

# A Review of Livestock-Associated Methicillin-Resistant Staphylococcus aureus (LA-MRSA) on Bovine Mastitis

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## ABSTRACT

Bovine mastitis is a disease in dairy cows that can cause productivity losses in the form of decreased quality and quantity of milk production. Staphylococcus aureus is the main pathogenic bacterium among a variety of bacteria that are responsible for mastitis cases in dairy cows. Staphylococcus aureus which is resistant to methicillin or known as Methicillin-resistant Staphylococcus aureus (MRSA) is resistant to most  $\beta$ -lactam antibiotics. Livestock associated-methicillin-resistant Staphylococcus aureus (LA-MRSA) is a global threat to the health of livestock and humans. This bacterial strain is responsible for a variety of diseases ranging from superficial skin infections to life-threatening diseases. LA-MRSA isolates from both animals and humans are sensitive to vancomycin antibiotics. In addition, LA-MRSA isolates were also sensitive to linezolid, amikacin, and teicoplanin. Prevention of LA-MRSA transmission can be done by improving the biosecurity and environmental cleanliness of dairy cattle pens, as well as regulating animal and human health care regularly.

**Keywords:** Bovine mastitis, LA-MRSA, Human health, Antibiotics resistance

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## INTRODUCTION

Bovine mastitis is a disease in dairy cows that can cause productivity losses in the form of decreased quality and quantity of milk production. Dairy cows suffering from mastitis have decreased milk production by 30% per quartile which can have an impact on decreasing milk production by 15% per dairy cow / lactation, making mastitis as one of the most important problems affecting the dairy industry worldwide [1]. Mastitis is generally associated with the relationship between milking management and infectious agents. Among various types of microorganism infectious agents, pathogenic bacteria are infectious agents that are very much found in the environment of dairy cows, which can be a threat to the production of dairy cows. In addition, one infected quartile can affect a decrease in milk production by 10% to 12% per cow / lactation [1].

Staphylococcus aureus is the main pathogenic bacterium among a variety of bacteria that is responsible for up to 40% of cases of mastitis in dairy cows [2].  $\beta$ -lactam antibiotic therapy which is often used in the treatment of mastitis cases in dairy cows [3], excessive and irrational antibiotic administration can cause a new problem namely the emergence of strains of bacteria that are resistant to antibiotics that are resistant to antibiotics [4].

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Staphylococcus aureus that is resistant to methicillin or known as Methicillin-resistant Staphylococcus aureus (MRSA) is resistant to most  $\beta$ -lactam antibiotics because of

the activity of penicillin-binding proteins (PBPs) that are inhibited by antibiotics replaced by PBP (PBP2a) function with low affinity for most  $\beta$ -lactam antibiotics. For these medicines. The low affinity of PBP2a is encoded by the *mecA* and *mecC* encoding genes (69% homologous with *mecA*) which are located on cellular genetic elements or commonly referred to as staphylococcal chromosome tapes (SCCmec) [4].

Based on the source of infection there are three types of MRSA categories described, namely hospital-related MRSA (HA-MRSA), community-related MRSA (CA-MRSA), and livestock-related MRSA (LA-MRSA) [5].

Little is known about MRSA related to livestock, especially in dairy cows. This type of MRSA belongs to the 398 clonal complex (CC398), known as cattle-related MRSA (LA-MRSA). This type of MRSA isolate can also be found in other animals and can cause cases of infection in humans [6].

The presence of Methicillin-resistant Staphylococcus aureus related to livestock (LA-MRSA / CC398) has been reported in food of animal origin in the livestock industry in various European countries [7]. Concerns arose over the widespread spread of LA-MRSA / CC398 on dairy farming, which could affect milk productivity and health of dairy cows. LA-MRSA isolates originating from different dairy cows from several countries have been reported and also explained the transmission of LA-MRSA transmission to humans [8].

Animal-related methicillin-resistant Staphylococcus aureus (LA-MRSA) is a global threat to the health of livestock and humans. This bacterial strain is responsible for a variety of diseases ranging from superficial skin infections to life-threatening diseases [9].

Therefore this article aims to describe about mastitis cattle, LA-MRSA microbiology, LA-MRSA epidemiology,

LA-MRSA risk factors, one health approach, and LA-MRSA control.

### Bovine Mastitis

Bovine mastitis is an infectious udder disease that is contagious to the milk glands of dairy cows, has a high prevalence rate throughout the world both in cattle and udder quarter [10-12]. Dairy milk sufferers of mastitis cannot be milked regularly because of damage to the mammary gland cells. In addition, clots form in the milk of cows with mastitis, due to enzymes produced by pathogenic bacteria, such as the coagulase enzyme, which cause conversion of fibrinogen to fibrin [13, 14]. In general, these factors can cause a decrease in milk production, the quality of milk that turns bad, and increase the cost of care and treatment for mastitis dairy cows, this causes the milk industry to suffer great losses [15, 16].

Pathogenic bacteria that cause mastitis include microorganisms that multiply and survive on the surface of the udder skin and quartile lesions, such pathogenic bacteria include *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Streptococcus dysgalactiae*, as well as environmental pathogenic bacteria such as *Escherichia coli*, *Streptococcus uberis* and other bacteria. [10, 17, 18]. This bacterium infects the milk glands of dairy cows through quartile ducts, where these bacteria multiply, colonize and release toxins that can damage the mammary gland cells [11, 12]. Infection in milk is characterized by increased activity of lactate dehydrogenase (LDH) in milk [19, 20]. Shortly after infection, an inflammatory response will arise, then affect the number of milk somatic cells and inflammatory cytokine levels, such as interleukin-6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [21-24]

To detect mastitis is usually based on inflammatory indicators, such as somatic cell count (SCC), enzyme activity (eg LDH and NAGase), electrical conductivity, and inflammatory cytokines. However, mastitis detection using the California Mastitis Test (CMT) is the most widely used for early detection of bovine mastitis, because this method is more practical, easy to use to measure somatic cell levels in milk, is faster, and is inexpensive [25].

Mastitis in dairy cows can be classified into two namely clinical mastitis and sub-clinical mastitis depending on the level of inflammation [26]. Clinical mastitis can be observed from the physical condition of damaged milk and abnormal udder conditions. Inflammation occurs in the mammary glands so that there is a noticeable change in the udder and milk. Clinical mastitis is characterized by reddish udder, increased udder temperature, pain in the udder, impaired udder function, and abnormalities in milk conditions [1]. Clinical mastitis can be classified based on the severity of the inflammatory response ranging from mild, acute, per acute, and chronic. Cases of clinical mastitis can occur in all groups of dairy herds, although the dairy herds have good maintenance management, dairy herds with high levels of milk production are likely to have high cases of clinical mastitis [27]. The most common pathogenic bacteria causing clinical mastitis are *Staphylococcus aureus*, *Klebsiella* spp, *Streptococcus uberis*, *Streptococcus dysgalactiae*, *Escherichia coli* [27]. Whereas sub-clinical mastitis is characterized by inflammation of the mammary gland without physical changes in the udder and no severe lesions are seen in the udder, but there is a clear change in the number of milk somatic cells through CMT examination [1, 28].

### Microbiology of *Staphylococcus aureus* and Methicillin-resistant *Staphylococcus aureus* (MRSA)

Mastitis microorganisms are classified as "contagious" and "environmental" based on their reservoir, source of infection, and mode of transmission [29, 30]. For infectious pathogens, infected mammary glands act as the main source of infection and transmission can occur during the milking process when clean areas are contaminated by infected milk droplets or when these droplets contaminate milking equipment, milking hands, and towels. For environmental pathogens such as ground level, cage floor, gutter, pasture. Environmental pathogens are usually associated with excessive humidity, mud and manure. Successful control of contagious microorganisms depends on maintaining clean and dry cage areas, whereas control of environmental microorganisms depends on aseptic milking systems [29].

*Staphylococcus aureus* is one of the main pathogenic bacteria that causes mastitis. Dairy cows infected with *Staphylococcus aureus* can be a major source of contamination in milk yields [31]. Especially for dairy cows with sub-clinical mastitis, *Staphylococcus aureus* infection can have a major effect on decreasing milk production and milk quality. *Staphylococcus aureus* is one of the most important pathogenic bacteria because of the combination of toxin-mediated virulence, antibiotic resistance, and invasion [32, 33].

Antibiotic-resistant *Staphylococcus aureus* is a major health problem in people throughout the world because antibiotics are widely used for the treatment and growth of livestock [34, 35]. Resistance of methicillin antibiotics and other  $\beta$ -lactam classes is obtained from a modified penicillin binding protein (PBP2a) which has a low affinity for  $\beta$ -lactam. PBP2a is encoded by the *mecA* and *mecC* encoding genes that are localized in a cellular genetic element called the *Staphylococcal Casette Chromosome mec* (SCCmec) [4]. Recent research reports that the *mecC* encoding gene is needed to confirm *Staphylococcus aureus* that is resistant to methicillin and other  $\beta$ -lactam class antibiotics, because the *mecC* encoding gene has a homologous nucleotide similarity of 69% with the *mecA* encoding gene [36-39]. The *mecC* encoding gene in MRSA has also been reported to be potential in zoonotic transmission [40, 41].

MRSA has become a major concern in society because these pathogenic bacteria are often found in farm animals and can infect humans. MRSA as a pathogen causing mastitis has been isolated in bulk tank milk [42-45]. Community-related MRSA infections (CA-MRSA) and hospital-related MRSA (HA-MRSA) have been reported in preliminary studies, whereas MRSA-related livestock (LA-MRSA) infections were first isolated from dairy cows [46]. Lately, LA-MRSA has become a major concern as pathogenic bacteria found in livestock, especially in dairy cows, which can transmit methicillin resistance to humans through meat or milk [47-58].

### Livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA)

*Staphylococcus aureus* consists of several lineages, each lineage associated with a specific host group (for example, cattle, poultry, cats, humans, etc.) [59]. In addition, previous studies have reported a lot of cross-species transmission between hosts (for example, from humans to animals or vice versa). The incidence of MRSA in animals was first reported in 1972 when MRSA was found in dogs [60] and dairy cows [61]. However, this first sporadic

report was caused by a strain of MRSA in humans. The sequence type ST398 known as LA-MRSA was first identified, later found in animals and food products of animal origin from continuous transmission and existing reservoirs. This strain has also been found in pigs, dairy cows, breeders, veterinarians, and people around the Netherlands in 2005 [62]. Since then, LA-MRSA CC398 in livestock has been widely reported throughout Europe and North America [63]. Other MRSA bloodlines have been found in pig populations in Italy (ST1, ST9, ST97) [64], Denmark (ST433) [65], Southeast Asia (ST9) [66-68] and Canada (ST5) [69]. LA-MRSA ST130 related to ruminants and humans is still rarely found in England. Whereas in Germany and Denmark a new methicillin resistance coding gene has been identified that has a homologous resemblance to *mecA*, the *mecC* encoding gene [36, 37, 70].

#### LA-MRSA on bovine mastitis

Cases of MRSA in livestock were first reported in the early 1970s, when the bacterium *Staphylococcus aureus* was isolated from milk of mastitis cows in Belgium [61] and categorized in the CC398 group [71]. Devriese and Hommez [72] suspected that the milk samples were contaminated by humans. Over the past few years, MRSA has been largely isolated from cows or milk in Korea [42, 73, 74], the Netherlands, Hungary, and Mexico [73, 75, 76]. There are also many reports of cases of MRSA from cows or milk in Brazil, the United States, Pakistan, Turkey, Italy, and Nigeria [77-79]. Later reports began to emerge about dairy cow infection caused by LA-MRSA CC398 [80]. On farms in the Netherlands, 18-31% of young calves are detected LA-MRSA [81]. In 2010, LA-MRSA was reported to be detected in 20% of calves in Germany [82]. In a survey study of 51 dairy farms in the Netherlands showing an average yield of 38% of breeders and 16% of their family members infected with LA-MRSA [83, 84] (Graveland *et al.*, 2011; Graveland *et al.*, 2010). Recently, there are other groups of LA-MRSA strains (CC1943, CC425, and CC130) that were originally specific lineages in dairy cows but also appeared in humans [85]. On dairy farms in Germany a number of LA-MRSA which are resistant to several antibiotics (multi-drug resistant) were isolated from mastitis cows [44, 80], most of which are MRSA ST398 related to animal strains, but these isolates are included in CC8 clonal complex groups were identified as strains of MRSA Irish-01 [86] epidemic in humans [87]. There has been a surge in cases of infection and colonization of CC398 in humans in the Netherlands, from 0% in 2002 to around 21% in 2006 [88]. A study in recent years shows that the annual incidence of MRSA cases in humans has more than tripled from 2001 to 2006 in which patients were infected with MRSA, 23% were infected from hospitals, 26% were infected from animals, 16% were infected from nosocomial transmission, and 10% are infected from the surrounding community [89]. The presence of LA-MRSA CC398 in dairy farms accompanied by an increase in LA-MRSA CC398 infection in humans is beginning to show that milk and dairy cows are risk factors, colonization, and the prevalence of LA-MRSA CC398 in humans in direct contact with dairy cows [88, 90-92]. This statement is further strengthened by the finding of a reduction in LA-MRSA CC398 infection rates in farmers who take breaks from direct care of dairy cows [83, 84]. People have come to dairy farms several times to collect samples at risk of LA-MRSA infection compared to people who rarely visit dairy farms, this study shows that

prolonged contact with dairy cows can be an important factor in increasing LA-MRSA colonization [93]. Meanwhile, most LA-MRSA isolates collected were from dairy cows with ST398 type [73], also found other ST types, such as ST72-t324, ST1-t286-SCCmec IV [43], ST59-t437-V [42], ST10-t127-SCCmec IVa genotype [75], SCCmec type IVg [94], t4795, t1730, and CC97 [95], and variants other than *mecA* called *mecC* ((*mecA*\_L GAGA251), have also been found in isolates MRSA ST425 and CC130 [36]. The *mecC* encoding gene has also been reported in Denmark MRSA CC130 isolated from dairy cows and their genotype characteristics, including MLVA (MT429), *spa* type (t843), and PFGE profile of dairy cow isolates that are similar to human isolates, allowing transmission between dairy cows to humans, humans to dairy cows, and fellow humans [40].

Geographical conditions in the origin of colonization, the prevalence of CC398, and cases of infection in humans are quite interesting to discuss. LA-MRSA isolates have been found in retail beef, but when sampling the nose and feces of 500 cattle in the Canadian cattle group, shortly before slaughtering, no LA-MRSA was found in cattle [96]. On the other hand, for a while cases of LA-MRSA CC398 infection in humans are the main cause of CA-MRSA infections in several European countries, LA-MRSA CC398 infections are still rare in North America although LA-MRSA CC398 is found in livestock [97]. The low cause of LA-MRSA CC398 infection in North America is likely due to differences in direct or indirect contact with livestock and food, and a much lower population level in livestock areas in North America, and the emergence of other MRSA strains that compete with human populations. Several previous studies have shown that MRSA found in cows is only specific to cows, most cases of MRSA infection in dairy cows have been reported also from humans [73, 75, 98, 99]. MRSA bovine, equine, porcine, feline, and canine isolates contained in the *pvl* gene and other virulence factors, such as *seb*, *sex*, *scn*, *chp* and *seq* genes, toxic toxin shock syndrome (*tst* or *tsst1*) [42, 100], proteases, Hemolysin, proteins such as capsules, superantigens, and genes related to biofilms [101-104], can pose serious health threats to people throughout the world.

#### LA-MRSA in milk

In general, cases of LA-MRSA from dairy cow isolates with mastitis have a fairly low prevalence rate [105]. After the first reports of MRSA cases appearing in mastitis dairy cows [61], sporadic MRSA cases began to appear in several herds, LA-MRSA strains have been detected from isolates between dairy cows with mastitis clinically and sub-clinically. In one study conducted in Korea [94], LA-MRSA isolated from dairy cow's milk had an isolation ratio of 0.18%. On dairy farms in Belgium it has been reported that a high percentage of LA-MRSA cases of 15% is found in nursing dairy cows, even cows have a previous history of LA-MRSA [105]. The long-term low prevalence rate in LA-MRSA dairy cows with mastitis is quite surprising, considering the time period of years since the LA-MRSA case was first reported in dairy cows and direct or indirect human contact with dairy cows. In the herd group in Germany, the LA-MRSA case was positive with the highest percentage of 45% of the veal swab nose sample when slaughtered and the lowest percentage of 4.1% of the bulk tank milk sample. Most of the LA-MRSA isolates originated from *spa* types t304 and t011 which had a CC398 clonal complex [106]. LA-MRSA CC398 isolated from bulk tank milk showed that dairy cows in the German herds were

colonized by udder and suffered from sub-clinical mastitis [106]. Direct contact between dairy cows and humans can cause transmission of LA-MRSA strain transmission. In one LA-MRSA case report that occurred in Hungary, there was an LA-MRSA isolate that was identical both to the phenotypic and genotypic examination of a cow with sub-clinical mastitis and a breeder indicating transmission of transmission between cattle and humans [75].

### Epidemiology of LA-MRSA

LA-MRSA was first isolated in dairy cows by Devriese *et al.* in 1972 in Belgium. Devriese and Homez (1975) reported that there were 68 MRSA isolates from 20 dairy cows on Belgian farms and found that the MRSA isolates originated from humans. In recent years, cases of LA-MRSA have started to be reported in various European countries with varying prevalence rates. Huber *et al.* [107] reported a low prevalence of LA-MRSA in cow's milk, 2 of 142 *Staphylococcus aureus* isolates on Swiss dairy farms. Then there is the LA-MRSA prevalence rate of 16.7% in German dairy farms [44] and 0.4% in Hungarian dairy farms [75]. In a recent study conducted by Paterson *et al.* [46] There are 7 LA-MRSA isolates found from 1500 samples of bulk tank milk in the UK. LA-MRSA dairy cattle with mastitis have also been reported in several North American states. A LA-MRSA prevalence of 0% has been reported in Virginia and North Carolina [108], but there is an LA-MRSA prevalence of 0.6% in Michigan [79], 1.8% in Wisconsin [109], and 4% in Minnesota [110].

Cases of LA-MRSA in dairy cows have also been reported in several Asian countries. Pu *et al.* [111] reported a prevalence of LA-MRSA cases of 47.6% in China. Then, a prevalence rate of 6.3% was reported in Korea [112], and 13.1% was reported in India [113]. In dairy cattle farms in Japan, 4 LA-MRSA isolates were found from 263 *Staphylococcus aureus* isolates collected from 260 dairy farms in Japan [87]. Cases of LA-MRSA in dairy cows have also been reported in several African countries such as Egypt [114] and Nigeria [115], the isolates were taken from the nose swabs of dairy cows and calves. Spohr *et al.* [44] reported cases of LA-MRSA in 5 of 7 dairy cows and 4 of 7 calves, the isolates were taken from dairy cow swabs on German farms. Huber *et al.* [107] reported 3 LA-MRSA isolates from 300 calf nasal swabs. Graveland *et al.* [116] reported LA-MRSA colonization of young calves on a Dutch farm. Initially, LA-MRSA CC398 was suspected as a strain that only occurs in animal infections. However, García-Alvarez *et al.* [36] reported a new MRSA finding of *yaitu mecA*[\_LGA251 or known as the *mecC* encoding gene with a prevalence of 2.8% on UK farms. Panton-Valentine (PVL) leukocidin is a cytotoxin associated with increased virulence of *Staphylococcus aureus*. MRSA positive cases of PVL have been reported in dairy cows on Korean farms [94].

### Impact on public health (Impact on public health)

The Centers for Disease Control (CDC) has reported 240,000 cases of *Staphylococcus* Food Poisoning (SFP) in the United States, [117] while in Europe there were 386 SFP cases in 2014. These cases were marked by severe vomiting and diarrhea, some time after swallowing foods containing SFP. From this event it can be concluded that there is involvement of super antigens and enterotoxins, including classic enterotoxins such as SEA-SEE and other newly identified enterotoxins [118].

It is necessary to identify *Staphylococcus aureus* sourced from animals because animals can also act as a reservoir

for transmission of transmission in subsequent infections. These pathogenic bacteria can also cause economic losses in the livestock industry [119]. The spread of infections that affect public health raises a new strain of LA-MRSA (*Staphylococcus aureus* which is resistant to methicillin related to livestock). Cases of LA-MRSA have been widely reported by farmers, veterinarians, and family members of farmers [120].

Livestock-Associated Methicillin-resistant *Staphylococcus aureus* produces enterotoxins that are resistant to high temperatures, is one of the causes of cases of food poisoning. This bacterium has a molecular weight of 26900-29600 Da, which until now there are almost 20 isolated species called *Staphylococcus enterotoxins* (SE) and proteins such as *Staphylococcus enterotoxins enterotoxic* (SEI). The prevalence rate of LA-MRSA enterotoxins has increased in several dairy industry companies. LA-MRSA enterotoxins have even contaminated milk and milk products [121].

On Turkish farms, LA-MRSA enterotoxins have been reported with a prevalence of 46.9% in samples isolated from cows with sub-clinical mastitis [87]. Samsun Province in Turkey reported a prevalence of 75% LA-MRSA enterotoxin derived from raw milk [122], while 68.4% came from sapid milk and pasteurized milk. The protein toxin from the LA-MRSA strain can produce nutrients for growth by exploiting host tissues. LA-MRSA enterotoxins are thought to cause emesis cases. Because there is activity associated with inflammatory mediators found in the digestive tract appearing with the upper part involving the intestine and stomach. Pathogenesis can be seen including exudates in the duodenum [122].

The prevalence of LA-MRSA has been reported as 10.4% not only in raw milk but also in dairy products, this study isolates five virulent genes that encode *Staphylococcus aureus enterotoxins*, toxin-1 syndrome, paton-valentine leukocidin, resistance methicillin and exfoliative toxin. More than 60% of strains have more than one virulent gene. This strain shows diverse responses to various classes of antibiotics. Cheese derived from goat milk may have this pathogenic strain because in several previous studies it has been found that 9.5% of the involvement of this pathogenic strain has positive coagulase, enterotoxigenic, and methicillin resistant properties. 6 new alleles (*pta-440*, *glpf-500*, *yqil-482*, and *yqil-496*, *aroe-552*, and *aroe-553*) and five new sequence types (ST) have been found, namely ST 3431, ST 3440, ST 3444, ST 3445, and ST 3461 on *Staphylococcus aureus* derived from goat milk. Isolation of new alleles in *Staphylococcus aureus* derived from goat milk is considered normal than isolation of new alleles in *Staphylococcus aureus* originating from cows and humans, in which focused research is indeed rare in goats [122].

### Risk factor

Older dairy cows are more susceptible to infectious cases because of the dilated quartering conditions, it could also be due to repeated exposure that occurs in previous infections, and lower immune conditions of dairy cows [123]. Old-age dairy cows have twice the risk of mastitis compared to young dairy cows. In addition, there are several studies that do not find that the age of dairy cows is a risk factor for cases of mastitis. Unhygienic conditions in the farm environment coupled with other risk factors can cause cases of infection in dairy cows regardless of the age of dairy cows. Dairy cows that are breastfeeding are more susceptible to LA-MRSA infections because the



spread of infectious pathogens is increasingly increased when the dairy cows are breastfeeding if the maintenance management system is not managed properly. Dairy cows in the peripartuisi period are most vulnerable to infectious diseases, because the immune system is down in this period. Several previous studies reported the prevalence of infectious diseases more frequently at the end of lactase, because the immune response of dairy cows was declining at the end of lactation [124]. In other studies dairy cows with early lactation are also susceptible to infectious diseases because high milk production can be followed by a higher spread of mastitis as well. Flea parasite agents also play a role in the spread of these pathogenic bacteria from one dairy cow to another dairy cow. Fleas can create an appropriate environment to help microbial pathogenesis. Most studies report a high prevalence of mastitis followed by a prevalence of head lice infection [124].

Dairy cows that are giving birth (parity) are more susceptible to infectious diseases. This is explained by the spread of infection from one parity to the next. Some studies have found no correlation of cases of mastitis with parity levels [125]. The spread of LA-MRSA is positively correlated with unhygienic milking systems. If the condition of the cleanliness of the cage is not properly maintained, it will cause the spread of LA-MRSA to be more widespread [126]. When conducting research related to LA-MRSA it is advisable to discard the milk jet first when taking milk samples. In the milking process it is recommended that the quartir be dipped with chlorhexidine and iodine at the time before and after milking to reduce the incidence of infection [127]. Previous studies have explained that LA-MRSA can be found in healthy cow's milk without symptoms of mastitis [128].

### One Health Approach

MRSA strains have been widely reported to be able to infect various species such as livestock, pets, and wildlife. MRSA cases cause significant economic losses including cases of mastitis in dairy cows, poultry deaths, and severe infections in farmed rabbits [4, 129-131]. Besides being seen from an economic and animal welfare perspective, LA-MRSA in animals can also act as a reservoir of transmission of zoonotic transmission in humans [4, 129, 130]. Especially the complex clone (CC) 398 or known as LA-MRSA which infects many livestock, and cases of infection in humans are also often associated with farm animals due to direct or indirect contact with farm animals, humans who are usually exposed to LA-MRSA between others, breeders, veterinarians, paramedics, family members of farmers, and residents around the farm, so LA-MRSA is recognized as a new form of MRSA epidemiology [4, 129, 130].

LA-MRSA in dairy cows has several lineages such as CC130, CC1943, and ST425 which are believed to be specific in dairy cows, but there are certain animal lineages have been reported by molecular typing in order to infect various animals and humans [129, 130]. In addition, *mecC* encoding genes that have homologous resemblance to *mecA* can cause methicillin resistance in *Staphylococcus aureus*, it has been described from dairy cow and human isolates found LA-MRSA *mecC* which reported up to now originates from a dairy hereditary line that acts as a zoonotic reservoir [4, 130]. MRSA *mecC* reports are currently limited and limited, but MRSA *mecC* can be a potential diagnostic problem because it is based on the

detection of *mecA* or PBP2a / PBP2 coding genes for the diagnosis of MRSA [4].

Therefore, the livestock and livestock industries have been reported to act as potential reservoirs for the emergence of new MRSA strains with the capacity to cross species barriers and survive host adaptive evolution, demonstrating the potential for transmission to human populations around the world as epidemic bloodlines [132, 133 ] In previous studies, among 195 cattle samples, 63 human samples, and 83 environmental samples from 12 different farms, only one human sample was detected positively LA-MRSA. This LA-MRSA isolate contains *nuc* and *mecA* genes, confirmed LA-MRSA comes from ST30 and *spa* type t9413. ST30 is one of the most common genetic lineages found in community-related MRSA (CA-MRSA) [134] and ST30 associated with methicillin-sensitive *Staphylococcus aureus* (MSSA) is one of the strains most commonly found in hospitals and communities in Portugal between 1992 and 2011 [135]. As far as is known, the MR30 ST30 clone was only found in healthy pigs in Portuguese farms [136] and the presence of the *spa* type t9413 was only reported to be related to ST22 in comparative genomic analysis taken from food borne samples of *Staphylococcus aureus* CC30 strain from Russia [137]. Therefore, LA-MRSA strains detected from human isolates may originate from livestock, LA-MRSA can be zoonotic. On the other hand, there are increasing reports of LA-MRSA isolation from dairy cows in Europe [4, 130, 138]. Farm locations adjacent to hospitals according to the 2018 report have an LA-MRSA prevalence of 30% [139].

Veterinary management is rarely done on farms so there is no prophylactic treatment (for example worming schedules, antibiotic therapy, and vaccinations) or biosecurity measures that still need to be implemented. In the case of sick dairy cows, veterinary assistance is only done when asked by breeders [140, 141].

### LA-MRSA control

All *Staphylococcus aureus* infections must also be considered LA-MRSA infections in both humans and animals. LA-MRSA isolates that are resistant to  $\beta$ -lactam antibiotics such as amoxicillin, cloxacillin, and penicillin are often also resistant to various drugs [73, 142]. LA-MRSA bovine mastitis has tet (M) so it can be resistant to tetracycline [46]. LA-MRSA isolates from both animals and humans are sensitive to vancomycin antibiotics. Similarly LA-MRSA isolates were also sensitive to linezolid, amikacin, and teicoplanin [73, 142, 143].

A modern dairy farming system characterized by densely populated livestock, intensive livestock farming, and excessive use of antibiotics can encourage the emergence of new LA-MRSA cases in the future. To avoid transmission of transmission from animal to human and animal to animal that is, adjusting the distance between cows, location of the cage that is not united with the kitchen, isolation of cows in separate cages, brushing dung, and bathing dairy cows regularly will be an effective method to reduce transmission LA-MRSA transmission [144]. Dairy cows that are collected close together will re-infect LA-MRSA [145]. Surveillance is needed to identify the initial LA-MRSA strain [46]. Improvement of biosecurity and environmental cleanliness of dairy cattle pens, as well as regular animal and human health care arrangements are important to prevent the spread of LA-MRSA strains [46, 146].

## Conclusion

The increasing prevalence of MRSA infections in pets, and lately in livestock has become a worldwide phenomenon. The wide spread of strains that are resistant to some drugs and antibiotic clones from bacteria facilitated by inherent or acquired molecular / genetic elements is alarming because it makes diagnosis and chemotherapy difficult. Transferring MRSA strains can occur between livestock and humans and vice versa. Guidelines for LA-MRSA control in livestock have been prepared by each institution based on those available for MRSA infection in humans. Risk factors for MRSA infections in livestock especially in dairy cows are currently being investigated and such data are very important for the preparation of specific guidelines for MRSA control in veterinary practice.

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