Manian, 2003). However, there was no clear evidence that the dog was the source of infection.

There is a concern that antimicrobial treatment of MRSA in companion animals may increase antimicrobial resistance, and have a subsequent effect on the zoonotic transmission or re-transmission to humans, especially if the humans involved are already in an immunocompromised state ((Baptise *et al*., 2005; Klevens *et al*., 2007).

THE ROLE OF WILD LIFE IN MRSA INFECTIONS

The first documented case of MRSA transmission between zoo animal and its caretakers was reported in March, 2009. Strain USA300 was isolated from an African elephant calf that was being treated for skin pustules; three of its caretakers were also colonized. The USA300 strain, which is the most common type associated with human CA-MRSA infections, has never been reported as originated from animals. The investigation concluded that the calf had acquired the MRSA infection from a colonized human caretaker (reverse zoonotic transmission) during the placement of an intravenous catheter, and that the calf then transmitted the infection to other human caretakers (zoonotic transmission) through contacts. Although transmission between caretakers cannot be ruled out, several factors may suggest that transmission occurred from the calf to other caretakers (CDC, 2009).

ZOONOTIC NATURE OF MRSA

Veterinary personnel are at increased risk of being MRSA reservoirs and zoonotic transmission of MRSA and subsequent MRSA colonization should be considered an occupational risk for members of the veterinary health care team, particularly those in large animal practices. At the 2005 American college of Veterinary Internal Medicine (ACVIM) forum, 6.5% of the attending veterinary personnel who volunteered to be tested were found to be colonized with MRSA. Large animal practitioner recorded the highest MRSA colonization with 15.6%, while small animal practice personnel colonization rate was 4.4% ($P < 0.001$) (AVMA, 2009).

Farmers are also at risk of being MRSA reservoirs. In a survey of pig farmers in the Netherlands, 23% of pig farmers were colonized with MRSA, a rate that was 760 times higher than the general Dutch population; however, only 2 of 40 pigs tested were MRSA positive (Huijsden *et al*., 2006; Wulf *et al*., 2006). In another investigation MRSA strains isolated from a pig farmer, his family and farm workers were similar to those seen in pigs; however, the original source of the MRSA was not established (Huijsden *et al*., 2006). In a comparative study human strains of MRSA sequence type (ST) 254 displayed molecular-typing results indistinguishable from those for strains of equine origin. Two other equine strains (ST22 and ST1117) showed similarity to ST22 human strains. The data from this study provide evidence that certain MRSA genotypes have adapted to more than one mammalian species (Walhter *et al*., 2009).

PREVALENCE OF MRSA IN ANIMALS WITH NON-CLINICAL INFECTIONS

Few data on MRSA colonization rates in non-clinically affected animals are available. Although identification of colonized or infected animals is important in the prevention of MRSA, the routine screening of all animals is not practicable, so there remains the possibility that a small percentage of colonized animals will remain undetected upon admission to a veterinary clinic or hospital (Moris *et al.,* 2006; Leonard and Markey, 2008). For instance a 20-year-old, male, captive, bottlenose dolphin, suspected of having pneumonia, was treated empirically with ciprofloxacin and co-trimoxazole. Despite treatment the dolphin died. A necropsy culture swab specimen of the anterior nares was submitted for bacteriologic examination. MRSA was isolated, which was shown by pulse-field gel electrophoresis (PFGE) to be the Canadian epidemic MRSA (CMRSA) 2 (USA 100) strain, the predominant hospital- and community-associated MRSA found in persons in Canada (Oehler *et al.,* 2006).

In a survey conducted in Ireland by Abbott *et al.* (2006), 0.6% prevalence of MRSA colonization was detected in non-clinically infected dogs, and 0.9% prevalence of MRSA colonization was detected upon admission to a veterinary clinic. A case study by Vitale *et al.* (2006) described a 3-year-old neutered male, domesticated cat with a history of multifocal patches of crusted and well-demarcated ulcers on the trunk. MRSA was isolated as USA300. Cluny *et al.* (2009) in a study of horses in Vienna Veterinary University Hospital between 2006 and 2007 showed that 20 of 140 horses with suspected wound infections were positive of clusters of MRSA strains MRSA ST1, ST254 and ST398. Similarly Weese *et al.* (2006) reported colonization rate of MRSA in horses admitted to a Veterinary Teaching Hospital to be 2.7% admissions.

Studies by Khann *et al.* (2008) and Smith *et al.* 2009) found MRSA colonization rates of 25% and 70% in pigs in Europe and U.S. respectively. Also in the Netherlands, Wulf and Voss (2008) revealed that 39% of the slaughtered pigs were positive for an unusual strain of MRSA ST398. From poultry flocks, Persoons *et al.* (2009) showed that the number of positive samples varied between 1/5 (20%) and 5/5 (100%). Strastkova *et al.* (2009) studied the occurrence of MRSA strains in a goat breeding farm. A total of 278 samples collected from animals, milk, environment and farm personnel between June 2006 and March 2008 were examined. Eight MRSA were detected in the study. Five of them originated from goat's milk and three were recovered from one human carrier of the farm personnel. All obtained MRSA were clonally consistent and were characterized as: SCC *mec* types IV, spa type t064, *seb* positive and for genes encoding TSST-1, PVL and exfoliative toxins A and B negative.

Similarly, Huber *et al.* (2010) worked on the prevalence of MRSA in humans in contact with farm animals, in livestock, and in food animal origin in Switzerland. A total of 2,662 samples collected from March to September 2009 were tested for the presence of MRSA. The collection comprised nasal swabs from 148 pig farmers, 133 veterinarians, 179 slaughtered house employees, 800 pigs, 300 calves, 400 cattle, 100 pooled neck skin swabs from chicken carcasses, and 460 food samples of animal origin. Moreover, 142 *S. aureus* strains isolated from bovine mastitis milk were included in the study. A total of 20 MRSA were detected, derived from samples from, 4 (3.0%) of 133 veterinarians, 10 (1.3%) of 800 pigs, 3 (1.0%) of 300 calves, 1 (0.3%) of cattle, and 2 (1.4%) of 142 mastitic milk samples. In contrast, the MRSA were not found in pig farmers, slaughtered house employees, poultry, and in food samples such as bulk tank milk (BTM), raw milk cheese, and minced meats. Genotyping of the MRSA strains was performed by multilocus sequence typing, *spa*- and SCC *mec*-typing, and revealed ST398 (n=18), ST8 (n=1), ST1 (n=1), *spa* types t011 (n=7), t034 (n=11), t064 (n=1), t127 (n=1), and SCC *mec* types IV (n=4) and V (n=16). All the 20 MRSA strains were susceptible to gentamycin and sulphamethoxazole/-trimethoprim and all but one were susceptible to ciprofloxacin.

Also Cuny *et al.* (2010) observed that the emergence of MRSA in animals such as horses, pet animals and productive livestock has raised questions of a probable human origin and in more general of host specificity of *S. aureus.* Particular clonal lineages are obviously specific for humans (e.g. ST15, ST25, and ST45) and

other for ruminants (e.g. ST151). MRSA of veterinary nosocomial infections (e.g. ST8 and ST254 in horses, ST22 in small animals) very likely have their origin in health care facilities. MRSA ST398 which became first known from widespread colonization in industrially raised pigs seems to have limited host specificity and is able to colonize and to cause infections in various hosts. Mechanisms of host adaptation and their genomic background are poorly understood.

To determine whether *Spa* type of methicillin-resistant *Staphylococcus aureus* (MRSA) in pigs belonged to sequence type (ST) 398, Guardabassi *et al.* (2009) analyzed nasal swabs from pig carcasses at Hong Kong markets in 2008. ST9 belonging to *spa* type t899 was found for 16/100 samples, which indicates that a distinct lineage has emerged in pigs. In contrast to ST398, which has the characteristic of being nontypeable by PFGE using *Sma* I, the 16 MRSA were typeable. They displayed 6 PFGE patterns; 2 predominant types (A1 and B1) were associated with SSC *mec* types IV and V, respectively. A search from the scientific literature and internet for information about the frequency of *S. aureus* ST9 in humans and animals indicated that ST9 is a clone of porcine origin (Guardabassi *et al.*, 2009).

PREVALENCE OF MRSA IN FOODS

Transmission of MRSA from animals to humans through animal food products has not been thoroughly investigated (Lee, 2003; Van Loo *et al.*, 2007b), but several factors by may suggest that transmission of MRSA through foods is possible. For instance, Pu *et al.* (2008) investigated the prevalence of MRSA in 120 retail meats from 30 grocery stores in Baton Rouge, Louisiana. They isolated MRSA from six meat samples (5 pork and 1 beef). The MRSA strains identified were USA300 and USA100, but the investigators did not determined if the original source was the meat itself or humans who handled the meat prior to purchase**.** Lee (2003) examined the prevalence of MRSA in major food animals. Out of the 1,913 specimens collected, 28 were MRSA positive, of which 15 were positive for *mec* A gene. 17 of the MRSA isolated were from milk while pig (meat and trachea) and chicken (meat and joint) had 3 and 8, respectively. Kwon *et al.* (2005) identified the staphylococcal cassette chromosome mec (SCC *mec*) in bovine milk and concluded that MRSA isolated from bovine milk harbored a unique SCC mec subtype, and they may not be correlated with the emergence of CA-MRSA in human infection in Korea.

Kitai *et al.* (2005) investigated the prevalence of MRSA in 444 raw meat chicken samples retailed at 145 different super markets in 47 prefectures through out Japan, between 2002 through 2003. *S. aureus* was isolated from 292 (65.8%) of 444 and from 131 of 145 different supermarkets. Two *mec* A-positive MRSA strains were isolated from raw chicken meat retailed at two supermarkets in two prefectures. Kwon *et al.* (2005) in related study showed that fourteen MRSA and a silent *mec* A-carrying methicillin-susceptible *S. aureus* (smMSSA) were isolated from the milk of cows with an isolation ratio of 0.18%. SCCmec of the 14 MRSA strains were designated as a new subtype IVg, and one smMSSA strain was not classified. All the 14 strains shared panton-Valentine leukocidin (PVL) and staphylococcal enterotoxin D (SED), SEI and SEJ; the smMSSA strain had only PVL. All the MRSA and smMSSA isolates showed no multidrug resistance and had community-acquired MRSA (CA-MRSA) characteristics. PFGE revealed that all the isolates except the smMSSA belonged to the same genetic lineage, and MLST analysis showed that they had no genetic relatedness with CA-MRSA which had caused human infection in Korea. The study concluded that MRSA isolated from bovine milk harboured a unique SCCmec subtype, and they may not be correlated with the emergence of CA-MRSA in human infection in Korea.

Also, Tuirkyilmaz *et al.* (2009) identified MRSA strains gathered from 2002 to 2006 from bovine milk samples in Aydin region in Turkey. Among 93 *S. aureus* isolated from bovine milk with mastitis, 16 (17.2%) were resistant to methicillin. The MRSA strains were multi-drug resistant, with susceptibility rates to antimicrobial tested as 0%, 0%, 0%, 0%, 6.25%, 16.25% and 57.25% for erythromycin, clindamycin, chloramphenicol, gentamycin, tetracycline, ciprofloxacin and vancomycin respectively. Similarly, Virgin *et al.* (2009) estimated the herd prevalence of MRSA among US dairy herds by testing bulk tank milk (BTM)

samples using genotypic and phenotypic methods. 190 MTM samples ere positive for *S. aureus,* out of which 7 were tested positive for *nuc* and *mec* A, and 2 tested positive for *mec* A only. *mec* A positive *Staphylococcus spp* nor MRSA was isolated from the remaining 4 samples.

PREVALENCE OF MRSA IN HUMANS NIGERIA

The epidemiology of MRSA is fast changing and has become one of the established pathogen in both hospital and community. MRSA infection and colonization have been reported in humans in Nigeria, in both hospital and outside the hospital environment. In Nigeria, several reports of human MRSA infections have been documented. Ike (2003) observed a prevalence rate of 43% at Jos University Teaching Hospital while Onanuga *et al.* (2006a) showed a prevalence rate of 76.7% and 68.5% from urine samples in Abuja and Zaria respectively among health women. The prevalence rate of 20% was also recorded in Zaria from non hospital sources (Olonitola *et al.*, 2007). Also Taiwo *et al*. (2004), Fusi Ngwa *et al.* (2007), and Olowe *et al.* (2007) in separate studies observed a prevalence rate of 34.7%, 54.9% and 47.8% in Ilorin (University of Ilorin Teaching Hospital), Lagos (Pediatric Unit, Lagos University Teaching Hospital and Oshogbo (Ladoke Akintola University of Technology, College oh Health Sciences) respectively.

Ghebremedhin *et al.* (2009) provided a comprehensive overview of the molecular epidemiology and genetic diversity of *S. aureus* strains at the largest university clinic in Ibadan, Nigeria. From 1,300 patients clinical samples collected at the University Teaching Hospital in Ibadan, Nigeria, during 1-year surveillance in 2007, 346 non duplicate *S. aureus* isolates were obtained. All isolates underwent antibiotic susceptibility testing, toxin gene analysis, multilocus sequence typing, *agr* group typing, and *spa* typing. For methicillin-resistant *S. aureus* (MRSA), staphylococcal cassette chromosome *mec* (SCC *mec*) typing was also performed. Of the 346 isolates, 20.23% were methicillin resistant. Thirty-three patients' isolates (47.15%) fulfilled the definition criteria for community-associated MRSA (CA-MRSA) according to a review of the medical charts. The first report of a Panton-Valentine leukocidin-positive ST88 strain (*agr* III, SCC *mec* IV) in Nigeria, as well as genetic analysis of this strain is present in their study. The ST88 strain was resistant to trimethoprim-sulphamethoxazole as well as to penicillin and oxacillin.

Similarly, Okon *et al.* (2009) in their study showed that ninety-six clinical isolates of *S. aureus* from Nigeria were characterized phenotypic ally and genetically. Twelve multidrug-resistant methicillin-resistant S. aureus (MRSA) isolates carrying a new staphylococcal cassette chromosome *mec* elements and a high proportion of Panton-Valentine leukocidin (PVL)-positive methicillin-susceptible *S. aureus* (MSSA) isolates was observed. The occurrence of multidrug-resistant MRSA and PVL positive MSSA isolates entails the risk of emergence of a multidrug-resistant PVL-positive MRSA clone. Also Fadeyi *et al.* (2010) worked on MRSA carriage amongst health workers of the critical care units in a Nigeria hospital. Of the 198 health worker screened, 104 had MRSA either in the nose, hand or both giving a carriage rate of 52.5%, nasal carriage (38.9%) was higher than hand (25.3%). Doctors (22.75%) or Nurses (16.7%) were the predominant carriers. MRSA isolates were resistant to commonly available antibiotics. Only 1 (1.3%) of the nasal isolates was vancomycin resistant. In Kano, Nwanko *et al.* (2010) studied methicillin-resistant *S. aureus* (MRSA) and their antibiotic sensitivity pattern. Their results showed that out of the 185 *S. aureus* tested, 53 (28.6%) were found to be methicillin resistant. While 38 (62%) isolates were obtained from in-patients 15 (28%) were from out-patients, and surgical wound infection had the highest prevalence of 32 (60%) isolates.

CLINICAL SIGNS OF MRSA IN ANIMALS

Not all animals who encounter MRSA develop clinical signs. While research is ongoing, it appears that only a small percentage become ill, while most eliminate the organism or become colonized without developing clinical signs. Among animals, the most commonly reported clinical signs are postoperative and wound infections, with less reported incidence of intravenous catheter site infections, urinary tract infections, pneumonia, skin and ear infections; skin and ear infections have been most commonly reported(Weese, 2005; Vitale *et al.,* 2006). CA-MRSA strains that cause skin and soft

tissues infections (SSTTIs) sometimes contain Panton-Valentine Leukocidin exotoxin (PVL). It is unclear whether PVL is a relevant virulence factor or a marker for some other factor, a toxin that produces tissue necrosis (tissue death). CA-MRSA infection may present as red, swollen, painful site with drainage (Vitale *et al*., 2006; Oehler *et al*., 2009).

DIAGNOSIS OF MRSA

Diagnosis should involve the identification of coagulase-positive *Staphylococci* to the species level, and all *S. aureus* should then be tested for oxacillin resistance, since Methicillin is less stable *in vitro* (Lee, 2003; Ikeh, 2003; Hanselman *et al*., 2006; Onanuga *et al*., 2006; Fusi Ngwa *et al*., 2007; Olonitola *et al*., 2007; Olowe *et al*., 2007). Another common laboratory test is a rapid latex agglutination test which detects the PBP2a protein. PBP2a is a variant penicillin binding protein that imparts the ability of *S. aureus* to be resistant to oxacillin (Persoons *et al.*, 2009). If there is a recurrent or persistent case of skin infection the animal, a small biopsy of either the infected skin or a sample of the exudates (drainage) from the site may be submitted for laboratory diagnosis. A sputum culture is recommended for bloodstream and urinary infections. If *S. aureus* is isolated, further tests are needed to determine if it is a MRSA strain (Seiken, 2009).

MOLECULAR EPIDEMIOLOGY OF MRSA

The most prominent molecular(genetic) typing methods are: pulsed field gel electrophoresis(PFGE), multilocus sequence typing(MLST), Staphylococcal chromosome cassette(SCC) and polymerase chain reaction(PCR)(Real-PCR and Quantitative-PCR) (Furtalo *et al*., 2006; , Anderson and Weese, 2007; David *et al*., 2008; Francois and Schrenzel, 2008; Denis *et al*., 2009). MLST study on the molecular epidemiology of MRSA in Alaska revealed that, 92% of the isolates carried Panton-Valentine Leucocidin (PVL) genes, all carried Staphylococcal Chromosomal Cassette *mec* (SCC *mec*) type IV, and none belonged to clonal complex(CC) 8 (David *et al*., 2008). Genotyped MRSA isolates by PFGE after digestion of chromosomal DNA with *sma* I, and MLST gave rise to three PFGE clonal groups (USA100[ST5, SCC *mec* type II], USA300[ST8, SCC *mec* type IV], and USA500[ST8, SCC *mec* type IV]) accounting for 85.2% of all the isolates (Tattevin *et al.*, 2009).

Rapid diagnosis of MRSA in animals is still in its early stages of development, and to date there is a significant delay from collection to acquisition of test results for animals, as compared to humans (Weese, 2005). Rapid tests that have been validated for use in human cases (i.e. real time-PCR) do not necessarily perform adequately in animal cases, so species-specific validation is required (Tattevin *et al*., 2009). There is a new typing method that uses several variable number tandem repeat (VNTR) sequences for typing animal MRSA isolates, but to date there is no published data available (Leonard and Markey, 2008).

TREATMENT OF MRSA INFECTIONS IN ANIMALS

CA-MRSA has a greater spectrum of antimicrobial susceptibility, including sulfa drugs, tetracycline, and clindamycin. HA-MRSA is resistant even to these antibiotics and often is susceptible only to Vancomycin. Vancomycin and teicoplanin are glycopeptides antibiotics used to treat MRSA infections (Rybak *et al.,* 1991). Teicoplanin is a structural congener of Vancomycin that has a similar activity spectrum but a longer half-life (Rybak *et al*., 1991). Because the oral absorption of Vancomycin and teicoplanin is very low, these agents must be administered intravenously to control systemic infections (Schentag *et al*., 1998). Treatment of MRSA can be complicated, due to its inconvenient route of administration. Moreover, many clinicians believe that the efficacy of Vancomycin against MRSA is inferior to that of anti-staphylococcal beta-lactam antibiotics against Methicillin-susceptible *Staphylococcus aureus* (MSSA) (Chang *et al.*, 2003; Siegman-Igara *et al*., 2005).

Several newly discovered strains of MRSA show antibiotic resistance even to Vancomycin and teicoplanin. These new evolutions of the MRSA bacterium have been dubbed Vancomycin intermediate resistant *S. aureus* (VISA) or Vancomycin-resistant *S. aureus* (VRSA) (Schito, 2006; Janknet, 1997). Linezolid, quinupristin/ dalfopristin, daptomycin, and tetracycline are used to treat more severe infections that do not respond to glycopeptides such as Vancomycin

(Mangkoloratanothai *et al*., 2003). MRSA infection can be treated with oral agents, including lineziod, rifampicin-fusidic acid, rifampicin + fluoroquinolone, pristinamycin, co-trimoxazole (trimethoprim - sulphamethoxazole), doxycycline or minocyline, and clindamycin (Birmingham *et al*., 2003). For MRSA mupirocin can potentially eliminate MRSA from mucus membrane colonization (Furtalo *et al*., 2006). A new antibiotic called platensimycin that had demonstrated successful use against MRSA (Wang, 2007). In another separate study in University of East London and University of York, allicin, a compound in garlic and small quantities of silver carbonate was found to successfully treat MRSA. There are different strains of MRSA, with different degrees of immunity to the effects of various antibiotics. It does not mean that antibiotics are completely powerless against it; it may simply require a much higher dose over a much longer period, or the use of alternative antibiotics to which the bacteria has less resistance. Therefore, if antibiotic treatment is necessary, it should be guided by the susceptibility of the organism (Seiken, 2009). In a study to of food animals in Chonju, Republic of Korea, it was observed that all MRSA isolates from the animals (chicken and cattle) were susceptible to amikacin and trimethoprim-sulphamethoxazole; all isolates from chicken were susceptible to norflacin and ofloxacin; and majority of cattle isolate were susceptible to tetracycline (Lee, 2003). In Belgium all MRSA strains isolated from poultry were susceptible to chloramphenical, ciprofloxacin, linezolid, mupirocin, quinopristin-dalfopristin, rifampin, and sulfonamides (Furtalo *et al*., 2006).

CONTROL AND PREVENTION OF MRSA INFECTIONS IN ANIMALS

As in human medicine, hand hygiene is an integral part of the intervention of the spread of MRSA between animals and humans. Frequent hand washing with soap/detergent and proper disinfection of hard surfaces and equipment between patients is essential (AVMA, 2009). Hand sanitizers should be provided in all consulting rooms and kennels to remind staff of the need for frequent hand sanitization ((AVMA, 2009). Uniforms, gloves, disposable aprons and masks should be worn when changing dressings on infected wounds or to prevent potential contact with body fluids or contaminated tissues (AVMA, 2009).Eye protection is indicated if splashing or aerosols are expected (AVMA, 2009). All surroundings in the clinic should be kept to a high standard of cleanliness. Although the cleanliness of floors does not appear to be as important as hand-touch sites in the control of human MRSA infections, the situation may be different in veterinary medicine because many animals are examined or treated on the clinic floor (AVMA, 2009).

Good hand hygiene by all who encounter the animals, both before and after touching the animal (AVMA, 2009). When placing an animal on a bed, a clean towel or absorbent pad should be placed between the pet and the bed linens (Leonard *et al*., 2008).

DISCUSSION

MRSA is now increasingly reported in animals' world wide, and new types appear to be evolving in animals. These pose a threat to human health through occupational exposure and ease of spread during the increased movement of livestock and contact with veterinary personnel. Asymptomatic colonization and shedding of MRSA by veterinary personnel couple with the unnecessary use of antibiotics may contribute to the establishment of MRSA.

The use of antibiotics for treating people and animals in most developing countries is unregulated such that antibiotics could be purchased in pharmacies, general stores, markets and even motor parks with the implication that there is a widespread and uncontrolled abuse. For example patients often do not take full course of treatment, and more so many antibiotics in the developing countries are of low qualities or faked and adulterated coupled with bad storage and management processes. All these may lead to phenotypic adaptations resulting in resistant isolates. MRSA can produce a host of conditions ranging from mild to severe skin infections to fatal pneumonias, osteomyelitis, septic arthritis, endocarditis, abscesses, bacteremias and septicemia.

Based on the numerous studies on MRSA worldwide in both humans and animals, there are increasing evidences that MRSA as an emerging and important zoonotic pathogen.

Interspecies transmission (human-to-animal and animal-to-man) occurred in many cases (Lee, 2003). Also, several researchers had documented similarities in both phenotypic and genotypic characteristics between MRSA strains isolated from humans and animals (Khann, *et al.,* 2008; Dennis *et al.,* 2009; George *et al.,* 2010).The threat over colonization and infection in animals is that they can become carriers or reservoirs of MRSA and subsequently may transmit the pathogen to humans that are in contact with them. Therefore, veterinary personnel can acquire MRSA from animals in the farms, clinics or hospitals and may spread it to humans who are at greater risk of developing MRSA infection or to their other patients.

The contamination of food animal products (meat, meat and milk products) occurred during production, processing and at retail point (Lee, 2003) and can be a potential threat to humans who handle the foods as well as those consume raw or undercooked food (Van Loo *et al.,* 2007).

Despite lack of basic research on the epidemiology of MRSA, it is likely that overcrowding and close contact between people and their animals have played major roles in the spread and persistence of MRSA on farms, in homes, and in veterinary clinics. Many common disease control practices used to protect public health may apply equally well to controlling MRSA at the animal-human interface. Proper hand washing, together with cleaning and disinfection of contaminated surfaces, are simple and effective mitigation measures that can be used to reduce MRSA risk in most situations. Depending on the circumstances, additional biosecurity measures could include screening of animals and animal care staff for MRSA, isolation of suspect cases, and strict asepsis during surgery (Leonard and Markey, 2008). Report on MRSA colonization and infection in humans, in both hospital and non hospital sources, involving healthy and ill persons have been reported and documented in several parts of Nigeria including Lagos, Abuja, Jos, Osogbo, Ilorin, Zaria and Kano, but however literature is scanty on the prevalence and/or infection in animals or veterinary related issues in Nigeria.

CONCLUSSION

The emergence and presence of MRSA in humans in Nigeria and other countries of the world is both veterinary and public heath concern and strongly suggest that there are interspecies transmissions, animal-to-animal, human-to-animal and animal-to human. The epidemiology of MRSA in animals may take parallel course to that of the humans, and may mean that failure to diagnose and treat MRSA conditions in animals can result to recurrent MRSA colonization and infections in humans. However, information is still scanty on the prevalence of MRSA and its association with infection in animals in Nigeria. But with the emergence of MRSA in animals from other countries of the world and also in humans in Nigeria, animals in Nigeria may not be an exception. Therefore studies are recommended to prove this.

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