

Review Article

Methicillin Resistant *Staphylococcus aureus* (MRSA): A Review

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Abstract | *Staphylococcus aureus* (*S. aureus*) is a gram positive organism that serves as an opportunistic pathogen and frequent colonizer of the epithelium causing severe diseases in human and animals. The widespread use of antibiotics both in human and Veterinary medicine resulted in the emergence of resistant strains of *S. aureus*. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common bacterial pathogen responsible for a variety of infections. Resistance to methicillin is determined by the *mecA* gene, which encodes the low-affinity penicillin-binding protein PBP 2. Lately, new methicillin resistance gene, *mecC* has been discovered from humans, animals and food products. MRSA infection was first considered hospital-associated (HA-MRSA) and community-associated MRSA (CA-MRSA) infections. However, another group emerged known as livestock-associated MRSA (LA-MRSA). The isolation of MRSA from different species, food products and the environment raised concern on the role of animals particularly livestock and wildlife in the epidemiology of MRSA. The spatial distribution of MRSA indicates interspecies transmission and colonization of different populations. This review summarizes the current knowledge, transmission pattern and the epidemiology of MRSA from hospitals, communities, animals and their products.

Keywords | HA-MRSA, CA-MRSA, LA-MRSA, Epidemiology, Transmission

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INTRODUCTION

Staphylococcus aureus is a bacterium of significant importance because of its ability to cause a wide range of diseases and capacity to adapt to diverse environmental forms (Lowy, 1998; Waldvogel, 2000). The organism colonises skin, skin glands and mucous membrane, causing infections both in human and animals such as rashes, inflammations of bones and the meninges as well as septicaemia (Aklilu et

al., 2010). In addition, *S. aureus* causes inflammation of the mammary gland in bovine and the lower part of the foot in poultry (Quinn et al., 2000). Penicillin and its derivatives, including methicillin have been used for the treatments of infections caused by *S. aureus* (Rayner and Munckhof, 2005). However, certain strains of *S. aureus* developed resistance known as methicillin resistant *Staphylococcus aureus* (MRSA). At present, less than 90% of *S. aureus* strains are resistant to most penicillin derivatives (Freeman-Cook

and Freeman-Cook, 2006) and ordinary antimicrobial agents like drugs from the family of aminoglycosides, macrolides, chloramphenicols, tetracyclines and fluoroquinolones (Lee, 2003).

A gene known as *mecA* gene is responsible for the resistance to methicillin which codes for penicillin-binding protein PBP 2A (Wienders et al., 2002). Lately, a new methicillin resistance mechanism gene, *mecC* was described in *S. aureus* (Porrero et al., 2014). García-Álvarez et al. (2011), Paterson et al. (2012), Walther et al. (2012) and Paterson et al. (2014) reported MRSA isolates carrying *mecC* gene from humans and animals. Harrison et al. (2013) suggested the public health hazard of *mecC*-positive MRSA isolates as it has been isolated in human case and their livestock.

Until recently, MRSA was associated with prior exposure to health care facility, and as such, was considered a nosocomial pathogen (Tiemersma et al., 2004). A number of publications on MRSA infections in populations lacking traditional risk factors (Herold et al., 1998) have been reported. This raised concern for infections originating from the community and veterinary species (Cohn and Middleton, 2010). Reports of MRSA isolation in domestic animals seems to be rising in number (Devriese and Hommez, 1975; Hartmann et al., 1997; Tomlin et al., 1999; Lee, 2003; Goni et al., 2004; Rich and Roberts, 2004). The epidemiology of MRSA isolates from human and animal sources showed that for certain strains, a cross-infection might have happened (Seguin et al., 1999; Strommenger et al., 2006; Weese et al., 2006). Studies conducted by Feirrer et al. (2011) and Verkade and Kluytman (2014) suggested that animals can be a potential source of MRSA infection to humans.

Therefore knowledge on the epidemiology of MRSA will underpin effective prevention and control strategies, including the rational use of antibiotics. This review article wishes to highlight the epidemiology and possible source of MRSA transmission in hospitals, community and livestock settings.

HISTORICAL BACKGROUND OF MRSA

Alexander Fleming conducted a research and reported the bactericidal effects of a fungal contaminant

that produced penicillin against *S. aureus* growing on culture plates (Fleming, 1929). A mass production of the drug from vats of cornsteep liquid growing on the mold was preceded due to the high mortalities during World War II (Neushul, 1993). Subsequently, there was a dramatic drop in death rates from bacterial pneumonia and meningitis in World War II compared to World War I. This led to the development of penicillin as the first major driver in selecting for resistant *S. aureus*. In 1940, an active β -lactam ring enzyme was described in *Escherichia coli* that are capable of hydrolyzing the penicillin. This enzyme was later named "penicillinase" (Abraham and Chain, 1940) while in 1944; penicillinase production was also discovered in *S. aureus* (Kirby, 1944). In 1948, it was observed that over 50% of staphylococcal isolates recovered from patients in a United Kingdom hospital were resistant to penicillin (Barber and Rozwadowska-Dowzenko, 1948). Since then to date, 90 to 95% of *S. aureus* strains worldwide are penicillin resistant, with the plasmid encoded penicillinase readily transferable via transduction or conjugation. A penicillinase-resistant penicillin known as methicillin was introduced in 1959 to combat penicillin-resistant *S. aureus*, but within a year, late Professor Patricia Jevons reported the first human *S. aureus* strain to be methicillin resistant in UK hospital (Kim, 2009). In 1962, an epidemic occurred at a hospital called Queen Mary's Children's Hospital, Carshalton. These strains became widespread in hospitals and into communities by the 1960's (Spink, 1978). In 1968, United States recorded the first outbreak of MRSA (Palavecino, 2004) while in the 1970s, *S. aureus* strains have become resistant to most penicillinase-stable penicillins. It was first assumed to be a disease of human origin until when MRSA was first isolated in 1972 in a mastitic cow (Deveriese et al., 1972). Thereafter, reports of MRSA infection became established in domestic and wild animals (Rich and Roberts, 2004; Wardyn et al., 2012).

EPIDEMIOLOGY OF MRSA

Epidemiological typing of MRSA strains resulted in the recognition of different lineages that are zoonotic, humanosis and/or host specific. Seventeen epidemic strains of human MRSA have been described in the United Kingdom (Aucken et al., 2002) but the most dominant are EMRSA-15 and EMRSA-16 (Hardy et al., 2004). The EMRSA-16 clone represents ma-

major cause of human MRSA infections in Europe and America (Holden et al., 2004). In Africa, epidemiological data on the predominant clones responsible for most epidemics is poorly documented. According to Breurec et al. (2011), the most predominant clones of African origin are ST88-IV, ST5-IV and ST239-III which are CA-MRSA. ST88-IV is a clone identified both in hospitals and community infections. The European lineage (EMRSA-16) has been described to originate from sub-Saharan Africa (Stegger et al., 2014) and has been reported in hospital and community acquired infections in Algeria (Abdulqader et al., 2014). Other lineages of human origin include CC1, CC5, CC8, CC22, CC30 and CC45 while MRSA lineage predominant in pigs and other food animals is CC398 (Witte et al., 2007; Feßler et al., 2012). Interspecies transmission of the strain CC398 (ST398) is a potential hazard and can be facilitated by frequent contact, environmental contamination and individual's immunity (Declercq et al., 2008). Three major settings were recognized according to host specification, reservoir and source of transmission (Millar et al., 2007).

HEALTHCARE-ASSOCIATED MRSA (HA-MRSA)

MRSA isolates from hospital settings has been gradually increasing in the United States and other parts of the world (Summary of MRSA prevalence from different countries across the world is presented in Table 1). However, reports in 2011 surveillance programme in USA suggest the recent decline in MRSA infections specific to hospital settings (Raymund et al., 2013). Depending on the study area and sample size, high rate of MRSA rates (>50%) have been reported in USA, Asia and Malta, intermediate rate (25-50%) reported in Africa, China and Europe while in some part of Europe, the prevalence rate is relatively lower than 50% (Mejia et al., 2010). Stefani et al. (2012) compiled the prevalence rates of HA-MRSA in some European countries like France, Ireland and UK and reported decline in hospital cases. While in Asia particularly South Korea (77.6%), Vietnam (74.1%), Taiwan (65%) and Hong Kong (56.8%) reports on HA-MRSA infections is still high. The major lineage responsible to the hospital spread of MRSA between these continents is CC8 (ST239) (Harris et al., 2010). For MRSA acquired in hospitals, colonisation do increases the chance for infection (Safdar and Bradley, 2008). Anterior nares is the usual site for MRSA

colonization, although other anatomical sites such as hands, perineal region, skin wounds, throat, genitourinary tract and the digestive tract may also be colonized (Sanford et al., 1994). High chance of hospital colonization may be from contact with MRSA colonized patient or contaminated objects. Respiratory infection is a predisposing factor for dissemination of MRSA through aerosols (Kucers and Bennett, 1987) which can cause serious infections and complications. Generally, HA-MRSA results in dermatitis, septicemias, heart and lung diseases which are mostly seen in immunocompromised people. Risk factors include hospitalization, surgery, dialysis and previous history of MRSA infection (Umaru et al., 2011).

COMMUNITY-ASSOCIATED MRSA (CA-MRSA)

MRSA strains acquired in the community were first reported in the late 1990s in patients with no history of exposure to healthcare settings (Umaru et al., 2011). The most common lineage in this case was USA300 (CC8-ST8) in the USA. These strains are mostly responsible to skin and soft tissue infections. In comparison, the most dominant lineage causing infection in Europe is CC80 (ST80). However the strain USA300 has also been reported in Europe (Tietz et al., 2005). Transboundary transmission of MRSA strain is reported between countries like North America and Middle East, Asia and South America (Stefani et al., 2012). The spread of CA-MRSA has extended to healthcare centres in USA and France (Donnio et al., 2004). Outbreaks of CA-MRSA is mostly seen from populations such as sports teams (Collins and O'connell, 2012), prisons (Palavecino, 2004), day care centers (Simmonds et al., 2008), military quarters (Marchese et al., 2000) homeless people (Yano et al., 2000), and intravenous drug users (Torres-Tortosa et al., 1994). Risk factors include international travel (Mikael et al., 2010), overcrowding, compromised skin, poor hygiene and sharing of items such as towels, sporting equipment and unsterilized first aid instruments (Kazakova et al., 2005).

LIVESTOCK-ASSOCIATED MRSA (LA-MRSA)

The scope of MRSA infection is not limited to human medicine only but also in Veterinary Medicine (Lee, 2003; Baptise et al. 2005; Voss et al., 2005; Khanna et al., 2008; Smith et al., 2008). MRSA was first considered a human infection until when it was isolated in a dairy cow with mastitis (Devriese et al., 1972) and in pigs (Stefani et al., 2012). The most pre

Table 1: Prevalence of MRSA carriage in some countries across the world

Country	Sample size	Prevalence %	Source	References
Argentina	591	16	Hospital	Egea et al., 2014
Bangladesh	49	53.1	Hospital specimens	Afroz et al., 2008
Bolivia	585	0.5	community	Batoloni et al 2013
Cameroon	295	34.6	Hospital staff/patients	Gonsu et al., 2013
Chile	246	80	Hospital	Guzman-Blanco, 2009
Columbia	538	92.4,65.1,43.6	Hospital record	Jiménez et al., 2012
Congo		60	patients	Iyamba et al., 2014
Costa Rica	674	58	Hospital	Guzman-Blanco, 2009
Cuba	80	6	Hospital	Guzman-Blanco, 2009
Equator	1363	25	Hospital	Guzman-Blanco, 2009
Ethiopia	118	44.1	Hospital	Shibabaw et al., 2013
Guatemala	1483	64	Hospital	Guzman-Blanco, 2009
Hongkong	NK	75	NK	Diekema et al., 2000
Honduras	393	12	Hospital	Guzman-Blanco, 2009
Indonesia	1502	4.3	Hospital	Santosaningsih et al., 2014
Japan	90	44.4	Environmental surfaces	Asoh et al., 2005
Kenya	950	7.0	Hospital	Aiken et al., 2014
Malaysia		26	Hospital	Norazah, 2008
Mexico	497	52	Hospital	Guzman-Blanco, 2009
Nepal	750	26.14	Hospital	Kumari et al., 2008
Netherland	9859	0.03	Hospital	Wertheim et al., 2004
Nicaragua	296	20	Hospital	Guzman-Blanco, 2009
Nigeria	208	19.2	Hospital	Olowe et al., 2013
North India	6743	46	Hospital	Arora et al., 2010
Paraguay	980	44	Hospital	Guzman-Blanco, 2009
Peru	1431	80	Hospital	Guzman-Blanco, 2009
Singapore		35	Hospital	Hsu et al., 2007
Sudan	426	69.4	Hospital	Elimam et al., 2014
Thailand		41.5	Hospital	Trakulsomboon and Thamlikitkul, 2008
Uganda	188	31.5	Hospital	Ojulong et al., 2008
Uruguay	2114	59	Hospital	Guzman-Blanco, 2009

NK: Not known

dominant lineage in livestock is CC398 which has been reported in Europe, USA and Asia (Monecke et al., 2011). However, the prevalence of LA-MRSA CC398 in these countries is still very low (Stefani et al., 2012). But in countries like Denmark, Netherland and Belgium, the report of MRSA CC398 in livestock is high (Köck et al., 2009a; Köck et al., 2009b). Epidemiological studies in UK indicate the spread of

LA-MRSA into hospitals particularly in individuals with frequent animal contact (Paterson et al., 2012). Recently, there is evidence of MRSA transmission between human-to-animals and animals-to-humans (Umaru et al., 2011). Voss et al. (2005) reported 23% of pig farmers colonized MRSA from a pig farm in the Netherlands with while VanRijen et al., 2008 found 32% of farm workers colonized with MRSA.

Table 2: Prevalence of MRSA infection and carriage rates in different animals

Year	Country	Species	Sample	Prevalence (%)	Detection Methods	MRSA Characterization	References
2010/2012	Germany	Dogs, cats, horses	Wound specimen	62.7, 46.4, 41.3	<i>Spa</i> , MLST	CC22, CC5, CC398	Vincze et al., 2014
2003/2004	Germany	Cats	Clinical	10	BA/ChromAgar	ST22/SCCmecIV	Walther et al., 2008
2007	Belgium	Horses	Clinical	10.9	Phenotypic, PCR	ST398, t011& t1451	Van den Eede et al., 2009
2007/2008	Netherland	Calves	Nasal sample	88.28	Phenotypic and PCR	ST398	Graveland et al., 2010
2010	Germany	Pigs	Healthy swabs	52	PCR, MLST	CC398	Alt et al., 2011
2006/2008	Czech Republic	Goat Farm	Goats milk	1.1	PCR	SCC _{mec} IV, spa type t064	Stastkova et al., 2009
2009/2011	Belgium	Cows/ Broilers	Nasal, cloaca	5.0, 5.0	PCR, MLST	CC599, CC130, CC398	Vandendriessche et al., 2013
2years	Malaysia Egypt	Tilapia Tilapia	Brain, eyes, kidney swabs	50	MSA/PCR	NK	Atyah et al., 2010, Soliman et al., 2014
2009		Elephant	Clinical	100	PFGE	USA300	Leggiadro, 2009
2006	Canada	Dolphin, Walrus	Necropsy Nasal swab	33.3, 16.7	PFGE	USA100	Faires et al., 2009

BA: Blood Agar; MSA: Mannitol salt agar; PCR: Polymerase Chain Reaction, NK: Not Known; PFGE: Pulse Field Gel Electrophoresis

Table 3: Prevalence of MRSA isolates from major food/meat product

Food Product	Samples collected	Prevalence (%)	Source	References
Beef	395	42 (10.6)	Farm	De Boer et al., 2009
Milk	894	265 (29.6)	Farm	Lee, 2003
Pork	395	26 (6.6)	Retail	O'Brien et al., 2012
Chicken	25	11 (44.0)	Retailer	Karmi, 2013
Turkey	116	41 (35.3)	Retail Trade	De Boer et al., 2009
Guinea fowl	118	4 (3.4)	Retail Trade	De Boer et al., 2009
Lamb/mutton	324	20 (6.2)	Retail Trade	De Boer et al., 2009
Tilapia Fish	559	198 (50)	Fish pond	Atyah et al., 2010
Game birds	178	4 (2.2)	Retail Trade	De Boer et al., 2009
Veal	119	20 (16.8)	Retail	Anonymous, 2007

Likewise, Stein (2009) conducted a study among pig farmers in North America and found colonization rates of 20%. These results backup other findings that revealed the chances of animals becoming reservoirs of human MRSA infections regardless of location (Feingold et al 2012). In addition, human-to-human transmission can occur following one's exposure

MRSA IN COMPANION ANIMALS

Animals such as dogs, cats and horses have become an important part of most families particularly in developed countries like USA and UK (chomel and sun 2011). Therefore, there are high chances of human colonization or infection with MRSA from these animals (Mustapha et al., 2014). In the UK, 1.5% of MRSA were recovered from samples of infected companion animals (Rich and Roberts, 2004) and dogs are more infected/colonized with MRSA in comparison to cats (Morgan, 2008). Skin and soft tissue infections are the main form of disease manifestation. MRSA strains isolated in most UK hospitals are identified as EMRSA-15 (ST22) and EMRSA-16 (ST36) (Ellington et al., 2010) while the strains isolated in USA pets are the USA100 (ST5) which has been documented in HA-MRSA infections in humans (McDougal et al., 2003). In addition, a study in UK recovered MRSA clone (ST398) in dogs and horses that were characteristic of livestock animals (Loeffler et al., 2009).

Reports of MRSA colonization in horses with a percentage rate of 0 to 11% has been published (Loeffler et al., 2011). Most cases and outbreak of MRSA infections were reported in large stables and post-operative complications (Weese et al., 2005; Morgan, 2008). In horses, MRSA lineages isolated were dis-

ting to colonized or infected animals due to isolation of MRSA strains from people with no animal contact (Huijsdens et al., 2006). High risk groups are the veterinary clinic personnel and the animals care givers (O'Mahony et al., 2005; Moodley et al., 2005; Wulf et al., 2006; Hanselman et al., 2006).

tinct from the strains isolated in humans (Loeffler and Lloyd, 2010).

MRSA IN WILDLIFE

Although the role of wildlife as reservoir for MRSA colonisation and/or infection has not yet been established, there are several studies that revealed the isolation of MRSA in many captive wildlife animals (Loncaric et al., 2014). A study by Wardyn et al. (2012) revealed the isolation of MRSA from cottontail rabbit and a lesser yellow migratory shore bird. Other studies include isolation of MRSA from Wild rat, (Himsworth et al., 2014), wood mice (Gómez et al., 2014) red deer, Iberian ibex, vulture, wild boar (Porro et al., 2012). In some of the studies, the homologue of *mecA* gene known as *mecC* strain (ST398 and ST1) were isolated and suspected to be of livestock and human origin (Porrero et al., 2012). Although the *mecC* homologue is currently uncommon in human infections globally, it has been identified recently in human and animal infections in the UK, Denmark and Ireland (Paterson et al., 2014b). The most common animal lineage that causes disease in wild life is CC130 and ST425 (Paterson et al., 2014a).

As the menace of MRSA colonization is extending

into the wild life, control of the disease in human and domesticated animals will become a new challenge. This is due to the fact that wild animals can serve as source of animal and human colonization (particularly park rangers and zoo keepers) as well as contamination of the environment (Guideline for management of zoonoses, 2011; Chethan Kumar et al., 2013). Summary of MRSA prevalence in animals (both wild and domesticated) is presented in Table 2 according to some reports published.

MRSA IN ABATTOIRS, FOOD PROCESSING UNITS AND ANIMAL PRODUCTS

The environment of abattoirs and food production units are contaminated with MRSA (EFSA, 2009). The sources of contamination can either be the animals moving into the abattoir for slaughter or the workers involved in processing the end product (Gilbert et al., 2012). Contaminated skin, feces, infected organs and water used in processing are the vital sources of contamination in abattoirs and food processing units (Soonthornchaikul et al., 2006). Some studies suggest that *S. aureus* from food handlers can be part of normal body flora that subsequently contaminates carcasses. Broens et al. (2011) conducted a study and found 12 out of 117 pigs tested MRSA positive in a slaughterhouse after being tested negative during and after transportation.

Animal food products such as meat, meat products and milk may become contaminated with MRSA through slaughter or milking of colonized/ infected animal, thus, contaminating the product and environment. MRSA strains have been discovered from foods such as bovine milk and cheese, pork and beef as well as raw chicken meat (Kwon et al., 2006; Normanno et al., 2007; Van Loo et al., 2007; O'Brien et al., 2012). The strains of MRSA isolated in most food samples include ST398, ST125 and ST217 (Faccioli-Martins and de Souza da Cunha, 2012) while the recent mecC homologue of mecA gene has been isolated in bovine milk in England (Paterson et al., 2014b). The presence of these strains on food products could suggest possible human or animal contamination. An important link in food borne infections connecting humans and food producing animals is the meat and milk or their products (Mayrhofer et al., 2004). Although food products may serve as vehicle for MRSA transmission, consumption of such meat carry only small risk as *S. aureus* found on meat surfaces and can be killed

by high temperature. However, there is high risk of transmission from live animal or raw meat to people working directly with animals or their products. The prevalence of MRSA isolation from food/meat products is presented in table 3.

MRSA TRANSMISSION IN HOSPITAL SETTINGS

For hospital infection, the hands and nostrils of colonized individuals are the major sources of MRSA transmission. MRSA is released into the hospital environment either through aerosol, skin cells or stools of infected patient (Klotz et al., 2005). Areas contaminated in the hospital include medical instrument, beddings, clothing, furnitures, toiletries and the atmosphere (Dancer, 2008). Gehanno et al. (2009) found similar strain of MRSA in patients of a hospital and the room atmosphere. While Loeffler et al. (2005) and Weese et al. (2004) reported MRSA in environmental samples collected from small animal veterinary hospital and equine veterinary hospital, respectively. Although, hospital cleaning reduces MRSA contamination of the environment, in some cases it does not eliminate it.

MRSA IN THE COMMUNITY

Some studies investigated environmental contamination of MRSA outside hospital settings (EFSA, 2007). Reports include continuous colonization of a medical staff which was related to contamination of home environment (Allen et al., 1997; de Boer et al., 2006). Again, contamination of animal housing revealed the possibility of human and animal colonization. Van Den Broek et al. (2008) isolated MRSA from pig house dust and humans working in MRSA positive pig farms.

Airborne MRSA in livestock settings are mostly seen in dust particles that are derived from the animals. MRSA was isolated in dust from infected herds which may be subsequently inhaled by workers in the farm (EFSA, 2007; Schulz et al., 2012). Transmission of disease through water may occur in aquatic animals such as fish. Transmission from fish to humans could be through injury from cleaning aquarium with bare hands (Alinovi et al., 1993) and exposure to fish tank water (Kern et al., 1989).

MRSA DETECTION IN HUMANS AND ANIMALS

In an effort to control MRSA in major settings (hospital, community, animals) colonized and infected

humans, animals and environmental surfaces must be identified. The menace of MRSA colonization and infection has extended from human, companion and food animals into wildlife animals. The screening of human carriers in hospitals and communities is necessary for the successful diagnosis and control of MRSA. In addition, companion animals with skin and soft tissue infections should be screened for MRSA. Sites for screening of MRSA colonized animals include nose, skin, perineum and rectal or cloacal swabs (de Neeling et al., 2007; Khanna et al., 2008) and nostril for humans (Peacock et al., 2001). Nasal screening alone identifies 80% of carriers, and addition of sampling from throat, may increase this to 92% (Grundmann et al., 2006). For environmental samples, swabs are taken from dust samples (EFSA, 2007; Broens et al., 2008), tables, containers, feed material or feces and bedding material (Lee, 2003). Other samples like milk and meat from animals and cloacal swab from poultry should be cultured for detection of MRSA.

Various methods are applied for the detection of MRSA through phenotypic and genotypic characterization of samples from infected sites such as skin lesions, abscesses or blood. Both has advantages and disadvantages such as speed, reliability and accessibility. Phenotypic methods involves standard microbiological technique of *S. aureus* detection which include Gram staining, colonial morphology, catalase and coagulase tests, pigment production and anaerobic growth (Karthy et al., 2009). Additional methods include Minimum Inhibitory Concentrations, methods that detect *mecA* gene or PBP2⁰ protein and media containing oxacillin (Louie et al., 2001). Selective enrichment media have been developed to achieve isolation and identification of MRSA in a single step, thus by-passing the conventional procedures (Stoakes et al., 2006). Ideal enrichment media contains indicators, inhibitory agents and antibiotics usually oxacillin or cefoxitin. Examples are Oxacillin Resistant Screening Agar Base (ORSAB) which result in intense blue colonies (Becker et al., 2002), CHROM agar which give rise to a rose to mauve color and MRSA ID which forms distinctive green colonies.

In addition to culture media, antimicrobial susceptibility tests (AST) such as agar disc diffusion technique or minimum inhibitory concentration are used in diagnostic laboratories to isolate MRSA (Aklilu et al., 2010). Detection of the *mecA* gene is considered as

the reference method for determining methicillin resistance (Chambers, 1997). Resistance of *S. aureus* to oxacillin and/or cefoxitin provides a clue for MRSA suspicion (van Enk and Thompson, 1992). Oxacillin and cefoxitin test are the preferred method for testing *mecA* resistant gene of *S. aureus* (CLSI, 2006). In order to report isolates as resistant or susceptible should be based on the result obtained on the cefoxitin test. Cefoxitin disc diffusion is the most sensitive methods for detecting MRSA isolates showing negative and positive predictive values of 100% and 98%, respectively (Valesco et al., 2005).

A more advanced technique usually accompanies the phenotypic methods in order to enhance specificity and time. Molecular methods such as PCR are used to detect *S. aureus* specific DNA sequences encoding for protein synthesis and the *mec* genes. Other molecular typing methods include pulsed-field gel electrophoresis (PGFE) and multilocus sequence typing (MLST), Staphylococcal Protein A Gene (*spa*) locus typing and Staphylococcal Cassette Chromosome (*SCC_{mec}*) typing. The strength and weaknesses of the above genotypic methods are presented in table 4.

TREATMENT AND CONTROL OF MRSA

The indiscriminate exposure of humans and animals to antibiotics created problem through acquisition and dissemination of MRSA which limit the choice of treatment. Most antibiotics used for treatment of MRSA infection has been reported to have developed resistance (Ayliffe, 1997). In order to manage the risk of antibiotic resistance in humans and animals, decolonization of carriers and monitoring of resistant strains through susceptibility test will surely help. The use of antibiotic to treat infection should depend on the result of antimicrobial susceptibility testing, although most strains appear ineffective during treatment even when sensitive in routine susceptibility test. Antibiotics such as trimethoprim-sulphamethoxazole, clindamycin and doxycycline are reported to be effective in the treatment of CA-MRSA infection (Ernst, 2012). Newer drugs such as oritavancin, telavancin omadacycline, tedizolid and dalbavancin have a promising impact on the treatment of MRSA. Other existing agents such as fosfomycin and fusidic acid are under investigation for potential used in the treatment of MRSA infection (Burke and Warren, 2014).

Table 4: Summary of the comparative strength and weaknesses of current genotypic methods used for MRSA typing

Methods	Principle	Strengths	Weaknesses	References
Pulsed-field gel electrophoresis (PFGE)	<i>S. aureus</i> DNA fragments are move down the gel, creating unique band patterns that are then compared with those of other isolates to identify related strains	High discriminatory power	Technically demanding Slow Limited inter laboratory portability Multiple nomenclature	Tenover et al., 1995
Multilocus sequence typing (MLST)	Uses sequence analysis of ~500-bp internal fragments of seven housekeeping genes: <i>arcC</i> , <i>aroE</i> , <i>glpF</i> , <i>gmk</i> , <i>pta</i> , <i>tpi</i> , and <i>ycjL</i> . The DNasequences are compared to those of previously identified alleles at each locus on the MLST online database	Phylogenetic structure of core genome Inter laboratory portability Standard nomenclature	Limited discriminatory power Low throughput Expensive	Enright et al., 2000
<i>S. aureus</i> protein A (<i>spa</i>)	Typing of a single locus zone in the polymorphic region X of <i>S. aureus</i> A which involves duplication and mutation in the variable repeats of 24bp	Rapid High throughput Inter laboratory portability Standard nomenclature Attribution of MLSTs by BURP algorithm	Moderate discriminatory power Misclassification of particular STs due to recombination/homoplasmy	Szabó (2014)
SCC _{<i>mec</i>} typing	Used to define the 7 major <i>mec</i> and <i>ccr</i> gene of 7 major SCC- <i>mec</i> types and subtypes ranging from 20 to 67kb	High discriminatory power	No universally used assay No nomenclature used but a combination of SCC _{<i>mec</i>} typing and MLST has been proposed	Chongtrakool et al., 2006
Rep-PCR typing	Polymorphism in chromosomal inter-repeat element spacers	Rapid High throughput	Limited discriminatory power No validated interpretation criteria No standard nomenclature	Struelens et al., 2009
Multilocus VNTR analysis (MLVA)	Polymorphism in number of chromosomal VNTR elements	Rapid High throughput	Limited discriminatory power No validated interpretation criteria No standard nomenclature	Struelens et al., 2009

As the MRSA epidemic becomes life threatening and beyond antibiotic therapy, development of vaccine to combat the disease became important (Cimolai, 2006). The first attempt to develop *S. aureus* vaccine was by the use of Streptococcus pneumonia and hemophilus influenza vaccine model. The formula was called Staphvax developed by biopharmaceuticals in 1990s though unsuccessful (Mckenna, 2014). Continuous attempts were made by different institutions like University of Chicago and the Absynth biologics which uses clotting factors to produce abscess and membrane protein, respectively (Cheng et al., 2010). However, trial on mice did not produce the desired result of abscess development and antibody production (Hu et al., 2013). Recently, Russell (2012) suggested the role of polyvalent pneumococcal vaccine to develop vaccine for staphylococcal infections. Therefore based on published data, researches are still being conducted on MRSA vaccine development but no established vaccine is available. In the absence of preventive measures such as vaccination, basic control options that will reduce MRSA colonisation or infection in humans and animals are necessary.

Basic hygiene, good husbandry and biosecurity measures on farms, abattoirs and food processing units have a tendency to reduce the spread of MRSA in animal population. Individuals with frequent animal contact should be educated on the risk of MRSA transmission in animals or their environment. In hospitals, hygienic measures particularly hand washing before and after contact with contaminated surfaces and the avoidance of close contact with discharges from nose, mouth and wounds of infected human and animals will surely reduce the chances of transmission. Decolonization of MRSA positive carriers' either through the use of antibiotic therapy (chlorhexidene or muricidin) or culling of affected animals or product will reduce the spread in the environment. Medical practitioners should be encouraged to choose antibiotic based on susceptibility test and to wear protective equipment during surgery and handling of patients to reduce contamination and spread.

CONCLUSION

In conclusion, the prevalence of MRSA isolation from hospitals, community, animals and their products has increased in different geographical locations. The continuous vigilance of MRSA through monitor-

ing of newer strains, their characteristic, host specificity and transmission routes in each of the settings (HA-MRSA, CA-MRSA, LA-MRSA) will help in effective control of MRSA. MRSA is no longer infection acquired in the hospital alone, but rather in communities through contact with domesticated and wild animals as well as food products and the environment. Therefore, there is need for effective control of MRSA in all the settings and the avoidance of indiscriminate use of antibiotics to prevent further selection of resistance by microorganisms.

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