# A review of horses as a source of spreading livestock-associated methicillin-resistant *Staphylococcus aureus* to human health

Aswin Rafif Khairullah<sup>1</sup><sup>(1)</sup>, Sri Agus Sudjarwo<sup>2</sup><sup>(1)</sup>, Mustofa Helmi Effendi<sup>3</sup><sup>(1)</sup>, Sancaka Chasyer Ramandinianto<sup>4</sup><sup>(1)</sup>, Agus Widodo<sup>1</sup><sup>(1)</sup>, and Katty Hendriana Priscilia Riwu<sup>1</sup><sup>(1)</sup>

 Doctoral Program in Veterinary Science, Faculty of Veterinary Medicine, Universitas Airlangga, Kampus C Unair, Jl. Mulyorejo, Surabaya, Jawa Timur 60115, Indonesia; 2. Department of Veterinary Pharmacology, Faculty of Veterinary Medicine, Universitas Airlangga, Kampus C Unair, Jl. Mulyorejo, Surabaya, Jawa Timur 60115, Indonesia; 3. Department of Veterinary Public Health, Faculty of Veterinary Medicine, Universitas Airlangga, Kampus C Unair, Jl. Mulyorejo, Surabaya, Jawa Timur 60115, Indonesia; 4. Lingkar Satwa Animal Care Clinic, Jl. Sumatera No. 31L, Gubeng, Surabaya, Jawa Timur 60281, Indonesia.

Corresponding author: Mustofa Helmi Effendi, e-mail: mhelmieffendi@gmail.com Co-authors: ARK: aswinrafif@gmail.com, SAS: ags158@yahoo.com, SCR: sancakachasyer@gmail.comand, AW: agus.widodo@vokasi.unair.ac.id, KHPR: cattypricyllia@gmail.com Received: 27-03-2022, Accepted: 24-06-2022, Published online: 11-08-2022

**doi:** www.doi.org/10.14202/vetworld.2022.1906-1915 **How to cite this article:** Khairullah AR, Sudjarwo SA, Effendi MH, Ramandinianto SC, Widodo A, and Riwu KHP (2022) A review of horses as a source of spreading livestock-associated methicillin-resistant *Staphylococcus aureus* to human health, *Veterinary World*, 15(8): 1906–1915.

#### Abstract

Livestock-associated methicillin-resistant Staphylococcus aureus (LA-MRSA) was first discovered in horses in 1989. Since then, LA-MRSA has begun to be considered an important strain of pathogenic bacteria in horses, which can cause LA-MRSA infection and colonization in humans with public health impacts. The anterior nares are the primary site of LA-MRSA colonization in horses, although LA-MRSA colonization may also occur in the gastrointestinal tract in horses. LA-MRSA-infected horses typically exhibit clinical infection or may not exhibit clinical infection. There are two potential risks associated with LA-MRSA colonization in horses: The possibility of disease development in horses infected with LA-MRSA and the possibility of LA-MRSA transfer to humans and other horses. The diagnosis of LA-MRSA in horses can be made by conducting in vitro sensitivity testing for oxacillin and cefoxitin, and then followed by a molecular test using polymerase chain reaction. LA-MRSA transmission in animal hospitals and on farms is most likely due to contact with horses infected or colonized by LA-MRSA. The history of prior antibiotic administration, history of prior LA-MRSA colonization, and length of equine hospitalization were described as risk factors in cases of infection and colonization of LA-MRSA in horses. Nebulized antibiotics may be a viable alternative to use in horses, but nebulized antibiotics are only used in horses that are persistently colonized with LA-MRSA. Controlling the spread of LA-MRSA in horses can be done by regularly washing horses, eradicating vectors in horse stalls such as rats, and maintaining the cleanliness of the stable and animal hospital environment. Meanwhile, cleaning hands, using gloves, and donning protective clothes are ways that humans can prevent the transmission of LA-MRSA when handling horses. This review will explain the definition of LA-MRSA in general, LA-MRSA in horses, the epidemiology of LA-MRSA in horses, the diagnosis of LA-MRSA in horses, the transmission of LA-MRSA in horses, risk factors for spreading LA-MRSA in horses, public health impact, treatment of LA-MRSA infection in horses, and control of the spread of LA-MRSA in horses.

Keywords: horse, LA-MRSA, public health, risk factors.

#### Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) is a strain of Staphylococcus aureus that is resistant to almost all  $\beta$ -lactam antibiotics and is often resistant to antibiotics other than  $\beta$ -lactams [1]. This resistance reaction occurs due to the activity of the penicillin-binding protein encoded by the *mecA* and *mecC* genes located on the Staphylococcal cassette chromosome *mec* (SCC*mec*) [2–5]. MRSA is known globally to spread nosocomially in hospital settings, known as hospital-acquired MRSA (HA-MRSA) [1, 6, 7]. In

Copyright: Khairullah, *et al.* Open Access. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/ by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons.org/publicDomain Dedication waiver (http:// creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated. addition, MRSA that occurs in the community without any association with healthcare facilities is known as community-acquired MRSA (CA-MRSA) [8]. MRSA in animals was first identified in dairy cows with cases of mastitis in 1972 [9], followed by sporadic observations of MRSA infections in various animals, including MRSA infections first identified in horses in 1989 [10], which eventually began to develop into known MRSA that occurs in livestock [11–14] and pets [15, 16] is known as livestock-associated MRSA (LA-MRSA) [17, 18].

Numerous livestock throughout Europe, North America, and Asia have been found to have the LA-MRSA strain with clonal complex 398 (CC398) [19]. Furthermore, since the first LA-MRSA in horses was found in 1989 [8], the recently emerging LA-MRSA CC398 has been identified in equine populations. LA-MRSA is starting to be considered an important pathogenic bacterial strain in horses, which can cause infection and colonization of LA-MRSA in humans [20–26]. Horses that have been infected with LA-MRSA may or may not exhibit clinical infection [27-32]. Skin infections, soft-tissue infections, septic arthritis, bacteremia, osteomyelitis, omphalitis, metritis, and pneumonia are just a few of the clinical diseases that LA-MRSA-infected horses might develop [33]. Since then, LA-MRSA in horses has begun to be considered a public health problem. Although the presence of LA-MRSA in horses has not been widely reported [25, 32, 34], the spread of LA-MRSA in horses is still regarded as a risk to public health [25, 32, 35], so it is important to understand the spread of LA-MRSA in horses so that later control strategies can be implemented to reduce the risk of spreading LA-MRSA to horses in farms and animal hospitals [25, 35, 36].

This review will explain the definition of LA-MRSA in general, LA-MRSA in horses, the epidemiology of LA-MRSA in horses, the diagnosis of LA-MRSA in horses, the transmission of LA-MRSA in horses, risk factors for spreading LA-MRSA in horses, public health impact, treatment of LA-MRSA infection in horses, and control of the spread of LA-MRSA in horses.

# LA-MRSA

LA-MRSA is an opportunistic strain of bacteria that can be identified in humans, livestock, and pets. In 1972, the first LA-MRSA case in livestock was a subclinical mastitis case in dairy cattle in Belgium, in which the LA-MRSA was of human origin [9]. Since then, LA-MRSA in livestock has been reported frequently and has even begun to be found in domestic animals [37]. Ceballos *et al.* [38] identified a new LA-MRSA lineage, the type (ST) 398 sequence that is in the CC398 grouping, which is now often found in livestock and domestic animals and infects humans. Thus, LA-MRSA-associated farm and domesticated animals with the CC398 clonal complex are starting to be widely reported globally [39], in horses [40], cattle [41], poultry [42], dogs [43], and cats [44].

# LA-MRSA in Horse

In 1989, LA-MRSA was first identified in a mare with metritis in Japan [10]. Since then, several investigators have identified the presence of LA-MRSA among horses in America, Europe, and Asia, with slight differences in the prevalence rates between regions [21, 43, 45–49]. In several cases of LA-MRSA infection in horses, clones that differ from those found in normal livestock and domestic animals have been identified, namely, the CC8 clonal complex, which was previously associated with HA-MRSA infection in the hospital [21, 47, 48, 50].

There are still few reports of LA-MRSA infection in horses. In 1997, Hartman *et al.* [51] reported that there was LA-MRSA infection in postoperative horses in the hospital, but the source of the LA-MRSA infection is still unknown. Following the discovery of LA-MRSA in 11 horses for 13 months at a veterinary hospital in Michigan, the USA, in 1999 [52], three medical personnel at the hospital were identified as infected with LA-MRSA originating from these horses. Over the past few years, several LA-MRSA infections have been reported in horses with wound infections, surgical site infections, pneumonia, arthritis, osteomyelitis pneumonia, metritis, catheter site infections, and dermatitis [53, 54].

Not all LA-MRSA infections in horses cause clinical infection. There are two potential risks of LA-MRSA colonization in horses; namely, there is a potential for disease development in horses infected with LA-MRSA and the potential for transmission of LA-MRSA transmission to other horses and humans. Moremi et al. [55] found that up to 29% of human patients infected with MRSA on discharge from the hospital developed subsequent MRSA infections, including bacteremia, osteomyelitis, septic arthritis, and pneumonia but this did not occur in cases of infection. LA-MRSA in horses, which is a clinical symptom in horses due to LA-MRSA infection only days to weeks after the presence of LA-MRSA in horses is discovered [56]. With this, the case of LA-MRSA infection in horses should be considered because it is thought to put the horse at risk of disease progression. The most common sites for MRSA colonization in humans are the nasal cavity, hair, nails, skin, vaginal axilla, and perineum. In contrast, the most common sites for MRSA colonization in horses are the nasal cavity [57].

In Europe, apart from LA-MRSA ST398 clones, CA-MRSA ST1 and CA-MRSA ST254 clones have also been identified in horses [25, 58, 59]. In a study conducted in England, only three horses out of 152 horses were identified with MRSA; the MRSA strains were included in clones of LA-MRSA CC398, HA-MRSA CC8, and HA-MRSA CC22 [53]. In Germany, the transition from a human-associated CA-MRSA clone to an LA-MRSA CC398 clone was reported in 2006 [60]. In a study conducted in Switzerland, changes in the distribution of LA-MRSA clones in horses included LA-MRSA strains collected from 2005 to 2011, whereas LA-MRSA ST398 was found in 2007 [26]. Risk factors for LA-MRSA infection in horses can come from the use of topical antibiotics, use of systemic glucocorticoids, and visits by a veterinarian [33]; this fact emphasizes that LA-MRSA infection in horses is associated with antibiotic use, immunosuppression, and hospitalization.

#### Epidemiology LA-MRSA in Horse

The epidemiology of LA-MRSA in horses has not been widely reported [61]. The anterior nares are the primary site of LA-MRSA colonization in horses, although LA-MRSA colonization may also occur in the gastrointestinal tract in horses [62]. Approximately 10% of the nasal cavities of healthy horses have LA-MRSA [63]. Within the reservoir of infected horses, LA-MRSA is likely to spread among the equine population [64]. LA-MRSA colonization rates are likely to vary widely among horse populations and different geographic areas, as much as 0-5% of the equine population has been examined in different regions, with the LA-MRSA prevalence rate in certain horse populations approaching 50% [65]. Although LA-MRSA colonization is usually transient in horses, LA-MRSA is easily transmitted among horse populations and is likely to continue to spread within equine populations [31]. Even though the majority of infected horses did not exhibit clinical illness, LA-MRSA colonization was a risk factor for disease cases in horses that were being treated by veterinarians in hospitals [31]. Horses infected with LA-MRSA are at risk of transmitting LA-MRSA to other horses and humans [66].

LA-MRSA infection in horses can occur sporadically or in outbreaks on farms and animal hospitals [19]. Horses of all ages can become infected with LA-MRSA, including foals that are <24-h-old [65]. The predisposition of horse age, sex, and race association with LA-MRSA infection in horses has not been reported [65]. LA-MRSA infection cases appear to occur more frequently in horse farms than in hospital animals, although there is still a lack of objective evidence of an increased risk of LA-MRSA transmission in horses [63]. Several risk factor analyses for LA-MRSA transmission in horses have been detailed, including the previous history of LA-MRSA colonization in horses, the previous discovery of LA-MRSA colonies in horses, antibiotic administration for the previous 30 days, and neonatal critical care in a veterinary hospital [66]. Administration of aminoglycosides and cephalosporins during hospitalization was associated with the rate of LA-MRSA colonization in horses [66].

In 1997, Hartmann et al. [51] reported one LA-MRSA strain isolated from postoperative wound infection in horses in the United States, whereas in 1999, Seguin et al. [52] reported a case of LA-MRSA infection in horses at the University of Michigan veterinary hospital in the United States. Depending on the region being examined, different forms of diseases in horses are caused by LA-MRSA colonization and infection. The Canadian MRSA-5 strain is seldom detected in people, while it is most frequently isolated in horses and horse workers in Canada [63]. In Europe, other LA-MRSA strains have been found in horses, including LA-MRSA ST398, in which the LA-MRSA CC398 strain is a strain of pig origin [58, 67]. In epidemiological and genome analytic studies, LA-MRSA ST398 was classified into two distinct phylogenetic clades, namely the livestock clade and the basal human clade [68, 69]. The main characteristics that lie in the preceding clade are the disappearance of the bacteriophage  $\Phi$ Sa3 and the acquisition of a Tn916like transposon carrying the tetM-encoding gene, LA-MRSA ST398 has a human-specific immune

avoidance cluster gene carrying *chp* and *scn*, encoding a chemotaxis inhibitor protein and a complement inhibitor Staphylococcus respectively [68, 69].

In certain cases, horses that have been infected by LA-MRSA have clones that are different from the clones found in livestock and domestic animals, but have the same clones as MRSA in humans; for example, CC8 clones (ST8 and ST254) were discovered in horses; these clones are HA-MRSA clones that are frequently detected in hospitals in Canada, but clones ST1, ST22, and ST254 that are also HA-MRSA clones have also been discovered among horse isolates in Europe [58]. Studies conducted in Canada and Europe have reported that the LA-MRSA clone that frequently infects horses is LA-MRSA CC398 (ST398) [31, 58, 60].

There are increasing reports of LA-MRSA's ability to spread among horse populations and communities, particularly in humans working on horse farms and animal hospitals. Farmers who had contact with foals infected with LA-MRSA ST8 (USA500) showed symptoms of a skin infection caused by the LA-MRSA strain in the foal [22]. Staff workers at veterinary hospitals and veterinarians are at a higher risk of contracting LA-MRSA from horses as long as cases of LA-MRSA infection occur in horses in veterinary hospitals [70]. However, LA-MRSA CC398 in horses is likely a specific clade of LA-MRSA occurring in general livestock, which does not spread beyond animal hospitals and horse farms [71].

#### **Diagnosis of LA-MRSA in Horse**

The diagnosis of LA-MRSA infection requires the isolation of S. aureus from the infected site and testing for methicillin resistance [72]. In vitro sensitivity to oxacillin is often used as a benchmark for methicillin resistance because oxacillin is more stable in use in vitro [73]. S. aureus strains resistant to oxacillin were considered resistant to methicillin, but false-positive and false-negative test results were obtained [74]. False-positive test results sometimes occur because LA-MRSA strains produce high levels of  $\beta$ -lactamase, which can lead to low levels of oxacillin resistance [75]. Such LA-MRSA strains can be identified by reviewing the sensitivity of other antibiotics because they may be sensitive to cephalosporins or penicillin-anti-\beta-lactamase combinations such as amoxicillin-clavulanic acid [76]. Any LA-MRSA isolate suspected to be sensitive to a combination of  $\beta$ -lactamase inhibitors or other  $\beta$ -lactam antibiotics needs further testing [77]. False-negative test results can be obtained due to incomplete expression of the mecA or mecC coding genes because oxacillin can be bad in vitro inducer of the mecA or mecC gene encoding genes [78]. Other antibiotics, such as cefoxitin, can also be used in in vitro sensitivity testing as a benchmark for methicillin resistance because cefoxitin has a greater ability to induce a  $\beta$ -lactam antibiotic resistance phenotype [79]. Isolates suspected of being LA-MRSA should be further tested to detect the mecA or mecC coding

gene by polymerase chain reaction [64] or for PBP2a by latex agglutination assay [80].

In some situations, screening in clinically healthy horses to identify LA-MRSA colonization may be indicated [64]. The culture method taken from horse nose swabs appears to be the optimal and frequently used method [81]. Samples were collected by inserting a 10-15 cm nasal swab into the horse's nasal cavity and letting the nasal swab touch the nasal mucosa on withdrawal [81]. Several types of culture media are used to detect LA-MRSA differential and selectively [73]. The use of enrichment media can increase the sensitivity of the test, but the drawback of using enrichment media is that it takes an incubation time of 24 h before results can be available [82]. In horses, molecular testing using real-time polymerase chain reaction of nasal swab specimens was used for LA-MRSA identification [83].

## **Transmission LA-MRSA in Horse**

MRSA is a health problem of worldwide concern. Approximately 30% of the general population has been infected with *S. aureus* and a small proportion of these *S. aureus* isolates are MRSA [84, 85]. However, hospital and farm environments have a higher proportion of LA-MRSA transmission; although there are different proportions in each country, people who act as health workers, veterinarians, and breeders will be more at risk of getting LA-MRSA [64, 86].

Healthy horses usually have a low LA-MRSA prevalence rate, compared to horses that are currently being treated in a veterinary hospital will have a higher LA-MRSA prevalence rate [87, 88] and nosocomial LA-MRSA infections in horses may cause serious, even fatal [89], cases of clinical infection in horses due to LA-MRSA colonization. However, the high prevalence of LA-MRSA in animal hospitals and farms poses a risk not only to horses but also to health workers, breeders, and veterinarians [90, 91]. In recent years, LA-MRSA in horses has been the subject of several scientific studies. Kuroda et al. [92] reported that horses in healthy conditions were rarely a source of LA-MRSA transmission; in addition, veterinarians who had been infected with LA-MRSA from other patients could be a source of LA-MRSA transmission in horses.

Nosocomial transmission of MRSA in the hospital is likely to occur through the hands of hospital staff contaminated with MRSA as a result of contact with patients infected or colonized by MRSA [93]. Hospital staff infected and colonized with MRSA can also transmit MRSA [93]. LA-MRSA transmission in veterinary hospitals and on farms is likely to occur in the same way as a result of contact with animals infected or colonized by LA-MRSA. The transmission of LA-MRSA transmission from veterinary and livestock hospital environments has not been well documented, although LA-MRSA contamination originating from animal hospitals and farms has been reported [64, 94, 95]. LA-MRSA isolates were

most often isolated from areas that had frequent contact with the horse's nasal cavity such as stable walls, hay, feed bins, and water buckets [96]. The environment of animal hospitals and farms is not considered an important source of LA-MRSA transmission, but the environment of animal hospitals and farms can be a source of LA-MRSA transmission if not properly managed [87]. Therefore, it is very important to maintain a clean environment in veterinary hospitals and farms, especially in areas that frequently come into contact with horse noses [96, 97].

## **Risk Factor for Spreading LA-MRSA in Horse**

LA-MRSA infection and colonization is a serious condition that can occur in horses as well as in humans. The risk factors reported in cases of MRSA infection and colonization in humans were history of antibiotic administration, contact with hospital staff, history of previous hospitalization, and hospital overcrowding [57, 98–101]. Meanwhile, the reported risk factors for LA-MRSA infection and colonization in horses have not been adequately evaluated [102].

Horses identified as LA-MRSA positive were more likely to have clinical LA-MRSA infection than horses that were identified as LA-MRSA negative [21]. LA-MRSA clones found in the nasal cavity of horses will still be found in cases of subsequent infection [25]. The administration of aminoglycosides and ceftiofur antibiotics is one of the risk factors that cause horses to become LA-MRSA-positive during treatment [21]. Examples of other antibiotics that are risk factors for LA-MRSA transmission are fluoroquinolone exposure [103] and the causal relationship between antibiotic use and LA-MRSA infection [104]. Horses from farms with positive LA-MRSA testing, horses from those farms, LA-MRSA contamination during hospitalization, and LA-MRSA contamination during surgery in a veterinary facility have all been described as risk factors in horses that have been identified as LA-MRSA positive [66]. A significant association between surgical incision scars and LA-MRSA nosocomial infection has also been reported [33].

Increased risk factors for veterinarians and veterinarians infected with LA-MRSA and the potential for further spread of LA-MRSA should be considered [25, 58, 70, 105]. In Dutch veterinary hospitals, the same type of *spa*, t011, and t2123 were identified in horses and animal hospital staff infected with LA-MRSA [25]. In a study conducted in an Israeli hospital, 12 horses out of 84 horses (14.3%) and 16 of 139 personnel (11.5%) were identified as having LA-MRSA ST5, a type of *spa* t535 [70]. In addition, there is a greater risk of LA-MRSA transmission to veterinarians, animal hospital staff, breeders, and people living near animal hospitals and farms [70].

#### **Public Health Impact**

The role of horses as a means of transportation and recreation can be a risk of colonization and LA-MRSA infection in humans [22]. In a study conducted in Denmark, it was found that practicing veterinarians were substantially more likely to be infected with LA-MRSA than those who had no contact with horses; exposure to horses was thought to increase the likelihood of LA-MRSA transmission [106]. Veterinary professionals attending international equine conferences have also been shown to have LA-MRSA colonization [105]. The care of horses that tested positive for LA-MRSA or had a prior year history of LA-MRSA infection was linked to an elevated risk of LA-MRSA colonization and infection [107].

Several studies [25, 47, 49, 52, 58] have reported that LA-MRSA isolates from horses and people working on horse farms differ from MRSA isolates in the general population. In Austria LA-MRSA ST254, spa type t036 and SCCmec type IV were mostly found in horses, followed by LA-MRSA ST398 spa type t011, SCCmec type IV, and LA-MRSA ST1 spa type t127, SCCmec type IV [58]. According to the PFGE classification as Canadian MRSA-5, the majority of LA-MRSA isolates reported in horses in Canada were LA-MRSA ST8 spa type t008 and SCCmec type IV. This suggests that the LA-MRSA clone discovered in humans originated from horses [32]. The LA-MRSA ST398 spa type t011 and LA-MRSA ST8 spa type t064 were discovered in horses in the Netherlands [25]. From 2000 to 2002, a total of ten horse farms and 27 people in Canadian veterinary hospitals were identified by LA-MRSA [20]. In another study conducted by Schulz et al. [94], there was one person, a veterinarian, who had a clinical infection and had the same type of LA-MRSA as the two horses were treated by him [94]. Three individuals who work on horse breeding farms have also reported experiencing skin illnesses caused by LA-MRSA in humans. LA-MRSA isolation tests have revealed that these three individuals had the same strain of LA-MRSA as the foals raised on these farms [22]. The results of screening tests on personnel during cases of LA-MRSA infection in veterinary hospitals indicate that people who have close contact with horses are more likely to be infected with LA-MRSA than people who do not come into contact with horses [25].

# Treatment of LA-MRSA Infection in the Horse

Eradication of colonization and LA-MRSA infection are desirable steps to reduce the likelihood of developing clinical infectious diseases and reduce the risk of further transmission to horses and humans [45]. However, measures to eradicate LA-MRSA colonization and infection have not been evaluated [108].

LA-MRSA colonization and infection are transient in the majority of adult horses and in most horses, the level of LA-MRSA colonization can be eliminated within few weeks of LA-MRSA infection, provided measures are taken to prevent reinfection of horses and other humans [45]. A minority of horses may continue to colonize LA-MRSA for months or even years after being infected with LA-MRSA [94]. In addition, the LA-MRSA infection control protocol may not be feasible in some situations where horse movement is indispensable for training, breeding, competition, or sales [109]. In this situation, antibiotic therapy to eradicate LA-MRSA colonization and infection is necessary; however, antibiotic therapy should not be underestimated because of the speed with which LA-MRSA isolates develop resistance and the limited choice of antibiotics available [110]. Antibiotic therapy may be necessary for persistent LA-MRSA infection or where recommendations for colonization control and LA-MRSA infection are unlikely to be followed [110].

Mupirocin antibiotic therapy administered intravenously is frequently coupled with other antibiotics, such as fusidic acid, to treat colonization, and MRSA infections in people [111]. The use of the topical intranasal antibiotic mupirocin has not been evaluated in horses, but the potential efficacy of this antibiotic therapy is questionable because of the difficulty of administering daily topical antibiotic therapy throughout the horse's nasal cavity [112]. Oral and parenteral antibiotics can be used for horses; however, most LA-MRSA isolates in horses are resistant to the most commonly used class of antibiotics, and eradication therapy for colonization and LA-MRSA infection will involve the use of the most appropriate antibiotics provided for the treatment of ongoing clinical or equine infections continuously undergoing LA-MRSA colonization [110]. Antibiotic nebulization or inhaler administration of antibiotics may be viable alternatives in horses, but nebulized antibiotics are only used in horses that are persistently colonized with LA-MRSA [113]. Nebulized amikacin (1750 mg in 21 mL total volume) or nebulized enrofloxacin (175 mg in 10 mL total volume) has begun to be used in horses that are continuously colonizing LA-MRSA with shown success in eradicating LA-MRSA colonization [113]. In addition, antibiotic nebulation is not appropriate in cases of LA-MRSA colonization that occurs in the gastrointestinal tract and guttural pockets in horses [114]. Therefore, the efficacy and safety of nebulized antibiotics still require further research.

#### Controlling the Spread of LA-MRSA in Horse

Dissemination of horse-derived LA-MRSA in animal hospitals and farms has been reported [25, 94]. Hand hygiene is rated as the most important step in the prevention of LA-MRSA infection nosocomially in humans [115]. LA-MRSA-contaminated hands will be the next major route of LA-MRSA transmission in animal and livestock hospitals [116].

The use of gloves while handling horses and, if necessary wearing protective clothing when handling a horse with a wound infection is basic hygienic precautions for people, breeders, and veterinarians, but they must be followed consistently and firmly [117]. Differences in glove material against LA-MRSA transmission and LA-MRSA transmission using dry gloves have been reported [118]. Nitrile gloves showed the lowest LA-MRSA transmission rate [118], but the absorption of tested body fluids increased LA-MRSA transmission significantly for all glove types. Therefore, it is important to change gloves regularly when handling horses, especially when operating on horses.

Horse mucus scattered in stables and animal hospitals could potentially be a source of LA-MRSA transmission, based on the fact that LA-MRSA has been detected on cell phones, twitches, horse snouts, floors, and medical equipment [94, 119]. In addition, LA-MRSA has also been detected on computer keyboards in veterinary clinics [120]; therefore, it is necessary to maintain the cleanliness of cages and veterinary hospitals to prevent the spread of LA-MRSA.

Bathing horses regularly are also the right step in tackling the spread of LA-MRSA, because it can also be an effort to clean the dust on the horse's skin surface that has the potential to carry LA-MRSA, the dust on horsehair is indeed difficult to avoid, so it is necessary to bathe the horse with care [121]. It also shows that humans infected with MRSA can spread MRSA through the air [122]. Foot hygiene should also be considered, as LA-MRSA can survive on dry surfaces for months [123].

Nosocomial spread of LA-MRSA in horses during hospitalization has been reported in previous studies [21, 25, 70]. This suggests that horses infected with LA-MRSA should be isolated so that the infection does not transmit LA-MRSA to other patients; in addition, strict isolation measures need to be implemented for horses that have been infected with LA-MRSA [124]. A measure to prevent the spread of LA-MRSA for veterinarians is to wear protective clothing, hat, boots, and gloves before entering the stable of horses that are being isolated [96].

Vector control must also be considered, as was the case in cattle and pig farms where LA-MRSA ST 398 was discovered, where LA-MRSA was also isolated from mice found in cattle and pig pens [125]. Whereas in a horse stable, several vectors are usually found, such as rats, birds, and other pests.

#### Conclusion

The LA-MRSA strain can be a bacterial pathogen that can infect horses. LA-MRSA colonization can usually be identified in the nasal cavity of horses. Horses that have been infected with LA-MRSA usually do not show clinical infection; however, there have been some cases that have shown clinical infection. LA-MRSA transmission in animal hospitals and on farms most likely occurs as a result of contact with horses infected or colonized by LA-MRSA. Floor surfaces and objects that frequently come into contact with the horse's nose are also common sources of LA-MRSA transmission. People who are at risk of getting LA-MRSA from horses are people who work on horse farms, veterinarians, and veterinarians. The spread of LA-MRSA can be controlled by maintaining the cleanliness of the enclosure environment and animal hospital.

## Authors' Contributions

ARK: Collected samples, analyzed data, and drafted the manuscript. SCR, AW, and KHPR: Designed the study and guidance. SAS and MHE: Revised the manuscript. All authors have read and approved the final manuscript.

## Acknowledgments

This study was funded in part by the Penelitian Pasca Sarjana - Penelitian Disertasi Doktor from PENELITIAN DRTPM KEMENDIKBUDRISTEK TAHUN 2022, with a grant from Universitas Airlangga, Indonesia (Grant no. 905/UN3.15/PT/2022).

## **Competing Interests**

The authors declare that they have no competing interests.

## **Publisher's Note**

Veterinary World remains neutral with regard to jurisdictional claims in published institutional affiliation.

#### References

- Fukunaga, B.T., Sumida, W.K., Taira, D.A., Davis, J.W. and Seto, T.B. (2016) Hospital-acquired methicillin-resistant *Staphylococcus aureus* bacteremia related to medicare antibiotic prescriptions: A state-level analysis. *Hawaii J. Med. Public Health*, 75(10): 303–309.
- 2. Reichmann, N.T. and Pinho, M.G. (2017) Role of SCCmec type in resistance to the synergistic activity of oxacillin and cefoxitin in MRSA. *Sci. Rep.*, 7(1): 6154.
- 3. Lee, A.S., de Lencastre, H., Garau, J., Kluytmans, J., Malhotra-Kumar, S., Peschel, A. and Harbarth, S. (2018) Methicillin-Resistant *Staphylococcus aureus*. *Nat. Rev. Dis. Primers*, 4(1): 18033.
- Ramandinianto, S.C., Khairullah, A.R., Effendi, M.H., Tyasningsih, W. and Rahmahani, J. (2020) Detection of enterotoxin Type B gene on methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from raw milk in East Java, Indonesia. *Syst. Rev. Pharm.*, 11(7): 290–298.
- Rahmaniar, R.P., Yunita, M.N., Effendi, M.H. and Yanestria, S.M. (2020) Encoding gene for methicillin-resistant *Staphylococcus aureus* (MRSA) Isolated from nasal swab of dogs. *Indian Vet. J.*, 97(2): 37–40.
- Pannewick, B., Baier, C., Schwab, F. and Vonberg, R.P. (2021) Infection control measures in nosocomial MRSA outbreaks results of a systematic analysis. *PLoS One*, 16(4): e0249837.
- Garoy, E.Y., Gebreab, Y.B., Achila, O.O., Tekeste, D.G., Kesete, R., Ghirmay, R., Kiflay, R. and Tesfu, T. (2019) Methicillin-resistant *Staphylococcus aureus* (MRSA): prevalence and antimicrobial sensitivity pattern among patients a multicenter study in Asmara, Eritrea. *Can. J. Infect. Dis. Med. Microbiol.*, 2019(1): 8321834.
- Turner, N.A., Sharma-Kuinkel, B.K., Maskarinec, S.A., Eichenberger, E.M., Shah, P.P., Carugati, M., Holland, T.L. and Fowler, V.G. (2019) Methicillin-resistant *Staphylococcus aureus*: An overview of basic and clinical research. *Nat. Rev. Microbiol.*, 17(4): 203–218.
- 9. Gopal, S. and Divya, K.C. (2017) Can methicillin-resistant

*Staphylococcus aureus* prevalence from dairy cows in India act as a potential risk for community-associated infections? A review. *Vet. World*, 10(3): 311–318.

- Anzai, T., Kamada, M., Kanemaru, T., Sugita, S., Shimizu, A. and Higuchi, T. (1996) Isolation of methicillin-resistant *Staphylococcus aureus* (MRSA) from mares with metritis and its zooepidemiology. *J. Equine Sci.*, 7(1): 7–11.
- Khairullah, A.R., Sudjarwo, S.A., Effendi, M.H., Ramandinianto, S.C., Gelolodo, M.A., Widodo, A., Riwu, K.H.P., Kurniawati, D.A. and Rehman, S. (2022) Profile of multidrug resistance and methicillin-resistant *Staphylococcus aureus* (MRSA) on dairy cows and risk factors from farmers. *Biodiversitas*, 23(6): 2853–2858.
- Effendi, M.H., Hisyam, M.A.M., Hastutiek, P. and Tyasningsih, W. (2019) Detection of coagulase gene in *Staphylococcus aureus* from several dairy farms in East Java, Indonesia, by polymerase chain reaction. *Vet. World*, 12(1): 68–71.
- Tyasningsih, W., Effendi, M.H., Budiarto, B. and Syahputra, I.R. (2019) Antibiotic resistance to *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from dairy farms in Surabaya. Indonesia. *Indian Vet. J.*, 96(11): 27–31.
- Harijani, N., Wandari, A., Effendi, M.H. and Tyasningsih, W. (2020) Molecular detection of encoding enterotoxin C gene and profile of antibiotic-resistant on *Staphylococcus aureus* isolated from several dairy farms in East Java, Indonesia. *Biochem. Cell. Arch.*, 20(1): 3081–3085.
- Decline, V., Effendi, M.H., Rahmaniar, R.P., Yanestria, S.M. and Harijani, N. (2020) Profile of antibiotic-resistant and presence of methicillin-resistant *Staphylococcus aureus* from nasal swab of dogs from several animal clinics in Surabaya, Indonesia. *Int. J. One Health*, 6(1): 90–94.
- Yunita, M.N., Effendi, M.H., Rahmaniar, R.P., Arifah, S. and Yanestria, S.M. (2020) Identification of spa gene for strain typing of methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from nasal swab of dogs. *Biochem. Cell. Arch.*, 20(1): 2999–3004.
- Khairullah, A.R., Ramandinianto, S.C. and Effendi, M.H. (2020) A review of livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) on bovine mastitis. *Syst. Rev. Pharm.*, 11(7): 172–183.
- Khairullah, A.R., Sudjarwo, S.A., Effendi, M.H., Harijani, N., Tyasningsih, W., Rahmahani, J., Permatasari, D.A., Ramandinianto, S.C., Widodo, A. and Riwu, K.H.P. (2020) A review of methicillin-resistant *Staphylococcus aureus* (MRSA) on milk and milk products: Public health importance. *Syst. Rev. Pharm.*, 11(8): 59–69.
- McCarthy, A.J., van Wamel, W., Vandendriessche, S., Larsen, J., Denis, O., Garcia-Graells, C., Uhlemann, A.C., Lowy, F.D., Skov, R., and Lindsay, J.A. (2012) *Staphylococcus aureus* CC398 clade associated with human-to-human transmission. *Appl. Environ. Microbiol.*, 78 (24): 8845–8848.
- Crespo-Piazuelo, D. and Lawlor, P.G. (2021) Livestockassociated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) prevalence in humans in close contact with animals and measures to reduce on-farm colonization. *Irish Vet. J.*, 74(1): 21.
- Chen, C. and Wu, F. (2021) Livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) colonisation and infection among livestock workers and veterinarians: A systematic review and meta-analysis. *Occup. Environ. Med.*, 78(1): 530–540.
- Algammal, A.M., Hetta, H.F., Elkelish, A., Alkhalifah, D.H.H., Hozzein, W.N., Batihag, G.E.S., Nahhas, N.E. and Mabrok, M.A. (2020) Methicillinresistant *Staphylococcus aureus* (MRSA): One health perspective approach to the bacterium epidemiology, virulence factors, antibiotic-resistance, and zoonotic impact. *Infect. Drug Resist.*, 13(1), 3255–3265.

- 23. Rohmera, C. and Wolz, C. (2021) The role of hlb-converting bacteriophages in *Staphylococcus aureus* host adaption. *Microb. Physiol.*, 31(2): 109–122.
- 24. Silva, V., Capelo, J.L., Igrejas, G. and Poeta, P. (2020) Molecular epidemiology of *Staphylococcus aureus* lineages in wild animals in Europe: A review. *Antibiotics (Basel)*, 9(3): 122.
- Vivas, R., Barbosa, A.A.T., Dolabela, S.S. and Jain, S. (2019) Multidrug-resistant bacteria and alternative methods to control them: An overview. *Microb. Drug Resist.*, 25(6): 890–908.
- 26. Dweba, C.C., Zishiri, O.T. and Zowalaty, M.E.E. (2018) Methicillin-resistant *Staphylococcus aureus*: Livestockassociated, antimicrobial, and heavy metal resistance. *Infect. Drug Resist.*, 11: 2497–2509.
- 27. Fetsch, A., Etter, D. and Johler, S. (2021) Livestockassociated meticillin-resistant *Staphylococcus aureus*-current situation and impact from a one health perspective. *Curr. Clin. Microbiol. Rep.*, 8: 103–113.
- Murra, M., Mortensen, K.L. and Wang, M. (2019) Livestock-associated methicillin-resistant *Staphylococcus aureus* (clonal complex 398) causing bacteremia and epidural abscess. *Int. J. Infect. Dis.*, 81: 107–109.
- 29. Aires-de-Sousa, M. (2017) Methicillin-resistant Staphylococcus aureus among animals: Current overview. *Clin. Microbiol. Infect.*, 23(6): 373–380.
- Back, S.H., Eom, H.S., Lee, H.H., Lee, G.Y., Park, K.T. and Yang, S.J. (2020) Livestock-associated methicillin-resistant *Staphylococcus aureus* in Korea: Antimicrobial resistance and molecular characteristics of LA-MRSA strains isolated from pigs, pig farmers, and farm environment. *J. Vet. Sci.*, 21(1): e2.
- Carfora, V., Caprioli, A., Grossi, I., Pepe, M., Alba, P., Lorenzetti, S., Amoruso, R., Sorbara, L., Franco, A. and Battisti, A. (2016) A methicillin-resistant *Staphylococcus aureus* (MRSA) sequence type 8, *spa* type t11469 causing infection and colonizing horses in Italy. *Pathog. Dis.*, 74(4): ftw025.
- 32. Sharma, M., Nunez-Garcia, J., Kearns, A.M., Doumith, M., Butaye, P.R., Argudín, M.A., Lahuerta-Marin, A., Pichon, B., AbuOun, M., Rogers, J., Ellis, R.J., Teale, C. and Anjum, M.F. (2016) Livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) clonal complex (CC) 398 isolated from UK animals belong to European lineages. *Front. Microbiol.*, 7: 1741.
- Haag, A.F., Fitzgerald, J.R. and Penadés, J.R. (2019) Staphylococcus aureus in animals. Microbiol. Spectr., 7(3): 60.
- Anjum, M.F., Marco-Jimenez, F., Duncan, D., Marín, C., Smith, R.P. and Evans, S.J. (2019) Livestock-associated methicillin-resistant *Staphylococcus aureus* from animals and animal products in the UK. *Front. Microbiol.*, 10(1): 2136.
- Bosch, T. and Schouls, L.M. (2015) Livestock-associated MRSA: Innocent or serious health threat? *Future Microbiol.*, 10(4): 445–447.
- 36. Mehndiratta, P.L. and Bhalla, P. (2014) Use of antibiotics in animal agriculture and emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) clones: Need to assess the impact on public health. *Indian J. Med. Res.*, 140(3): 339–344.
- Elstrøm, P., Grøntvedt, C.A., Gabrielsen, C., Stegger, M., Angen, Ø, Åmdal, S, Enger, H., Urdahl, A.M., Jore, S., Steinbakk, M. and Sunde, M. (2019) Livestock-associated MRSA CC1 in Norway; introduction to pig farms, zoonotic transmission, and eradication. *Front. Microbiol.*, 10: 139.
- Ceballos, S., Lozano, C., Aspiroz, C., Ruiz-Ripa, L., Eguizábal, P., Campaña-Burguet, A., Cercenado, E., López-Calleja, A.I., Castillo, J., Azcona-Gutiérrez, J.M., Torres, L., Calvo, J., Martin, C., Navarro, M., Zarazaga, M., Torres, C. and The Study Group of Clinical LA-MRSA. (2022) Beyond CC398: Characterisation of other tetracycline and methicillin-resistant *Staphylococcus aureus*

genetic lineages circulating in Spanish hospitals. *Pathogens*, 11(3): 307.

- Butaye, P., Argudin, M.A. and Smith, T.C. (2016) Livestockassociated MRSA and its current evolution. *Curr. Clin. Microbiol. Rep.*, 3(1): 19–31.
- Bortolami, A., Williams, N.J., McGowan, C.M., Kelly, P.G., Archer, D.C., Corro, M., Pinchbeck, G., Saunders, C.J. and Timofte, D. (2017) Environmental surveillance identifies multiple introductions of MRSA CC398 in an equine veterinary hospital in the UK, 2011–2016. *Sci. Rep.*, 7: 5499.
- 41. Hansen, J.E., Ronco, T., Stegger, M., Sieber, R.N., Fertner, M. E., Martin, H.L., Farre, M., Toft, N., Larsen, A.R. and Pedersen, K. (2019) LA-MRSA CC398 in dairy cattle and veal calf farms indicates spillover from pig production. *Front. Microbiol.*, 10: 2733.
- 42. Tao, C.W., Chen, J.S., Hsu, B.M., Koner, S., Hung, T.C., Wu, H.M. and Rathod, J. (2021) Molecular evaluation of traditional chicken farm-associated bioaerosols for methicillin-resistant *Staphylococcus aureus* shedding. *Antibiotics*, 10(8): 917.
- Chueahiran, S., Yindee, J., Boonkham, P., Suanpairintr, N. and Chanchaithong, P. (2021) Methicillin-resistant *Staphylococcus aureus* clonal complex 398 as a major MRSA lineage in dogs and cats in Thailand. *Antibiotics*, 10(3): 243.
- Haenni, M., Chatre, P., Dupieux-Chabert, C., Metayer, V., Bes, M., Madec, J.Y. and Laurent, F. (2017) Molecular epidemiology of methicillin-resistant *Staphylococcus aureus* in horses, cats, and dogs over a 5-year in France. *Front. Microbiol.*, 8: 2493.
- 45. Walther, B., Klein, K.S., Barton, A.K., Semmler, T., Huber, C., Merle, R., Tedin, K., Mitrach, F., Lübke-Becker, A. and Gehlen, H. (2018) Equine methicillin-resistant sequence type 398 *Staphylococcus aureus* (MRSA) harbor mobile genetic elements promoting host adaptation. *Front. Microbiol.*, 9: 2516.
- 46. Zomer, T.P., Wielders, C.C.H., Veenman, C., Hengeveld, P., van der Hoek, W., de Greeff, S.C., Smit, L.A.M., Heederik, D.J., Yzermans, C.J., Bosch, T., Maassen, C.B.M. and van Duijkeren, E. (2017) MRSA in persons not living or working on a farm in a livestock-dense area: Prevalence and risk factors. J. Antimicrob. Chemother., 72(3): 893–899.
- Petersen, A., Larssen, K.W., Gran, F.W., Enger, H., Haeggman, S., Mäkitalo, B., Haraldsson, G., Lindholm, L., Vuopio, J., Henius, A.E., Nielsen, J. and Larsen, A.R. (2021) Increasing incidences and clonal diversity of methicillin-resistant *Staphylococcus aureus* in the nordic countries results from the nordic MRSA surveillance. *Front. Microbiol.*, 12: 668900.
- Harrison, E.M., Coll, F., Toleman, M.S., Blane, B., Brown, N.M., Török, M.E., Parkhill, J. and Peacock, S.J. (2017) Genomic surveillance reveals low prevalence of livestock-associated methicillin-resistant *Staphylococcus aureus* in the East of England. *Sci. Rep.*, 7(1): 7406.
- Weese, J.S., Rousseau, J., Traub-Dargatz, J.L., Willey, B.M., McGeer, A.J. and Low, D.E. (2005) Community-associated methicillin-resistant *Staphylococcus aureus* in horses and humans who work with horses. *J. Am. Vet. Med. Assoc.*, 226(4): 580–583.
- Shuping, L.L., Kuonza, L., Musekiwa, A., Iyaloo, S. and Perovic, O. (2017) Hospital-associated methicillin-resistant *Staphylococcus aureus*: A cross-sectional analysis of risk factors in South African tertiary public hospitals. *PLoS One*, 12(11): e0188216.
- 51. Hartmann, F.A., Trostle, S.S. and Klohnen, A.A.O. (1997) Isolation of methicillin-resistant *Staphylococcus aureus* from a post-operative wound infection in a horse. *J. Am. Vet. Med. Assoc.*, 211(5): 590–592.
- 52. Seguin, J.C., Walker, R.D., Caron, J.P., Kloos, W.E., George, C.G., Hollis, R.J., Jones, R.N. and Pfaller, M.A. (1999) Methicillin-resistant *Staphylococcus aureus* outbreak in a veterinary teaching hospital: Potential human-to-animal

transmission. J. Clin. Microbiol., 37(5): 1459-1463.

- de Araujo, F.P., Monaco, M., Grosso, M.D., Pirolo, M., Visca, P. and Pantosti, A. (2021) *Staphylococcus aureus* clones causing osteomyelitis: A literature review (2000– 2020). *J. Glob. Antimicrob. Resist.*, 26: 29–36.
- 54. Sauvé, F. (2021) Staphylococcal cutaneous infection in horses: From the early 2000s to the present. *Can. Vet. J.*, 62(9): 1001–1006.
- 55. Moremi, N., Claus, H., Vogel, U. and Mshana, S.E. (2019) The role of patients and health-care workers *Staphylococcus aureus* nasal colonization in occurrence of surgical site infection among patients admitted in two centers in Tanzania. *Antimicrob. Resist. Infect. Control*, 8: 102.
- 56. Weese, J.S. (2004) Methicillin-resistant *Staphylococcus* aureus in horses and horse personnel. *Vet. Clin. North Am.* Equine Pract., 20(3): 601–613.
- Othman, A.A., Hiblu, M.A., Abbassi, M.S., Abouzeed, Y.M. and Ahmed, M.O. (2021) Nasal colonization and antibiotic resistance patterns of *Staphylococcus* species isolated from healthy horses in Tripoli, Libya. *J. Equine Sci.*, 32(2): 61–65.
- Maalej, S.M., Trabelsi, J.J., Claude-Alexandre, G., Boutiba, I., Mastouri, M., Besbes, S., Barguellil, F., Laurent, F. and Hammami, A. (2019) Antimicrobial susceptibility and molecular epidemiology of methicillin-resistant *Staphylococcus aureus* in Tunisia: Results of a multicenter study. *J. Infect. Dis. Epidemiol.*, 5(2): 71.
- Zarfel, G., Luxner, J., Folli, B., Leitner, E., Feierl, G., Kittinger, C. and Grisold, A. (2016) Increase of genetic diversity and clonal replacement of epidemic methicillin-resistant *Staphylococcus aureus* strains in South-East Austria. *FEMS Microbiol. Lett.*, 363(14): fnw137.
- Witte, W., Strommenger, B., Stanek, C. and Cuny, C. (2007) Methicillin-resistant *Staphylococcus aureus* ST398 in humans and animals, Central Europe. *Emerg. Infect. Dis.*, 13(2): 255–258.
- 61. Parisi, A., Caruso, M., Normanno, G., Latorre, L., Miccolupo, A., Fraccalvieri, R., Intini, F., Manginelli, T. and Santagada, G. (2017) High occurrence of methicillin-resistant *Staphylococcus aureus* in horses at slaughterhouses compared with those for recreational activities: A professional and food safety concern? *Foodborne Pathog. Dis.*, 14(12): 735–741.
- Smith, T.C., Moritz, E.D., Larson, K.R.L. and Ferguson, D.D. (2010) The environment as a factor in methicillin-resistant *Staphylococcus aureus* transmission. *Rev. Environ. Health*, 25(2): 121–134.
- Simor, A.E., Ofner-Agostini, M., Bryce, E., Green, K., McGeer, A., Mulvey, M., and Paton, S. (2001) Canadian Nosocomial Infection Surveillance Program, Health Canada. The evolution of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals: 5 years of national surveillance. *CMAJ*, 165: 21–26.
- 64. Van den Eede, A., Martens, A., Feryn, I., Vanderhaeghen, W., Lipinska, U., Gasthuys, F., Butaye, P., Haesebrouck, F. and Hermans, K. (2012) Low MRSA prevalence in horses at farm level. *BMC Vet. Res.*, 8: 213.
- 65. Weese, J.S. (2008) Current therapy in equine medicine. In: Robinson, N.E. and Sprayberry, K.A., editors. Elsevier Health Sciences, St. Louis, New York. p167.
- 66. Pirolo, M., Visaggio, D., Gioffrè, A., Artuso, I., Gherardi, M., Pavia, G., Samele, P., Ciambrone, L., Di Natale, R., Spatari, G., Casalinuovo, F. and Visca, P. (2019) Unidirectional animal-to-human transmission of methicillin-resistant *Staphylococcus aureus* ST398 in pig farming; evidence from a surveillance study in Southern Italy. *Antimicrob. Resist. Infect. Control*, 8: 187.
- 67. Sieber, R.N., Larsen, A.R., Urth, T.R., Iversen, S., Møller, C.H., Skov, R.L., Larsen, J. and Stegger, M. (2019) Genome investigations show host adaptation and transmission of LAMRSA CC398 from pigs into Danish health-care institutions. *Sci. Rep.*, 9(1): 18655.

- Kraushaar, B., Hammerl, J.A., Kienöl, M., Heinig, M.L., Sperling, N., Thanh, M.D., Reetz, J., Jäckel, C., Fetsch, A. and Hertwig, S. (2017) Acquisition of virulence factors in livestock-associated MRSA: Lysogenic conversion of CC398 strains by virulence gene-containing phages. *Sci. Rep.*, 7(1): 2004.
- Kashif, A., McClure, J.A., Lakhundi, S., Pham, M., Chen, S., Conly, J.M. and Zhang, K. (2019) *Staphylococcus aureus* ST398 virulence is associated with factors carried on prophage \$\phi\$33. Front. Microbiol., 10: 2219.
- Schwaber, M.J., Navon-Venezia, S., Masarwa, S., Tirosh-Levy, S., Adler, A., Chmelnitsky, I., Carmeli, Y., Klement, E. and Steinman, A. (2013) Clonal transmission of a rare methicillin-resistant *Staphylococcus aureus* genotype between horses and staff at a veterinary teaching hospital. *Vet. Microbiol.*, 162(2–4): 907–911.
- Cuny, C., Abdelbary, M.M.H., Kock, R., Layer, F., Scheidemann, W., Werner, G. and Witte, W. (2016) Methicillin-resistant *Staphylococcus aureus* from infections in horses in Germany are frequent colonizers of veterinarians but rare among MRSA from infections in humans. *One Health*, 2: 11–17.
- 72. Lakhundi, S. and Zhang, K. (2018) Methicillin-resistant *Staphylococcus aureus*: Molecular characterization, evolution, and epidemiology. *Clin. Microbiol. Rev.*, 31(4): e00020–18.
- 73. Alalaiwe, A., Wang, P.W., Lu, P.L., Chen, Y.P., Fang, J.Y. and Yang, S.C. (2018) Synergistic anti-MRSA activity of cationic nanostructured lipid carriers in combination with oxacillin for cutaneous application. *Front. Microbiol.*, 9: 1493.
- McClure, J.A., Conly, J.M., Obasuyi, O., Ward, L., Ugarte-Torres, A., Louie, T. and Zhang, K. (2020) A novel assay for detection of methicillin-resistant *Staphylococcus aureus* directly from clinical samples. *Front. Microbiol.*, 11: 1295.
- Bush, K. and Bradford, P.A. (2019) Interplay between β-lactamases and new β-lactamase inhibitors. *Nat. Rev. Microbiol.*, 17(5): 295–306.
- Bush, K. and Bradford, P.A. (2016) β-Lactams and β-Lactamase inhibitors: An overview. *Cold Spring Harb. Perspect. Med.*, 6(8): a025247.
- 77. Harrison, E.M., Ba, X., Coll, F., Blane, B., Restif, O., Carvell, H., Köser, C.U., Jamrozy, D., Reuter, S., Lovering, A., Gleadall, N., Bellis, K.L., Uhlemann, A.C., Lowy, F.D., Massey, R.C., Grilo, I.R., Sobral, R., Larsen, J., Larsen, A.R., Lundberg, C.V., Parkhill, J., Paterson, G.K., Holden, M.T.G., Peacock, S.J. and Holmes, M.A. (2019) Genomic identification of cryptic susceptibility to penicillins and β-lactamase inhibitors in methicillin-resistant *Staphylococcus aureus. Nat. Microbiol.*, 4(10): 1680–1691.
- Liu, P., Xue, H., Wu, Z., Ma, J. and Zhao, X. (2016) Effect of bla regulators on the susceptible phenotype and phenotypic conversion for oxacillin-susceptible *mecA*-positive staphylococcal isolates. *J. Antimicrob. Chemother.*, 71(8): 2105–2112.
- 79. Khalifa, S.M., El-Aziz, A.M.A., Hassan, R. and Abdelmegeed, E.S. (2021)  $\beta$ -lactam resistance associated with  $\beta$ -lactamase production and porin alteration in clinical isolates of *E. coli* and *K. pneumonia. PLoS One*, 16(5): e0251594.
- Silvestri, S., Rampacci, E., Stefanetti, V., Trotta, M., Fani, C., Levorato, L., Brachelente, C. and Passamonti, F. (2021) Immunofluorescence targeting PBP2a protein: A new potential methicillin resistance screening test. *Front. Vet. Sci.*, 8: 740934.
- 81. Nikolaou, E., German, E.L., Blizard, A., Howard, A., Hitchins, L., Chen, T., Chadwick, J., Pojar, S., Mitsi, E., Solórzano, C., Sunny, S., Dunne, F., Gritzfeld, J.F., Adler, H., Hinds, J., Gould, K.A., Rylance, J., Collins, A.M., Gordon, S.B. and Ferreira, D.M. (2021) The nose is the best niche for detection of experimental pneumococcal colonisation in adults of all ages, using nasal wash. *Sci. Rep.*, 11(1):

18279

- Peretz, A., Pastukh, N., Isakovich, N., Koifman, A., Brodsky, D., Mizrahi, H., Aharon, I. and Labay, K. (2016) Efficacy of an enrichment media for increasing threshold for carbapenem-resistant Enterobacteriaceae screening. J. Clin. Lab. Anal., 30(5): 563–566.
- 83. Tenover, F.C. and Tickler, I.A. (2022) Detection of methicillin-resistant *Staphylococcus aureus* infections using molecular methods. *Antibiotics*, 11(2): 239.
- Sarrafzadeh, F., Sohrevardi, S.M., Abousaidi, H. and Mirzaei, H. (2021) Prevalence of methicillin-resistant *Staphylococcus aureus* in Iranian children: A systematic review and meta-analysis. *Clin. Exp. Pediatr.*, 64(8): 415–421.
- Wangai, F.K., Masika, M.M., Maritim, M.C. and Seaton, R.A. (2019) Methicillin-resistant *Staphylococcus aureus* (MRSA) in East Africa: Red alert or red herring? *BMC Infect. Dis.*, 19(1): 596.
- Bastard, J., Andraud, M., Chauvin, C., Glaser, P., Opatowski, L. and Temime, L. (2020) Dynamics of livestock-associated methicillin-resistant *Staphylococcus aureus* in pig movement networks: Insight from mathematical modeling and French data. *Epidemics*, 31: 100389.
- Van Balen, J., Mowery, J., Piraino-Sandoval, M., Nava-Hoet, R.C., Kohn, C. and Hoet, A.E. (2014) Molecular epidemiology of environmental MRSA at an equine teaching hospital: Introduction, circulation and maintenance. *Vet. Res.*, 45(1): 31.
- Tirosh-Levy, S., Steinman, A., Carmeli, Y., Klement, E. and Navon-Venezia, S. (2015) Prevalence and risk factors for colonization with methicillin-resistant *Staphylococcus aureus* and other *Staphylococci* species in hospitalized and farm horses in Israel. *Prev. Vet. Med.*, 122(1–2): 135–144.
- Brans, R., Kaup, O. and Schürer, N.Y. (2018) Occupational MRSA infection: Risk factor, disposition, prevention, and therapy. In: Kanerva's Occupational Dermatology. Springer, Berlin. p1–12.
- Fertner, M., Pedersen, K, Jensen, V.F., Larsen, G., Lindegaard, M., Hansen, J.E. and Chriél, M. (2019) Within-farm prevalence and environmental distribution of livestock-associated methicillin-resistant *Staphylococcus aureus* in farmed mink (*Neovison vison*). *Vet. Microbiol.*, 231: 80–86.
- 91. Cuny, C. and Witte, W. (2017) MRSA in equine hospitals and its significance for infections in humans. *Vet. Microbiol.*, 200: 59–64.
- 92. Kuroda, T., Kinoshita, Y., Niwa, H., Shinzaki, Y., Tamura, N., Hobo, S. and Kuwano, A. (2016) A methicillin-resistant *Staphylococcus aureus* colonisation and infection in thoroughbred racehorses and veterinarians in Japan. *Vet. Rec.*, 178(19): 473.
- Sassmannshausen, R., Deurenberg, R.H., Köck, R., Hendrix, R., Jurke, A., Rossen, J.W.A. and Friedrich, A.W. (2016) MRSA prevalence and associated risk factors among health-care workers in non-outbreak situations in the Dutch-German EUREGIO. *Front. Microbiol.*, 7: 1273.
- Schulz, J., Boklund, A., Toft, N. and Halasa, T. (2019) Effects of control measures on the spread of LA-MRSA among Danish pig herds between 2006 and 2015 a simulation study. *Sci. Rep.*, 9: 691.
- Grema, H.A., Geidam, Y.A., Gadzama, G.B., Ameh, J.A. and Suleiman, A. (2015) Methicillin-resistant *Staphylococcus aureus* (MRSA): A review. *Adv. Anim. Vet. Sci.*, 3(2): 79–98.
- 96. Kinross, P., Petersen, A., Skov, R., Van Hauwermeiren, E., Pantosti, A., Laurent, F., Voss, A., Kluytmans, J., Struelens, M.J., Heuer, O., Monnet, D.L. and The European Human LA-MRSA Study Group. (2017) Livestockassociated methicillin-resistant *Staphylococcus aureus* (MRSA) among human MRSA isolates, European Union/ European Economic Area countries, 2013. *Eurosurveillance*, 22(44): 16–00696.
- 97. Koop, G. (2016) MRSA transmission between horses

and vets: Who's doing the infecting? Vet. Rec., 178(19): 471–472.

- Hu, X., Hu, K., Liu, Y., Zeng, L., Hu, N., Chen, X. and Zhang, W. (2022) Risk factors for methicillin-resistant *Staphylococcus aureus* colonization and infection in patients with human immunodeficiency virus infection: A systematic review and meta-analysis. *J. Int. Med. Res.*, 50(1): 3000605211063019.
- Nillius, D., von Müller, L., Wagenpfeil, S., Klein, R. and Herrmann, M. (2016) Methicillin-resistant *Staphylococcus aureus* in Saarland, Germany: The long-term care facility study. *PLoS One*, 11(4): e0153030.
- Mitevska, E., Wong, B., Surewaard, B.G.J. and Jenne, C.N. (2021) The prevalence, risk, and management of methicillin-resistant *Staphylococcus aureus* infection in diverse populations across Canada: A systematic review. *Pathogens*, 10(4): 393.
- 101. Gebremedhn, G., Gebremariam, T.T., Wasihun, A.G., Dejene, T.A. and Saravanan, M. (2016) Prevalence and risk factors of methicillin-resistant *Staphylococcus aureus* colonization among HIV patients in Mekelle, Northern Ethiopia. *Springerplus*, 5(1): 877.
- 102. Feingold, B.J., Silbergeld, E.K., Curriero, F.C., van Cleef, B.A.G., Heck, M.E.O. and Kluytmans, J.A.J. (2012) Livestock density as a risk factor for livestock-associated methicillin-resistant *Staphylococcus aureus*, the Netherlands. *Emerg. Infect. Dis.*, 18(11): 1841–1849.
- 103. Couderc, C., Jolivet, S., Thiébaut, A.C.M., Ligier, C., Remy, L., Alvarez, A.S., Lawrence, C., Salomon, J., Herrmann, J.L., Guillemot, D. and *Staphylococcus aureus* Resistant to Antibiotics (ASAR) Study Group. (2014) Fluoroquinolone use is a risk factor for methicillin-resistant *Staphylococcus aureus* acquisition in long-term care facilities: A nested case-case-control study. *Clin. Infect. Dis.*, 59(2): 206–215.
- 104. Kinoshita, T., Tokumasu, H., Tanaka, S., Kramer, A. and Kawakami, K. (2017) Policy implementation for methicillin-resistant *Staphylococcus aureus* in seven European countries: A comparative analysis from 1999 to 2015. *J. Mark. Access Health Policy*, 5(1): 1351293.
- 105. Liu, Y., Li, W., Dong, Q., Liu, Y. and Ye, X. (2021) Livestock-associated and non-livestock-associated *Staphylococcus aureus* carriage in humans is associated with pig exposure in a dose-response manner. *Infect. Drug Resist.*, 14: 173–184.
- 106. Moodley, A., Nightingale, E.C., Stegger, M., Nielsen, S.S., Skov, R.L. and Guardabassi, L. (2008) High risk for nasal carriage of methicillin-resistant *Staphylococcus aureus* among Danish veterinary practitioners. *Scand. J. Work Environ. Health*, 34(2): 151–157.
- 107. Schnitt, A., Lienen, T., Wichmann-Schauer, H., Cuny, C. and Tenhagen, B.A. (2020) The occurrence and distribution of livestock-associated methicillin-resistant *Staphylococcus aureus* ST398 on German dairy farms. *J. Dairy Sci.*, 103(12): 11806–11819.
- 108. Crnich, C.J. (2013) Impact and management of MRSA in the long-term care setting. *Curr. Transl. Geriatr. Exp. Gerontol. Rep.*, 2(3): 125–135.
- 109. Kavanagh, K.T., Abusalem, S. and Calderon, L.E. (2018) View point: Gaps in the current guidelines for the prevention of Methicillin-resistant *Staphylococcus aureus* surgical site infections. *Antimicrob. Resist. Infect. Control*, 7: 112.
- Hassoun, A., Linden, P.K. and Friedman, B. (2017) Incidence, prevalence, and management of MRSA bacteremia across patient populations-a review of recent developments in MRSA management and treatment. *Crit. Care.* 21(1): 211.

- 111. Fernandes, P. (2016) Fusidic acid: A bacterial elongation factor inhibitor for the oral treatment of acute and chronic Staphylococcal infections. *Cold Spring Harb. Perspect. Med.*, 6(1): e025437.
- 112. Boyle, A.G., Timoney, J.F., Newton, J.R., Hines, M.T., Waller, A.S. and Buchanan, B.R. (2018) *Streptococcus equi* infections in horses: Guidelines for treatment, control, and prevention of strangles-revised consensus statement. *J. Vet. Int. Med.*, 32(2): 633–647.
- 113. Parra-Sanchez, A., Lugo, J., Boothe, D.M., Gaughan, E.M., Hanson, R.R., Duran, S. and Belknap, J.K. (2006) Pharmacokinetics and pharmacodynamics of enrofloxacin and a low dose of amikacin administered via regional intravenous limb perfusion in standing horses. *Am. J. Vet. Res.*, 67(10): 1687–1695.
- 114. Boyle, A.G., Rankin, S.C., Duffee, L.A. and Morris, D. (2017) Prevalence of methicillin-resistant *Staphylococcus aureus* from equine nasopharyngeal and guttural pouch wash samples. *J. Vet. Int. Med.*, 31(5): 1551–1555.
- 115. Marimuthu, K., Pittet, D. and Harbarth, S. (2014) The effect of improved hand hygiene on nosocomial MRSA control. *Antimicrob. Resist. Infect. Control*, 3(1): 34.
- 116. Angen, Ø., Feld, L., Larsen, J., Rostgaard, K., Skov, R., Madsen, A.M. and Larsen, A.R. (2017) Transmission of methicillin-resistant *Staphylococcus aureus* to human volunteers visiting a swine farm. *Appl. Environ. Microbiol.*, 83(23): e01489–17.
- 117. Albrecht, J.S., Croft, L., Morgan, D.J. and Roghmann, M.C. (2016) Perceptions of gown and glove use to prevent methicillin-resistant *Staphylococcus aureus* transmission in nursing homes. *J. Am. Med. Dir. Assoc.*, 18(2): 158–161.
- 118. Souverein, D., Houtman, P., Euser, S.M., Herpers, B.L., Kluytmans, J. and Den Boer, J.W. (2016) Costs and benefits associated with the MRSA search and destroy policy in a hospital in the region Kennemerland, The Netherlands. *PLoS One*, 11(2): e0148175.
- 119. Julian, T., Singh, A., Rousseau, J. and Weese, J.S. (2012) Methicillin-resistant staphylococcal contamination of cellular phones of personnel in a veterinary teaching hospital. *BMC Res. Notes*, 5: 193.
- 120. Mairi, A., Touati, A., Pantel, A., Martinez, A.Y., Ahmim, M., Sotto, A., Dunyach-Remy, C. and Lavigne, J.P. (2021) First report of CC5-MRSA-IV-SCCfus "Maltese Clone" in bat guano. *Microorganisms*, 9(11): 2264.
- 121. Klous, G., Huss, A., Heederik, D.J.J. and Coutinho, R.A. (2016) Human-livestock contacts and their relationship to transmission of zoonotic pathogens, a systematic review of literature. *One Health*, 2: 65–76.
- 122. Bos, M., Verstappen, K., van Cleef, B., Dohmen, W., Dorado-García, A., Graveland, H., Duim, B., Wagenaar, J.A., Kluytmans, J.A.J. and Heederik, D.J.J. (2016) Transmission through air as a possible route of exposure for MRSA. *J. Expo. Sci. Environ. Epidemiol.*, 26(3): 263–269.
- 123. Bauchner, H., Fontanarosa, P.B. and Livingston, E.H. (2020) Conserving supply of personal protective equipment a call for ideas. *J. Am. Med. Assoc.*, 323(19): 1911.
- 124. van de Sande-Bruinsma, N., van Hall, M.A.L., Janssen, M., Nagtzaam, N., Leenders, S., de Greeff, S.C. and Schneeberger, P.M. (2015) Impact of livestock-associated MRSA in a hospital setting. *Antimicrob. Resist. Infect. Control*, 4: 11.
- 125. Lienen, T., Schnitt, A., Hammerl, J.A., Maurischat, S. and Tenhagen, B.A. (2021) Genomic distinctions of LA-MRSA ST398 on dairy farms from different German federal states with a low risk of severe human infections. *Front. Microbiol.*, 11: 575321.

\*\*\*\*\*\*