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A look at staphylococci from the one health perspective

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ABSTRACT

Staphylococcus aureus and other staphylococcal species are resident and transient multihost colonizers as well as conditional pathogens. Especially *S. aureus* represents an excellent model bacterium for the "One Health" concept because of its dynamics at the human-animal interface and versatility with respect to host adaptation. The development of antimicrobial resistance plays another integral part. This overview will focus on studies at the human-animal interface with respect to livestock farming and to companion animals, as well as on staphylococci in wildlife. In this context transmissions of staphylococci and of antimicrobial resistance genes between animals and humans are of particular significance.

1. Introduction

Currently, the genus *Staphylococcus* comprises more than 50 validly described and proposed species and subspecies besides *S. aureus* (non-aureus staphylococci, NAS) including coagulase-negative staphylococci (CoNS) as well as coagulase positive-staphylococci (CoPS). During the past decade some new species were described. Furthermore, the taxonomy of this genus was revised several times. Some former subspecies became species (Munson and Carroll, 2023) and, in addition, species of the former *S. sciuri* group were established as the separate genus *Mammaliococcus* (Madhaiyan et al., 2020). Furthermore, whole genome sequencing revealed that isolates from specific *S. aureus* lineages are divergent from classical *S. aureus*. They were designated as closely related but separate coagulase-positive species, representing together with *S. aureus* the *S. aureus*-related complex according to Tong et al., 2015, namely *S. argenteus*, *S. schweitzeri*, *S. roterdami* and *S. singaporensis* (Chew et al., 2021; Schutte et al., 2021; Tong et al., 2015). Since these NAS species share phenotypical characteristics used for species identification with *S. aureus,* misidentification can happen (Becker et al., 2019). Staphylococci are part of the natural microbiota of human and animal skin and mucous membranes. Depending on predispositions, *S. aureus* can potentially be a causative agent for various kinds of infections in humans and animals (Lowy, 1998; Peton and Le Loir, 2014). The rise in documented infections caused by NAS is mainly associated with an increasing number of persons showing predispositions for staphylococcal infections, such as the increased number of premature neonates, more severely ill, elderly and immunocompromised patients. Furthermore, the increasing use of implanted foreign prosthetic material and indwelling catheters predisposes more patients to NAS infections (Becker et al., 2014). Besides *S. aureus,* several other staphylococcal species are of significant veterinary importance.

S. pseudintermedius is the cause of pyoderma in dogs and a big reservoir of antimicrobial resistance genes for the genus (Guardabassi et al., 2004). Diverse CoNS emerged as udder pathogens affecting ruminants (Vanderhaeghen et al., 2014). A deeper understanding of the emergence and spread of staphylococci at the human-animal interface, of their role as conditional pathogens and of antimicrobial resistance development corresponds to the one health approach. This concept recognizes the health of humans, domestic and wild animals, plants, and the environment (including ecosystems) as linked and inter-dependent (One Health High-Level Expert Panel, 2022).

2. *S. aureus* in different host species

2.1. Population structure of S. aureus from humans and animals and host-switching

S. aureus is primarily a commensal but also a facultative pathogen. The question of host specificity became of interest in the first decades after World War II, when frequent clusters of human mastitis occurred. Infections in newborns, but also outbreaks of mastitis in animals such as cows associated with mechanical milking or infections in industrially

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raised chicken, were observed. At that time characterization of *S. aureus* isolates by means of phenotypical traits suggested the existence of host-adapted so-called "ecovars", such as for humans, cattle, sheep, and chicken (Hajek and Marsalek, 1969; Meyer, 1967; Witte et al., 1977). Due to a low level of recombination affecting its core genome the population structure of species *S. aureus* is clonal. This allows to attribute isolates from humans and from animals to particular Multi Locus Sequence Types (STs) and to clonal complexes (CCs) (overview by Cuny et al., 2015c; Shepheard et al., 2013). As it will be discussed below, distinct clonal complexes and lineages of *S. aureus* are commonly associated with particular hosts. On the other side, there were many host-switching events which occurred during its evolution. There are CCs and ST`s which were observed only in humans so far such as CC5-ST105, CC5-ST111, CC5-ST125, CC5-ST225, CC5-ST228, CC8-ST239, CC12, CC59, CC72, CC88. Others were preferentially reported from animals such as CC49, CC71, CC131, CC151, CC350, CC385, CC425, CC522. A number of clonal complexes were reported from humans as well as from companion animals, livestock, and wildlife: CC1, CC5, CC6, CC7, CC8, CC9, CC15, CC20, CC22, CC30-ST34, CC45, CC97, CC101, CC121, CC130, CC188, CC228 (overview by Cuny et al., 2015c; Shepheard et al., 2013).

2.2. Host-switching and phylogeny

Attribution of isolates from humans and from animals to the same clonal complex can either be due to a jump between hosts, which leads to different host adapted subpopulations, or to a spillover to a new host. This can be decided by a phylogenetic analysis based on detection of single nucleotide polymorphisms (SNP`s), which are deduced from whole genome comparisons. For most of the CC's listed above, host jumps from humans to animals have most likely taken place. The additional use of the specific algorithms like BEAST (Bayesian Evolutionary Analysis by Sampling Trees; https://www.beast2.org/) allows tracing back the evolution of a particular clonal lineage or CC according to a time scale. Thus, for CC133, the initial jump from humans to cattle was estimated to have taken place about 6000 years ago (Guinane et al., 2010). The jump of CC5 from humans to chicken was traced back to 240 years ago (Lowder et al., 2009) and that of CC97 from cattle to humans obviously happened about 50 years ago (Spoor et al., 2013). Also, for CC9, which is observed in humans, pigs and cattle, a jump from humans to pigs was likely to have happened about 200 years ago and was followed by spillover to cattle (Yu et al., 2021). A more recently performed population genomic analysis of more than 800 representative *S. aureus* isolates provided a high-resolution picture of the dynamics of *S. aureus* in the context of its host (Richardson et al., 2018). It was shown that for CC`s recently observed in humans as well as animals numerous jumps from humans to animals very likely have taken place.

The evolutionary history of bovine *S. aureus* was examined in depth by use a global dataset of 10,254 *S. aureus* genomes including 1896 bovine isolates from 32 countries in 6 continents (Yebra et al., 2022). There were host jumps from humans to cattle that led to the at present most prevalent clones of *S. aureus* causing bovine mastitis around the world. The first of the host jumps occurred up to 2500 years ago by the ancestor of contemporary bovine CCs such as CC151, CC350, CC133, and CC50, and the multi animal host associated CC49. Of particular interest is the subsequent host jump back into humans which led to the emergence of the epidemic community associated methicillin resistant *S. aureus* (CA-MRSA) ST59 clone, that is currently widely disseminated in East Asia (Ward et al., 2016). Another host jump back into humans led to the emergence of CC121, a global disseminated CC which mainly is associated with skin and soft tissue infections in humans (Azarian et al., 2021). A further human-to-bovine jump of the progenitor of the bovine CC97 occurred about 330 years ago CC97 is prevalent as the cause of bovine mastitis worldwide. The jump back into humans led to a methicillin susceptible *S. aureus* (MSSA) subpopulation which is widely spread, and to the emergence MRSA CC97 which is also disseminated in the community. Furthermore, the limited host specificity of CC130, observed in hedgehogs, ruminants, pigs, humans, and of livestock associated methicillin resistant *S. aureus* (LA-MRSA) CC398, observed in pigs, cattle, horses, humans, carnivores and birds, was confirmed by these studies.

In many cases host-switching is accompanied by changes in the accessory genome. *S. aureus* from humans typically contains the φSa3 prophages carrying a human immune evasion gene cluster (IEC) consisting of genes *scn, chp, and sak*, which encode the staphylococcal complement inhibitor protein (SCIN), the chemotaxis inhibitor protein (CHIPS), and staphylokinase (SAK), respectively. SAK inhibits the bactericidal activity of α-defensins and possesses anti-opsonic properties by activating human plasminogen into plasmin at the bacterial surface. LA-MRSA CC398 containing the IEC was less efficiently ingested by polymorphonuclear neutrophils in equine and human blood than their parental strains (Jung et al., 2017). The φSa3 prophage is often lost when *S. aureus* of human origin adapts to an animal host (Fitzgerald, 2012). Thus, both insertion (human adapted isolates) and excision (animal adapted isolates) of the φSa3 prophages could potentially confer a fitness advantage to *S. aureus* (Rohmer et al., 2022). Furthermore, pathogenicity islands that encode superantigens or von Willebrand factor-binding proteins with ruminant specific activity have been acquired in association with jumps to ruminants and horses (Guinane et al., 2010; Viana et al., 2010). The host jump of CC8 was associated with acquisition of staphylococcal cassette element (SCC), containing a gene for a surface binding protein, besides loss of the IEC (Resch et al., 2013).

MRSA CC398 from horses, that are typically associated with equine hospitals, represent a separate subpopulation of this clonal complex (Abdelbary et al., 2014). It obviously acquired a phage encoding a novel equine allele of the staphylococcal inhibitor of complement (*s cn*). This phage also encodes the *luk*P/Q leukocidin, recently characterized to have equine-specific activity (de Jong et al., 2018; Koop et al., 2017; Walther et al., 2018). Furthermore, (Richardson et al., 2018) described changes in biological pathways associated with amino acid metabolism and iron acquisition associated with host jumps, which suggests diversification with respect to nutrient availability in different host niches. The host jump from humans to rabbits was associated with a single nucleotide mutation in the *dlt*B gene encoding the D-alanine lipoteichoic acid and wall teichoic acid esterification protein (Viana et al., 2015).

On one hand, distinct clonal complexes and lineages of *S. aureus* are commonly associated with particular hosts, on the other hand, there were many host-switching events which occurred during its evolution. Because of the dynamics at the human-animal interface this species represents an excellent model of the "One Health" concept.

2.3. S. aureus and other species of the Staphylococcus aureus-complex in wildlife

During the past 10 years the occurrence of *S. aureus* in wildlife became of growing interest, as the role of *S. aureus* as a possible pathogen or colonizer in wild populations has not yet been studied systematically. Little is known about whether the occurrence in wildlife is due to recent spill overs from humans or from livestock populations or due to adaptation and persistence. In this context, it should be kept in mind, that humans and livestock are major sources of environmental contamination with a bacterium that is capable of causing disease in diverse host species. In case of persistent carriage of a novel emergent clonal lineage of *S. aureus* in wild animal species, there may be a risk to the health of humans, companion animals and livestock. According to the results from an extensive study on prevalence and molecular typing, *S. aureus* collected from various wildlife in Germany, Austria and Sweden can be attributed to a variety of clonal complexes, that are known from humans and companion animals, livestock, or all of them (Monecke et al., 2016). This is largely consistent with results from other studies (for review see Heaton et al., 2020; Silva et al., 2020; Abdullahi

et al., 2023). Studies on phylogeny, including genomes of isolates from wildlife as well as from humans, companion animals and livestock, are rare so far. Results from a recent study performed in Spain, including isolates from bats, birds (Eurasian magpie), carnivores, ungulates (red deer, Iberian ibex, wild boar), revealed that isolates from humans and animals attributed to CC5 and CC15 and MSSA CC398 grouped together, suggesting no adaptation to a particular host. MSSA CC398 containing *erm*(T) were not grouped into a separate cluster, suggesting that this particularly virulent MSSA, which is on the rise among humans in Western Europe, was also acquired by wildlife. However, the isolates from the animals investigated had lost the IEC (Martinez-Seijas et al., 2023). It has to be mentioned, that these particular MSSA CC398 containing the IEC were previously detected in nestlings of the white stork (Gomez et al., 2016b) as a migrating bird.

The first example of a transmission of infectious agents through animals from a historical perspective was the spread of the plague in the late Middle Ages by the brown rat (*Rattus norwegicus*) (Kohler and Kohler, 2003). Nowadays, brown rats may contribute to spread of multi-resistant bacterial pathogens such as multi-resistant gram--negative bacteria and MRSA. This was shown by detection of two CA-MRSA isolates, attributed to CC1 and CC22, among 62 animals caught in Vienna (Desvars-Larrive et al., 2019). When wild living rats caught in Germany and in Czech Republic were investigated for staphylococcal colonization, two MRSA isolates, attributed to CC30 and CC130, were detected in 145 animals. MSSA detected in these animals were attributed to CC7, CC15, CC49 and CC88. Interestingly, colonization of isolates attributed to CC49 and CC130 was maintained when the animals were kept in captivity (Raafat et al., 2020). Given the increasing urbanization worldwide, rodent control remains important for public health in cities.

S. aureus including MRSA has also been isolated from flies. A high proportion of MRSA isolated from flies was reported from Botswana (Seetswane et al., 2022). Furthermore, LA-MRSA was also detected on a fly caught in the centre of a German city neighbouring an area with high density of pig farms (Schaumburg et al., 2016).

An example for natural occurrence of MRSA in wildlife is MRSA CC130 in hedgehog (Larsen et al., 2022), which is discussed in more detail below. In connection with the investigation into the occurrence of highly pathogenic viruses, non-human primates in Sub-Saharan Africa were also checked for colonization with staphylococci. The finding of a significant proportion of *S. aureus* from colonization of African non-human primates, which were attributed to clonal lineages known from humans, suggested human to animal transmission (Schaumburg et al., 2012a). Among *S. aureus* isolates from sanctuary chimpanzees from Zambia and Uganda a high proportion of antibiotic resistant most likely human associated clonal lineages was observed by Schaumburg et al. (2012b). This finding points to risks of dissemination of human associated *S. aureus* among the wild ape population through reintroduction of the animals to their natural habitats. In a study reported by performed in Côte d'Ivoire, Gabon, and Democratic Republic of Congo *S. schweitzeri* was found in monkeys from all study sites (Schaumburg et al., 2015). So far, three cases of colonization of humans became known from Gabon (Ateba Ngoa et al., 2012; Okuda et al., 2016): re-investigation of isolates from colonization of humans originally described as *S. aureus* attributed them to *S. schweitzeri* (Akoua-Koffi et al., 2022). The isolates from the three cases of colonization of humans share many virulence-associated characteristics and nearly 80% of virulence-associated genes with *S. aureus* (Grossmann et al., 2021). Isolates from infections in humans might have been misidentified in the past as *S. aureus* by conventional bacteriological diagnostics. Therefore, zoonotic infections in humans in Sub-Saharan Africa cannot be excluded (Akoua-Koffi et al., 2022). However, human-associated *S. aureus* CC1, CC6 and CC15 were detected in domestic animals and nonhuman primates. This suggests a transmission from human to monkey in the wild. Re-investigation of isolates from colonization of humans originally described as *S. aureus* attributed them to *S. schweitzeri* (Akoua-Koffi et al., 2022). The occurrence of *S. schweitzeri* is essentially limited to particular Sub-Saharan African countries., *S. argenteus* was initially mainly reported from Thailand and other South East Asian countries. Meanwhile, there are also reports from other areas worldwide. *S. argenteus* was also detected in animals, such as bats in Nigeria (Olatimehin et al., 2018) and gorillas in Gabon (Schuster et al., 2017). Its virulence potential (Zhang et al., 2017) and the spectrum of infections caused by it (Thaipadungpanit et al., 2015) correspond to that of *S. aureus*. Beyond that, *S. argenteus* was also observed to be a nasal colonizer of long tailed macaques (Pumipuntu et al., 2022), and a causative agent of bovine mastitis in Thailand (Pumipuntu et al., 2017). It also resulted in infections, including skin and soft tissue infections (SSTI), in rabbits (Indrawattana et al., 2019), suggesting a broad host spectrum. These findings are in line with a report on a postoperative infection in a golden retriever dog in The Netherlands (Meijer et al., 2022). Of great interest was the detection from retail meat products and also in slaughterhouses in Japan (Wakabayashi et al., 2022). It remains to be shown whether this wide dissemination is due to spill overs from humans to animals and if there are transmissions back to humans. In the following, we will discuss host-switching in the evolution of LA-MRSA, which mainly occurred from humans to animals.

3. MRSA clonal complexes in livestock

Methicillin resistance in staphylococci is mainly based on the acquisition of *mec*-genes contained in staphylococcal cassette chromosomes (SCC*mec*), as mobile genetic elements, that are integrated in the core genome; so far, there are at least 14 types (Uehara, 2022). *Mec*--genes code for alternative penicillin-binding proteins (PBP) with low affinity to nearly all ß-lactams. Besides the most prevalent *mec*A gene, the existence of the homologues *mecB*, *mecC* and *mecD* became known (for review see Lakhundi and Zhang, 2018). More recently, alternative mechanisms have been identified, which are PBP-independent (Sommer et al., 2021).

LA-MRSA emerged in livestock almost 20 years ago. In humans they mainly appear as colonizers in humans. Infections in humans are infrequent and primarily associated with intense and permanent contact to livestock. These strains observed so far, are significantly attributed to clonal complexes CC1, CC5, CC9, CC93, CC97, CC130 with the predominant part of CC398. Isolates of CC130 and probably also CC97 most likely originate from MSSA ancestors. The switch from humans to animals was associated with adaptation to the new host (Price et al., 2012; Richardson et al., 2018; Matuszewska et al., 2020).

3.1. LA-MRSA CC398

Among LA-MRSA observed so far, LA-MRSA of the CC398 are the most widely disseminated ones. They were first observed in France among staphylococcal isolates collected from pigs between 1996 and 2002 (Armand-Lefevre et al., 2005) and only little later as nasal colonizers of farmers in The Netherlands (Voss et al., 2005). Further evidences for veal calves (Graveland et al., 2009), poultry (Nemati et al., 2008), dairy cattle (Vanderhaeghen et al., 2010), and in turkeys (Richter et al., 2012) followed. The emergence of LA-MRSA CC398 was reported from nearly all of the European countries with particular prevalence in those with substantial pig farming, such as Denmark, the Netherlands, and Germany. It was also reported from both Americas, from Asia, where it is less prevalent, and later on from Australia associated with healthy horses (review by Cuny et al., 2015c). More recently, it also emerged in New Zealand, where a particular subpopulation exists (Goncalves da Silva et al., 2017). Genome-based comparisons using data of 250 isolates deposited in data banks and additional 5 new whole genome sequences revealed that the jump of MSSA CC398 from humans to pigs took place in Europe around 1964 (Matuszewska et al., 2022). At this time, intensive pig farming had started and might have been associated with changes in the microbiome of pigs and alterations in

competitive microflora. During the past nearly 80 years, losses and reacquisitions of SCC*mec* elements have taken place. The investigation of isolates from nasal colonization of farm workers and farm visitors in North Rhine Westphalia, Germany, using core genome multilocus sequence typing (cgMLST) and BEAST analysis suggests an origin in late 1990 (Effelsberg et al., 2019). The different results could be explained by epidemiological differences in the analysed data sets, such as geographical sources of isolates and time of collection. The jump from humans to pigs and subsequent adaptation was associated by loss of the IEC, which is typical for *S. aureus* from humans, and alterations in adhesion genes (Price et al., 2012; Uhlemann et al., 2012). The acquisition of phage encoded host defence and virulence associated traits by LA-MRSA CC398 from horses was discussed above. The ancestral human-adapted MSSA population was rather associated with the human host. LA-MRSA seem to be less host-specific: isolates from cattle, poultry, and humans appear phylogenetically interspersed among pig isolates (Hansen et al., 2019; Sieber et al., 2019; Matuszewska et al., 2020). However, LA-MRSA CC398 became also prevalent in horse clinics (Cuny et al., 2016) and represent a separate subpopulation (Abdelbary et al., 2014). It remains to be seen whether further adaptation on LA-MRSA CC398 to a particular new host will lead to new host specificity. Of particular significance for public health is the re-adaptation of LA-MRSA 398 to humans. The re-acquisition of the IEC might be a first indication. In a study preformed in Germany, the IEC was observed in 16% of isolates from different kinds of infections in humans. In this study IEC was absent from all of the investigated isolates from pigs and humans in contact to them (Cuny et al., 2015a). The IEC was also detected among LA-MRSA CC398 isolates, which originated in the community and caused infections in healthcare facilities in Denmark (Sieber et al., 2019). However, the increase of the prevalence of CC398 among MRSA from infections in humans living in a German area with high density of pig farms from 1,8% in 2000 to 29,4% in 2014 was not paralleled by an increase of the proportion of isolates possessing the IEC (van Alen et al., 2018). The IEC seems to be not essential for the first steps of nasal colonization of humans with *S. aureus* but possibly for maintaining colonization (Verkaik et al., 2011). Interestingly, a study including well characterized MSSA and MRSA isolates attributed to ST398 revealed that differences in the virulence potential in the *Caenorhabditis elegans* infection model are based on the presence or absence as well on the structure of prophage φSa3, which carries IEC (Kashif et al., 2019). As shown by (Sieber et al., 2020), horizontal acquisition of IEC in the human host was associated with increased household transmission of LA-MRSA and spillover into the community and healthcare settings. There was no evidence to suggest that IEC-positive LA-MRSA isolates have become self-sustainable in the general population.

3.2. LA-MRSA CC1

It was at first reported from dairy cattle in Hungary (Juhasz-Kaszanyitzky et al., 2007). At the same time its introduction into the horse clinic of the Vienna University Veterinary School in Austria was observed (Cuny et al., 2008). Later it was mainly reported from Southern Europe such as Italy, where besides pigs also other farm animals such as cattle but also sheep were affected (Pirolo et al., 2019a). LA-MRSA CC1 was also observed in other countries and also emerged in Northern Europe such as Finland and Norway (Elstrom et al., 2019). There are only a few data on phylogeny of LA-MRSA CC1. However, for MSSA CC1 it was shown that there were at least 8 host jumps from humans to dairy cattle since 1940, which led to bovine- specific clusters (Yebra et al., 2022). Among humans, MRSA ST1 is widely disseminated as a CA-MRSA containing *luk*PV coding for Panton-Valentine leukocidine (Mediavilla et al., 2012) and also prevalent as *luk*PV-negative HA-MRSA in Europe (Grundmann et al., 2010). Phylogenetic analysis of isolates from humans revealed, that the European *luk*PV-negative MRSA CC1 represent a distinct clade and probably originated in Romania (Earls et al., 2021). LA-MRSA CC1 were not included in this set of isolates investigated. Molecular characterization of European isolates from pigs, cattle, and humans by means of *spa*-typing, pulse field gel electrophoresis and demonstration of IEC suggested relatedness and probably a human origin (Alba et al., 2015). Furthermore, (Richardson et al., 2018) have shown human ancestry for *S. aureus* CC1 from rabbits. However, phylogenetic analysis of Norwegian isolates from pig farms (pigs and workers) and from infections in humans in the community revealed no relatedness and suggests that MRSA CC1 from humans and animals represent different subpopulations (Elstrom et al., 2019).

3.3. LA-MRSA CC5

This clonal complex consists of different subpopulations, that had acquired different SCC*mec* elements and that were disseminated independently from each other (Nubel et al., 2008). In Northern America, in particular in the USA, clonal spread of MRSA ST5, *spa*-type t002 and SCC*mec* II (the so called USA100 clone), is widely disseminated in health care settings, but was also reported from infections in the community (Limbago et al., 2009). Therefore, the emergence of MRSA attributed to ST5 in conventionally raised pigs attracted attention (Frana et al., 2013). However, genomic comparisons revealed that LA-MRSA ST5 represent a rather uniform subpopulation, that is different from MRSA "USA100" (Hau et al., 2018b). As opposed to MRSA "USA100", LA-MRSA ST5 contain SCC*mec* types IV or III. LA-MRSA ST5 from pigs and humans with contact to them, were also found to be negative for the IEC in contrast to isolates from humans with no relation to pig farming (Hau et al., 2015). As has been described for other LA-MRSA, LA-MRSA CC5 also colonize humans in contact with pig farming (Hau et al., 2015). Its capacity for adherence to human keratinocytes corresponds to that of MRSA ST5 of human origin (Hau et al., 2018a).

3.4. LA-MRSA CC9

It is particularly prevalent in China and countries in Southern Asia and more infrequent in Europe and Northern America (Chuang and Huang, 2015). There is strong evidence from phylogenetic analysis (Yu et al., 2021), that it evolved from human associated MSSA ST9 and adapted to the animal host by loss of the IEC and acquisition of a SaPIbov4-like element-encoding *vwb* gene, which is an animal-specific virulence factor responsible for the clotting of animal plasma. Furthermore, LA-MRSA ST9 from China and from Taiwan has acquired a multidrug resistance genetic element (MDR ST9), which is integrated in the chromosome and contains genes conferring resistance to ß-lactams (*bla*Z), and genes which are typically associated with staphylococci of livestock origin and conferring resistance to aminoglycosides [*aac*(6`)-Ie/*aph*(2`)-Ia], tetracyclines [*tet*(L)], and lincosamides [*lnu*(B), and *lsa*E)]. The jump to the animal host is estimated to have taken place at the beginning of the last century, the acquisition of the SaPIbov4-like element which is typically contained by the largest subpopulation dates back to the mid 1980ties (Yu et al., 2021). The latter is consistent with findings reported by (Jiang et al., 2021). LA-MRSA ST9 humans emerged also in contact with pig farming and also to cattle (Fang et al., 2014).

3.5. LA-MRSA ST93

It was reported from pigs in Australia 6 years ago (Sahibzada et al., 2017). Phylogenomic analysis suggests that it originated from highly virulent community-associated MRSA ST93, which is widely disseminated at this continent (Coombs et al., 2022b). The host jump was associated with loss of *luk*PV and of the IEC in the majority of pig isolates (Sahibzada et al., 2017).

3.6. MRSA CC97

As described above, CC97 in humans originated from a bovine to

human host jump. MSSA CC97 is still prevalent as a causative agent of bovine mastitis in Europe, Asia, and the Americas and has less commonly also been observed in small ruminants and pigs (Smith et al., 2005; Smyth et al., 2009). MSSA CC97 is also prevalent as a colonizer of healthy humans (Holtfreter et al., 2016). Furthermore, it is widely disseminated among humans in Australia as a *luk*PV-negative CA-MRSA (Coombs et al., 2022b), and was also reported from an outbreak in a Danish hospital (Rubin et al., 2018). Sporadic cases of infections are known from many countries (Spoor et al., 2013). The human subpopulation of MSSA CC97 acquired the IEC and SCC*mec* IV later after the host jump, when establishing in the human host (Spoor et al., 2013). The occasional detection of MRSA CC97 in ruminants (Feltrin et al., 2016) is most likely due to spillover events from humans (Yebra et al., 2022).

3.7. MRSA CC130

This MRSA is not originally associated with livestock and evolved independent of human activities, although the first isolate described was obtained from dairy cattle and humans in Denmark (Garcia-Alvarez et al., 2011). MRSA CC130 contains the *mec*-homologue *mec*C, carried by an SCC*mec* element of type XI. A little later it was reported for MRSA isolates from a diverse range of host species (Paterson et al., 2012) such as cattle, sheep, goat, red deer, roe, hare, wild boar, and birds. Hedgehog surveys from Denmark and Sweden demonstrated a surprisingly high prevalence of MRSA carrying *mec*C (Rasmussen et al., 2019) and suggested that the evolution of these MRSA was driven forward by natural selection in wildlife. Already 40 years ago it was observed that *S. aureus* from skin lesions of hedgehogs are frequently resistant to penicillin (Smith and Marples, 1965). Hedgehogs often suffer from infection of skin with *T. erinacei*. Results from in vitro experiments indicate that *mec*C contributes to the reduced susceptibility of *mec*C-MRSA to ß-lactam antibiotics present in culture broth of *T. erinaceid.* This fungus produces two β-lactams, penicillin G and 6-(5-hydroxy-n-valeramido)-penicillanic acid (Larsen et al., 2022). Phylogenetic analysis of *S. aureus* carrying *mec*C and attributed to CC130, CC425 and CC1943 suggests that the first emergence of *mec*C containing MRSA predates the introduction of benzylpenicillin into the human chemotherapy. MRSA CC1943 is probably circulating since about 200 years (Larsen et al., 2022). Most likely hedgehogs are the main reservoir from which transmission to other animals, preferentially ruminants, started.

4. MRSA in animals and humans in animal husbandry

4.1. Prevalence and epidemiology of LA-MRSA in livestock

In Europe, LA-MRSA is widely disseminated in intensive farming systems, in particular in the Netherlands, Denmark, Germany, France, Italy and Hungary (for summary see European Food Safety Agengy and European Centre for Disease Prevention and Control (2009)). It is also reported from both Americas, Northern Africa, Asia, and Australia (for review see (Cuny et al., 2015c). Initially, LA-MRSA were observed in pigs, later in veal calves and poultry, followed by dairy cattle and turkeys (Cuny et al., 2015c). In the Northwestern area of Germany about 70% of conventional pig farms were positive for LA-MRSA CC398 (Kock et al., 2009). In the Netherlands this was the case for about 60% (Broens et al., 2011). The resistance monitoring programme of the European Union revealed that in countries voluntarily participating in this survey detection rates for MRSA in pigs were still high in 2019 and 2020 with the exception of Norway (European Food Safety Agengy and European Centre for Disease Prevention and Control (2023)). Among the different populations studied at pig farms were multiplier herds in Denmark in 2019 (94.5% [69/73]) positive), herds of fattening pigs in the Netherlands 2020 (79.0% [49/62]) and Belgium 2019 (58.3% [105/180]), and herds of breeding pigs in Belgium in 2019 (46.4% [83/179]). In Germany a lower prevalence of LA-MRSA positive herds of fattening pigs was observed (35.7% [139/389]). In contrast, in Norway MRSA was only detected in 0.14% [1/722] of pig herds in 2019, and 0% [0/641] in 2020.

Infections in farm animals mainly occur as soft tissue infections, mastitis and necrotizing dermatitis, but were rare so fare. However, there is concern about the zoonotic potential. The main route of transmission between farms is above all driven by trade of animals, was shown for weaned piglets that are provided by specialized producers (Broens et al., 2011; Sieber et al., 2018; Pirolo et al., 2020). Theoretically, sanitation of the breeding lines should solve the problem. In Norway, where intensive farming represents a small sector, spread of LA-MRSA CC1 was at the very beginning and its eradication was achieved by practicing a complex eradication approach. The first step was banning of trade of live pigs, other than directly to slaughter, followed by depopulation through slaughter or culling of MRSA positive pig herds. The final step was thorough cleaning and disinfection of farm premises (Elstrom et al., 2019). In the Netherlands the government launched a policy to restrict antimicrobial usage in industrial farming in 2010, that resulted in a substantial reduction of antibiotic use in food-producing animals (SDa-report, 2015), but did not have an effect on the MRSA carriage rate of pigs entering the slaughterhouse five years later (Dierikx et al., 2016). Zinc oxide is widely used as feed additive for prevention of diarrhoea, in particular in weaning piglets. The majority of LA-MRSA CC398 from pigs contains the *czr*C- gene, which confers resistance to zinc and to cadmium, and is integrated into the SCC*mec*-V element (Cavaco et al., 2010). Use of zinc in pigs co-selects for LA-MRSA CC398 (Slifierz et al., 2015). Because of detrimental environmental effects such as accumulation of zinc in manured soil (Asada et al., 2010), the use of zinc in livestock was banned by the European Commission in 2022 (European Medicines Agency, 2017). It remains to be seen, whether this ban will result in a reduced prevalence of LA-MRSA CC398 in pigs.

The prevalence of LA-MRSA in pig farms is obviously influenced by animal keeping conditions. A study performed in Germany (Cuny et al., 2012) has shown, that MRSA were not detected in pigs raised in an alternative system ("organic farming": stronger indications for antibiotic use, straw bedding, own reproduction). A much lower prevalence of LA-MRSA in pigs raised in these "organic farms" was also reported from the United States of America (Smith et al., 2013) and from the Netherlands (van de Vijver et al., 2014). Interestingly, a pilot study in Germany indicates that keeping pigs on straw and simple cleaning can lead to decolonization during the fattening period (Schollenbruch et al., 2021). Furthermore, an influence of keeping of fattening pigs on straw on the nasal microbiome of the animals was shown (Effelsberg et al., 2023). Very likely epiphytic microorganisms contained in straw have a strong influence on the nasal microbiome of pigs and a protective effect with respect to colonization with LA-MRSA.

4.2. LA-MRSA colonization of humans exposed to livestock

Remark: most of the data discussed below originate from cross sectional studies on detection of nasal colonization and therefore record both, permanent and intermittent colonization (den Heijer et al., 2013; Sakr et al., 2018). Nasal colonization of humans working in MRSA-positive stables is common and has initially been reported from The Netherlands and from Germany, where 77–86% revealed as colonized with LA-MRSA CC398 (Cuny et al., 2009; Van Den Broek et al., 2009). Lower prevalence of nasal carriage (20%−45%) was observed in Italy (Pirolo et al., 2019b) and in Northern America (Khanna et al., 2008; Smith et al., 2009; Hau et al., 2015; Nadimpalli et al., 2016). The extension of colonization seems to be dependent upon the duration of exposure and upon the intensity of animal contacts (Graveland et al., 2011). Transmission of *S. aureus* between hosts is primarily mediated by physical contact. Dust in stables with MRSA-colonized pigs is heavily contaminated (Masclaux et al., 2013, Madsen et al., 2018). Therefore, it seems likely that colonization of humans working in these areas takes place by inhalation of MRSA-contaminated dust (Bos et al., 2016). Also

touching surfaces at which dust has sedimented followed by touching the face, might be a possible route, too. According to studies performed in Germany (Friese et al., 2013) and in Demark (Madsen et al., 2018), the concentrations of viable, inhalable, airborne MRSA on pig farms are high (803 cfu/m^3 and 447 cfu/m^3 air respectively). It was calculated that if a farmer with no respiratory protection inhales 1.1 m^3 air/h and works for 4 h in the stable under these conditions, 870 cfu of S. aureus may potentially deposit in the airways (Madsen et al., 2018). A study performed in Denmark on short term visitors of pig farms suggests that acquisition of these MRSA strains in LA-MRSA positive stables is most probably associated with inhalation of MRSA loaded dust particles rather than with touching contaminated surfaces and direct physical transfer between the hands and the face (Angen et al., 2017). It was also shown that 94% of volunteers with no respiratory protection were MRSA-positive after 1 h of occupancy in an MRSA-positive stable and 59% still carried MRSA 1 h after leaving the stable, after 48 h LA-MRSA was no more detectable, which corresponds to a former report from the Netherlands (van Cleef et al., 2011). These data show that inhalation of dust in pig farms for a short time can already lead to preliminary acquisition of MRSA bound to dust. Real short time colonization with regard to adhesion to keratinocytes seems less likely. A study on pig truck drivers in Denmark over a workweek has shown that most of them were negative for LA-MRSA CC398 and became increasingly positive during the workday, acquisition of MRSA was associated with dynamic and drastic changes of the nasal microbiome (Ingham et al., 2021). It is questionable whether the microbiome detected in the drivers nose when MRSA positive not simply represent the microbiome of the dust particles. A previously performed study in Switzerland revealed that the microbiomes detected in samples from pigs, air, and pig farmers form distinct, but related clusters, which are all clearly separated from samples from cow farmers and office workers (Kraemer et al., 2018).

In pig farm workers acquisition of LA-MRSA prolongs for longer times. It seems to be associated with changes in the nasal microbiome and to be sufficient for former transmission to household contacts (Islam et al., 2020). Furthermore, LA-MRSA was still detected in 53% pig farm workers after holidays (Kock et al., 2012). Nasal colonization of workers with contact to living pigs in slaughter houses is also quite frequent (Van Cleef et al., 2010). Other people residing on swine farms (e.g., household members) were less frequently colonized with 4–5% (Cuny et al., 2009; van Cleef et al., 2015). Detection of LA-MRSA CC9 in nasal swabs from household members of swine farmers was reported from the USA (Randad et al., 2021). As intrafamilial transmission of *S. aureus* is common (Sakr et al., 2018), on the first look this seems also to apply to LA-MRSA and household members of pig farmers. Furthermore, it is discussed that household members might acquire LA-MRSA by the dust from stables. However, LA-MRSA was not only obtained from nasal swabs of veterinarians attending pig farm, but also from persons living in households of them (Cuny et al., 2009; Verkade et al., 2014); which suggests intrahousehold human-to-human transmission. We know that intrafamilial transmission of *S. aureus* is common (Sakr et al., 2018). Acquisition of MRSA by occupational exposure in pig stables can be prevented by respiratory protection (dust-masks) (Nadimpalli et al., 2018; Angen et al., 2018). As to be expected, LA-MRSA CC398 disseminated among dairy cattle also spreads to the environment of farms affected and is also detected in nasal swabs of farm workers (Schnitt et al., 2020). Phylogenetic analysis revealed close relatedness of isolates from cattle, environment and humans (Lienen et al., 2021). A study performed in Poland reported further transmission to household members of the cattle farmers (Krukowski et al., 2020). As similar situation was reported for broiler, duck and turkey farms affected by MRSA CC398, where 65 - 67% of the farm workers were found to be colonized (Wendlandt et al., 2013; Geenen et al., 2013, van Duijkeren et al., 2016).

4.3. Dissemination of LA-MRSA beyond farms

The observation of cases of infections with LA-MRSA in humans, who themselves as well as their household member, have no direct contact to livestock farming, was reported from Germany (Deiters et al., 2015), the Netherlands (Lekkerkerk et al., 2012; van Rijen et al., 2014) and Denmark (Larsen et al., 2015). A recent study in the Netherlands has shown that LA-MRSA CC398 isolates originating from a few intra-household transmissions among humans without relations to farming did not represent a separate lineage with better transferability among humans (Konstantinovski et al., 2022). In Denmark increasing frequencies of cases of household transmission of LA-MRSA and emergence in the community and in healthcare settings were observed (Sieber et al., 2020). Different from the situation in Europe, there was no dissemination of LA-MRSA among humans beyond farms in China. The LA-MRSA observed in China are evolutionary unrelated to those disseminated in Europe and the Americas (Zou et al., 2022).

In Europe three routes of transmission to humans beyond farms must be taken into consideration: acquisition by dust loaded with LA-MRSA and emitted from stables, handling of food that is contaminated with LA-MRSA and human-to-human contacts in the community.

4.3.1. Spread of LA-MRSA from farms to the environment

Emission of LA-MRSA in exhausted air from conventional farms has been shown by several studies, and LA-MRSA has been found in air up to 350 m downwind from stables and up to 500 m distant on the soil surface (Schulz et al., 2012; Friese et al., 2013; Angen et al., 2021). For acquisition of LA-MRSA by humans, besides inhalation of dust, also contact with contaminated surfaces (e.g., grass, soil) has to be taken into consideration, as a die-off rate of LA-MRSA bound to sampled dust from pig farms of 66 days was observed (Feld et al., 2018). There is, of course, a dynamic of MRSA sediments in the environment due to continued sedimentation and reduction by environmental influences (e.g., sunlight). Further transmission of LA-MRSA from farms and their environments may also be mediated by flies and rats (see above). For humans living in pig- and poultry-dense areas in Germany a cross sectional survey reported 1% nasal carriers of LA-MRSA CC398 (Bisdorff et al., 2012). This was higher than reported by studies from the general population 0025% (Holtfreter et al., 2016). However, the difference in MRSA prevalence between humans living closer (< 500 m) to a farm and those living more distantly (>500 m) was not significant. Regular visits to farms and to farm shops revealed as risk factors (Bisdorff et al., 2012). A nation-wide survey in Denmark reported a higher incidence of LA-MRSA CC398 infections of unknown origin (patients without direct or indirect livestock contact) in rural than in urban areas. However, within three pig-farming-dense municipalities, these patients did not live closer to pig farms than population controls (Anker et al., 2018). The results from both surveys indicate that direct environmental spread of LA-MRSA CC398 from neighbouring pig farms seems to be unlikely. Results from an extensive epidemiological study in Pennsylvania, USA, where skin and soft tissue infections with MRSA were found more frequently in humans living close to fields that were fertilized with manure from conventional farms, have been interpreted to mean that these people acquired LA-MRSA by dust from these fields (Casey et al., 2013). However, this conclusion was not confirmed by results from typing of a sufficient number of MRSA isolates both of animal (manure) and human origin. A more recently performed study in Denmark (Astrup et al., 2021) reported, that LA-MRSA was not found in all manure samples investigated, despite that all farms were LA-MRSA-positive among pigs. Furthermore, it was observed that LA-MRSA was detected in some soil samples before the spreading of manure on some locations, and not after spreading of manure on other locations. This suggests that manure is probably not a major source of LA-MRSA in the environment and consequently not an important source for human exposure. Nevertheless, liquid manure must be considered a source of contamination of the environment with LA-MRSA CC398. This clonal complex was also detected in nasal swabs from wild boars (killed while hunting) in North Western Germany (Meemken et al., 2013), in Portugal (Sousa et al., 2017) and in Spain (Mama et al., 2019). Rather likely it was acquired by

the animals when rooting around in the fields. Interestingly, no LA-MRSA were detected in wild boars from the large forest in the outskirts of Berlin (Cuny et al., 2012). Furthermore, LA-MRSA CC398 was also observed in migratory and resident populations of rooks in Austria (Loncaric et al., 2013). The detection of LA-MRSA CC398 in manure as well as in soil leads to the question of whether it has also been detected in surface water. This was reported from Spain (Porrero et al., 2016). In another study in Spain the occurrence of MRSA ST425 containing *mecC* in river water was shown, which might have been of either livestock or wildlife origin (Concepcion Porrero et al., 2014). For HA-MRSA of hospital origin occurrence in river water was recently reported from Japan (Azuma et al., 2022). There is also a report on detection of LA-MRSA CC398 in waste water from an urban waste water treatment plant (Gomez et al., 2016a).

4.3.2. Acquisition of LA-MRSA by humans via handling meat and meat products

Raw meat products can be contaminated with LA-MRSA during processing. In the Netherlands, MRSA contamination was found for 10.7% of pork, 15.2% of beef, 15.2% of veal, 6.2% of lamb, and 35.3% of turkey meat (de Boer et al., 2009). In Germany, contamination was detected in 2.8% of pork products (Beneke et al., 2011), 33% of broiler chicken carcasses (Cuny et al., 2011) and in 32% of turkey meat samples (Vossenkuhl et al., 2014). Similar contamination frequencies were reported from the Northern Americas (Pu et al., 2009; Weese et al., 2010), as well as from Taiwan (Lin et al., 2009). Involvement of MSSA/MRSA CC398 in food intoxication has not been reported to date, and isolates attributed to this clonal complex only rarely seem to contain enterotoxin genes (Kadlec et al., 2009; Argudin et al., 2011). If LA-MRSA would be acquired by handling contaminated meat and/or raw meat products, professional cooks, butchers and meat sellers should be the ones most likely to be affected by LA-MRSA colonization. First, this question was addressed by two studies in Hong Kong. MRSA colonization was identified in 1.15% of food handlers working in commercial kitchens in Hong Kong; however, results from *spa*-typing attributed the isolates to HA-MRSA ST45 for which livestock association has not been described (Ho et al., 2014). In the same city, 5.6% of butchers investigated were colonized, of which 3% of them carried LA-MRSA ST9, which indicates pig origin (Boost et al., 2013). Nasal MRSA colonization was not detected in a small pilot study in the Netherlands involving 95 professional meat handlers (de Jonge et al., 2010). In contrast, a high prevalence of MRSA (51%) from nasal swabs of food handlers was reported from a city in Nigeria (Nnachi, 2014). However, the situation there may be not comparable to that in European countries. In a more extensive study in Germany 286 butchers and meat sellers in 26 butcheries and 319 cooks handling meat in 16 professional canteen kitchens were sampled for nasal colonization with MSSA and MRSA (Cuny et al., 2019). MRSA was detected in two persons (0,33%), the isolates were attributed to HA-MRSA ST22, which represents the most prevalent clonal lineage of HA-MRSA in Germany at that time (Layer et al., 2015). The MRSA prevalence was even lower than that observed for human carriers in Northern Germany (0,12%) at nearly the same time (Mehraj et al., 2014). However, the detection of MSSA ST7 not containing the IEC in three persons suggested, that acquisition of *S. aureus* by handling meat may be possible. The findings from this study suggest that the risk of LA-MRSA colonization from handling meat seems to be very low for professionals working in canteen kitchens and butcheries. We can, however, not exclude this route of acquisition.

A study from Denmark reported the emergence of an unusual genotype of MRSA CC398/CC9, which colonized and infected 10 humans living in urban residences. For all but one of them there was no association with livestock farming. Two persons worked in a mink farm. This genotype exhibiting *spa* type t899 represents a hybrid genotype that consists of a CC398 core genome and a smaller region from CC9, which contains the staphylococcal protein A (*spa*) gene (Price et al., 2012). It is observed sporadically in humans and also in livestock pigs, cattle, poultry, and retail foods in European countries, including France, Germany, Italy, Netherlands, and Spain. MRSA with this genotype had not been observed in livestock in Denmark but frequently detected as contaminants of imported turkey meat. The assumption that at least in seven of the urban cases it was acquired by handling imported turkey meat was backed by whole genome phylogenetic analysis including isolates from turkey (Larsen et al., 2016).

4.4. Infections with LA-MRSA CC398 in humans

According to the manifold clinical pictures of infections caused LA-MRSA CC398, it seems to possess the same virulence potential as *S. aureus* from humans in general (Ballhausen et al., 2017). Outside of the hospital setting infections of skin and soft tissue that require surgical interventions predominate (Goerge et al., 2017). In the case of infections that require antibiotic treatment, the current antibiotic resistance profile of LA-MRSA leaves sufficient alternatives. Usually LA-MRSA is resistant to β-lactams, macrolides, lincosamides, streptogramins, tetracyclines, and in part to fluoroquinolones as well as to cotrimoxazole. It is susceptible to glycopeptides, daptomycin, tigecycline, rifampicin, fusidic acid, fosfomycin, and with few exceptions also to linezolid (see below). Affected patients are primarily persons with occupational exposure to livestock and those with occasional contact with livestock. LA-MRSA represents a considerable proportion of MRSA-linked severe skin and soft tissue infections (Goerge et al., 2017). Although the incidence of these infections in Germany is not known, they seem to occur rarely. LA-MRSA can enter hospitals either via patients who suffer from infections caused by these bacteria and who need appropriate treatment or by patients with nasal colonization. The latter can lead to nosocomial infections such as surgical site infections, infections after joint arthroplasty, ventilator associated pneumonia, or septicaemia (Witte et al., 2007; van Cleef et al., 2011; Becker et al., 2017). A survey on MRSA colonization at hospital admission in the south of Brandenburg federal state of Germany, an area with a low density of livestock farms, reported colonization with LA-MRSA CC398 in 0.08% among the 13,855 investigated individuals (Juretzek et al., 2011). In the Ems-Dollart area of North Rhine Westphalia federal state, which has a substantial density of livestock farms, the proportion of LA-MRSA CC398 among all MRSA detected by screening at hospital admission (altogether 1.6% of all individuals) increased from 14% in 2008 to 23% in 2011. Correspondingly the proportion of LA-MRSA among MRSA from wound infections increased from 7% to 10% during the same period of time (Kock et al., 2013). The proportion of LA-MRSA among MRSA from septicaemia in this area amounted to 10% (Kock et al., 2013; Cuny et al., 2015b), whereas it is substantially lower (1.8%) in all North Rhine Westphalia (Kock et al., 2013). The proportion of LA-MRSA CC398 among all MRSA sent in for typing to the German National Reference Centre for Staphylococci and Enterococci in 2021 was 6% and did not substantially change during the past decade (Layer et al., 2021). However, due to inclusion criteria (all MRSA isolates from a particular area vs. a sample of MRSA isolates selected by different criteria and representing 3% of MRSA isolates from Germany) these frequencies are not directly comparable to those from North Rhine Westphalia.

In the Netherlands, a country with low MRSA incidence, the reported number of MRSA CC398 strains from humans (from screening and from clinical cases) has been around 40% of all MRSA strains reported to the Dutch MRSA surveillance since 2008 (Lekkerkerk et al., 2015). In Denmark, another country with low MRSA incidence, the number of human infections with LA-MRSA increased from 2008 to 2014, where LA-MRSA CC398 accounted for 16% of the isolates from blood cultures and 21% from SSTI of all MRSA (Sieber et al., 2018). In both countries all MRSA isolates derived from clinical bacteriology are subjected to typing. As well in Spain, the prevalence of the zoonotic CC398 in hospitals was reported closely related to pig-farming density (Ceballos et al., 2019). According to a survey of the European Center for Disease Control (ECDC), LA-MRSA represented 3.9% of 13,756 typed MRSA

human isolates in all Europe, but it represented ≥ 10% in five countries (Belgium, Denmark, Spain, the Netherlands and Slovenia). For further monitoring the spread of LA-MRSA and for facilitating targeted control measures, ECDC advocates periodic systematic surveys or integrated multi-sectorial surveillance (Kinross et al., 2017).

In epidemiological investigations it may be necessary to discriminate LA-MRSA CC398 associated with deep seated SSTI from *luk*PV-positive CA-MRSA which are prevalent in China (Zhao et al., 2012) and evolved from the human adapted subpopulation of CC398. The core genomes of both subpopulations of CC398, the human one and the animal adapted one, differ by canonical SNP`s which allow discrimination (Price et al., 2012). Discrimination by either PCR based assays (Stegger et al., 2013; Cuny et al., 2015a) or by whole genome sequencing based analysis revealed that *luk*PV-positive MRSA CC398 observed in Denmark (Moller et al., 2019) and in Australia (Coombs et al., 2022a) corresponded to the human-adapted subpopulation. It would have been of interest to know whether this also applies to l*uk*PV-positive MRSA CC398 recently reported from the Netherlands (Schouls et al., 2023). Screening prior or after admission of MRSA carriage followed by rapid bacteriological diagnostics and decolonization revealed an effective prevention of MRSA infections of previous MRSA carriers and of intrahospital dissemination (Larsen et al., 2014).

In Denmark, Germany and Netherlands guidelines for prevention of nosocomial infections recommend targeted screening of humans with occupational exposure to livestock. Although LA-MRSA are less transmitted in hospitals than other MRSA (Hetem et al., 2013; van de Sande-Bruinsma et al., 2015), these recommendations should be retained. The consequences of MRSA carriage are especially severe in intensive care units with respect bloodstream infections and ventilator-associated pneumonia, in bone and joint surgery as well as in heart surgery.

4.5. Introduction of MRSA of human origin into farms

The emergence of MRSA attributed to lineage ST239 in a Belgian pig farm was reported (Peeters et al., 2015). MRSA ST239 exhibits a broad multiple resistance phenotype, it is world-wide disseminated, and particularly prevalent in the Near East Asia (Abd El-Hamid et al., 2022). Mairi et al. (2019) observed CA-MRSA ST80 in Algeria not only in humans but also in livestock. CA-MRSA ST80 is especially prevalent in Europe (Mairi et al., 2020).

5. Staphylococci in companion animals and in humans, which are in contact with them

5.1. S. aureus

Companion animals are often regarded as a probable reservoir for antibiotic resistant microorganisms, in particular MRSA (Khairullah et al., 2023). However, from the one health perspective, we have to look in both directions. The first question deals with mutual transfer of *S. aureus*. Nasal colonization of dogs has been reported. It is, however, considerably less frequent than in humans (Kaspar et al., 2018). The question, if this colonization is associated with *S. aureus* carriage by human contact, was addressed by studies in Korea (Han et al., 2016), Hong Kong (Boost et al., 2008), and the United States (JC et al., 2017); which resulted in different findings with respect to the frequencies of concomitant colonization of dogs and owners. This could be due to the study design in connection with concomitant sampling of humans and dogs, and to not sampling all household members and finally, to the limited number of participants. Transmission of MRSA from colonized or infected humans to dogs and vice versa living in the same household was observed in North America (Morris et al., 2012); (Bender et al., 2012). A recent study in Germany (Cuny et al., 2022), which included dogs and humans (112 and 179 respectively) living in 84 households, revealed that 8.9% of the dogs and 36.9% of the humans were colonized with *S. aureus*. Colonization of dogs was only observed in families, in which also humans were colonized. Isolates from dogs and humans residing in one and the same family were attributed to the same clonal complex. Typing by means of *spa*-typing and whole-genome sequencing (WGS) indicated 8 transmissions of *S. aureus* between humans and dogs in 8 of 42 (19.0%) households. MRSA, attributed to sequence type ST22 and ST130, were detected in two (1.1%) humans but in none of the dogs. The observation that there were no households with colonized dogs but colonized humans suggests, that humans are the primary source for colonization with MRSA of dogs. Interestingly, in one human in one household previous carriage of *S. aureus* attributed to CC15 was replaced by *S. aureus* CC45 when a second new dog was acquired that also carried *S. aureus* CC45. To what extend *S. aureus* colonization of dogs can be permanent or is intermittent should be investigated in longitudinal studies. The absence of MRSA carriage from healthy dogs in the community observed by (Cuny et al., 2022) corresponds to the data from cross sectional studies in other countries such as Denmark (Bagcigil et al., 2007) and Canada (Hanselman et al., 2008). It may be different when either dogs or humans are still positive for MRSA after hospital discharge. However, in a recent study performed in Spain a multi-resistant MRSA CC5 also exhibiting resistance to linezolid (not based on *cfr*, but on mutations in the 23 SrRNA) was detected in both humans and a dog in one of the families investigated (Abdullahi et al., 2023). An introduction of epidemic HA-MRSA into hospitals for small animals happened several times. A more detailed molecular characterization of MRSA from humans and dogs suggested that there were no canine-associated clones among MRSA and indicated a spill over of HA-MRSA into veterinary hospitals (Vincze et al., 2013). This particularly applies to HA-MRSA attributed to clonal complexes CC22 (ST22) and CC8 (ST8, ST254) which were the most prevalent ones in a Berlin veterinary hospital (Vincze et al., 2013). HA-MRSA ST22 is most prevalent in human hospitals in Central Europe and also worldwide disseminated as evident from a whole genome sequencing based population analysis (Holden et al., 2013). The phylogenetic analysis of isolates from humans, dogs and cats demonstrated that a shared population of HA-MRSA ST22 can infect both humans and companion animals without undergoing host adaptation (Harrison et al., 2014). MRSA ST254 was particularly prevalent in the North West of Germany during the 1990ties (Witte et al., 2008). MRSA attributed to CC8 were also reported from veterinary hospitals in the UK, Ireland (Moodley et al., 2006) and Northern America (Weese and van Duijkeren, 2010). LA-MRSA CC398 represented a minor proportion of isolates from a German small animal veterinary hospital (Vincze et al., 2014). In veterinary clinics in China, MRSA prevalent in human hospitals (ST59, ST239) were also isolated from infections in pets and from nasal swabs of veterinary staff (Zhang et al., 2011). Thus, there may be a risk of transmission of MRSA to humans if small animals come home after discharge from a veterinary hospital at which MRSA are prevalent (Loeffler and Lloyd, 2010). However, loss of MRSA colonization of dogs was observed already one week after discharge.

5.2. S. pseudintermedius and S. epidermidis

Different from *S. aureus*, *S. pseudintermedius* is the major CoPS species that colonizes dogs and cats, and also the most prevalent causative agent of canine bacterial infections (Bannoehr and Guardabassi, 2012). Methicillin-resistant *S. pseudintermedius* (MRSP) is usually pan-resistant against antibiotics and has globally emerged as a nosocomial pathogen in hospitals for small animals (Pires Dos Santos et al., 2016). Although still infrequent so far, *S. pseudintermedius* was also isolated from infections in humans after dog bites, as well as from other kinds of infections, including septicemia (Borjesson et al., 2015; Somayaji et al., 2016). There are a few studies on human nasal colonization with *S. pseudintermedius* in dog-owning households performed in Korea (Han et al., 2016), Portugal (Rodrigues et al., 2018; Abdullahi et al., 2023) and Germany (Cuny et al., 2022). A prevalence of 0,6 – 4.5% was

reported for humans and 25 – 65.9% for dogs, respectively. Transmission to humans as confirmed by WGS - based typing was obviously rare (in one of the 84 households in the study in Germany and one of the 27 households in the second study performed in Portugal). However, in a recent study performed in Norway transmission of MRSP from infected dogs to humans was observed in two of eight dog owners (Roken et al., 2022). It seems that *S. pseudintermedius* is not a regular colonizer of humans. However, adaptation to humans may occur. A recent pilot study has shown diversity between the isolates attributed to the same clonal lineage from infections in humans and in dogs with respect to pathogenicity islands and virulence gene containing prophages (Phumthanakorn et al., 2021). MRSP were not detected among dogs investigated in Germany and in Portugal. This indicates that MRSP are rarely disseminated outside veterinary hospitals. MRSP were detected as colonizer in small animal veterinarians (Paul et al., 2011), although they seemed infrequent. Veterinarians should be aware of this zoonotic risk and proper preventative measures should be taken to avoid MRSP acquisition from animal patients.

Methicillin resistant *S. epidermidis* (MRSE) attributed to ST2 and ST5 possess a particular virulence potential (biofilm production, adherence properties) and are the major cause of catheter-associated bloodstream infections in human hospitals (Becker et al., 2014). Methicillin susceptible *S. epidermidis* (MSSE) ST2 and ST5 were also isolated from infections in dogs and cats treated in a University veterinary hospital (Kern and Perreten, 2013). The detection of colonization of dogs living in households in Spain with MSSE ST5 (Gomez-Sanz et al., 2019) needs attention. It will be of interest to explore whether colonization of dogs with MSSE ST5 may contribute to nosocomial infections in dog owners and vice versa.

5.3. Carriage of S. aureus and S. pseudintermedius by dogs engaged in animal assisted intervention

Dogs engaged in animal assisted intervention in hospitals and stationary care and which are colonized with S. aureus and *S. pseudintermedius* need to be considered as potential transmission vectors. Acquisition of MRSA carriage by a therapy dog has been reported (Enoch et al., 2005). There is, however, consensus that the benefits of AAI outweigh the risks with respect to the transmission of pathogens, in particular MRSA (Bert et al., 2016). A current study in a paediatric hospital in the USA has shown sharing of microbiota between dogs and children and the effectiveness of a decolonization procedure on dogs in case of MRSA carriage (Dalton et al., 2021). The recent study on *S. aureus* colonization of dogs in Germany (Cuny et al., 2022) included a separate cohort comprising 59 dogs active in AAI and their 60 handlers. MRSA were absent, MRSP was detected in one of the dog handlers, not in the dogs. Guidelines for therapy animal organizations, facilities, and therapy animal handlers providing AAI in healthcare facilities were developed in several countries (Murthy et al., 2015; Deutsche Gesellschaft für Krankenhaushygiene, 2017). Given the transferability of MRSA between humans and dogs in cases where screening of dogs is required (e.g., for outbreak investigations), their handlers should also be screened.

6. MRSA in horses and in humans in contact with them

6.1. MRSA in horses and veterinary personnel in horse clinics

Looking at the emergence of MRSA in horses is important, as an increasing number of horses are kept as pets and for sports. Thus, there are about 1,2 million horses in Germany and roughly 30,000 riding accidents are recorded per year. In horse clinics, MRSA mainly causes surgical site infections in surgery and orthopaedics. Nasal colonization seems not to precede infections, direct transmission to surgical sites in connection with insufficient hygiene is more likely (Gehlen et al., 2023). An outbreak of MRSA infections in horses in a veterinary hospital was at first reported from the United States in 1999 (Seguin et al., 1999), followed by reports on clusters of MRSA infections in equine hospitals in Canada (Weese, 2004) and a few years later in Central Europe (Friedrich et al., 2004; Cuny et al., 2008). The majority of the Canadian MRSA isolates from horses and staff, has typically been identified as Canadian epidemic MRSA-5, equivalent to "USA500", which accounted for nearly 10% of MRSA in Canadian hospitals by the end of the 1990 (Simor et al., 2001). It exhibited MLST ST8 (CC8), *spa*-type t064 and contained SCC*mec*IV. An introduction from human hospitals into the veterinary sector was very likely. There were two reports on infections in humans originating from contact with horses (Weese et al., 2005; Weese et al., 2006b). Furthermore, a cluster of skin and soft tissue infections in humans working in a Canadian horse clinic was observed (Weese et al., 2006a). This strain type was later on also reported for MRSA isolates from horses from Ireland (O'Mahony et al., 2005), from the Netherlands (van Duijkeren et al., 2010) and from Germany (Walther et al., 2009) suggesting international dissemination. At this time the Central European MRSA isolates from nosocomial infections in horses were attributed to ST254 (CC8), exhibiting *spa*-type t036, and containing SCC*mec*IVh (Friedrich et al., 2004; Cuny et al., 2008). These characteristics were typical for epidemic HA-MRSA ST254 isolates which at that time were prevalent in human hospitals in the North West of Germany (Witte et al., 2008). Furthermore, strong relatedness was shown by a more detailed analysis with respect to antibiotic resistance and virulence associated genes (Walther et al., 2009). As already observed in Northern America, an introduction of a prevalent HA-MRSA into veterinary hospitals was likely. Later MRSA ST254 was replaced by LA-MRSA CC398, which represents a separate subpopulation (Abdelbary et al., 2014). Its first emergence in an equine clinic was observed in Vienna in 2005, into which it was introduced by a colonized internship veterinarian (Cuny et al., 2006). Meanwhile, MRSA CC398 is prevalent as a nosocomial pathogen in veterinary clinics, particularly in those for horses in Austria, Belgium, Germany, Netherlands, Switzerland, and the United Kingdom (for overview see Cuny and Witte, 2017). The decline of certain clonal types and substitution by others over time is also known from human hospitals (Witte et al., 2008). The reasons are still unknown.

Nasal colonization with MRSA of veterinary personnel attending horse clinics is frequent (up to 30% of the individuals) shown by studies in different European countries (Cuny et al., 2008; Cuny et al., 2016; van Duijkeren et al., 2011; Sieber et al., 2011; Van den Eede et al., 2013). Although colonization of humans in contact with horses with colonization and/or infection with LA-MRSA CC398 is frequent, infections are obviously rare. There is one case report on a wound infection in a girl, who had contacted a foal, which previously was treated in a veterinary hospital. MRSA attributed to clonal lineage ST1 (not containing *luk*PV) was for the first time observed in an Austrian veterinary hospital in 2007 (Cuny et al., 2008), where it was still present in 2014 (Loncaric et al., 2014). Furthermore, this strain type was reported from a Swiss university veterinary hospital (Sieber et al., 2011). MRSA attributed to CC1 are known from infections in humans as well as in animals (see above). Horses may have them acquired from cattle, where these LA-MRSA are prevalent in South-Eastern Europe. In a study conducted in an Israeli veterinary teaching hospital, 14.3% of horses and 11.5% of humans were identified as having MRSA ST5 with *spa*-type t535 (Schwaber et al., 2013). Two years later MRSA ST5, *spa*-type t002, SCC*mec*II was obviously introduced into the same hospital by a veterinarian colonized with this MRSA and detected in horses as well as in veterinary staff (Steinman et al., 2015). At the same time HA-MRSA ST5 exhibiting the same typing characteristics, was prevalent in human hospitals in Israel (Adler et al., 2012). This is an additional example for a spill over of HA-MRSA into an equine hospital. Further MRSA attributed to CC8, CC22, ST130 and ST1660 were only rarely observed in horses (Cuny et al., 2016). In most cases LA-MRSACC398 colonization is usually transient in horses, but this clonal complex may easily spread into the horse population. In Denmark the prevalence of MRSA collected from 409 horses at farms or prior to

admission to an equine clinic was 4%, the isolates were attributed to the horse clinic associated subpopulation of LA-MRSA CC398, a lower prevalence was observed for LA-MRSA which are known from pigs, and also MRSA ST130 (Islam et al., 2017). These findings suggest that carriage of MRSA by horses in the community is rare.

6.2. MRSA in healthy horses at the community

The prevalence of MRSA beyond horse clinics is infrequent, as indicated from sampling of horses prior to hospital admission with 3.5% in Germany (Walther (2022)) and 4% in Denmark (Islam et al., 2017). However, transmission of MRSA CC130 from a horse to a veterinarian was just recently reported from Hungary (Albert et al., 2023).

7. Transferable antibiotic resistance in staphylococci of livestock origin

As shown in Table 1, most of the transferable antibiotic resistance genes of staphylococci were observed in isolates of both human animal origins thus indicating a common pool of transferable resistance. Especially staphylococci from animals often contain combinations of genes conferring resistance to members of the same antibiotic class. Multiresistance to compounds of several antibiotic classes was frequent among coagulase negative staphylococci (CoNS) from pig farm dust (Schoenfelder et al., 2017). Many of the resistance genes are part of mobile genetic elements in particular, transposons or plasmids (Wendlandt et al., 2015; Schwarz et al., 2021; Kruger-Haker et al., 2023). Therefore, it is likely that staphylococci (and their relatives) from animals may serve as a reservoir of transferable antibiotic resistance genes exemplified by the emergence of *mecB* in *S. aureus*. It was first observed in *Macrococcus caseolyticus* (formerly *Staphylococcus caseolyticus*) as part of a staphylococcal cassette chromosome *mec*-like element (Tsubakishita et al., 2010). An infection of a dog with a *mecB* containing *M. caseolyticus* was observed in Spain (Gomez-Sanz et al., 2015). The emergence of plasmid located *mecB* in *S. aureus* from an infection in a human was reported by (Becker et al., 2018). Although there were no further reports on the emergence of *mec*B in staphylococci, this finding demands further attention, as plasmids containing resistances genes may spread more easily among staphylococci than SCC*mec*-elements. As already discussed by (Otto, 2013), transmission of SCC*mec* elements from CoNS to *S. aureus* may contribute to the evolution of new MRSA clones. Data from comparative genomic characterizations suggested that SCC*mec* elements contained by MRSA originated from CoNS (John et al., 2019). Of particular significance from the one health perspective is transferable resistance to linezolid, a synthetic antibiotic that is critically important in human medicine (World Health Organization, 2017). Gram-positive bacteria can develop resistance to linezolid by several mechanisms (Schwarz et al., 2021): (i) 23 S rRNA mutations (C2161T), (ii) mutations in the genes coding for ribosomal proteins, and (iii) via ribosomal protection mediated by proteins with ATP-binding cassettes and encoded by *optr*A as well as *by pox*tA (for review see Schwarz et al., 2021), or (iv) methylation of A2503 in the 23S rRNA which is mediated by *cfr* of which four subtypes (A - D) are known so far. This methylation leads to cross-resistance against substances of several antibiotic classes such as phenicols (chloramphenicol and florfenicol), lincosamides (clindamycin), selected 16-membered macrolides (josamycin and spiramycin), pleuromutilins (tiamulin and valnemulin), oxzolidinones (linezolid) and streptogramin A compounds (virginiamycin, dalfopristin). Thus, selective pressure in favour of *cfr* can be mediated by several antibiotics, which are commonly used in veterinary and human medicine. With a few exceptions, *cfr* was found on plasmids and often in close proximity to insertion sequences, which play a crucial role in the mobility of *cfr* (Wendlandt et al., 2015). These mobile structures have been detected among several Gram-positive bacteria other than staphylococci, such as *Enterococcus faecium* and *E. faecalis*, *Macrococcus caseolyticus*, *Jeotgalicoccus pinnipedialis*, *Bacillus spp*., *Streptococcus suis*, as well as in

Table 1
Antimicrobial resistance genes harboured by staphylococci from animals and humans.

Antibiotic class	Resistance mechanism	Genes	Association with isolates of human and/or animal origin (reported so far)
Aminoglycosides	Acetylation, phosphorylation	*aacA-aphD*	both
	Adenylation	*aaD, aaE, s tr*	both
	Phosphorylation	*aphA3*	both
Aminocylitols	Adenylation	*spc, sp, spw*	both
	Enzymatic inactivation	*apmA*	animals
ß-lactams	Enzymatic inactivation	*blaZ*	both
	Alternative target	*mecA, mecB, mecC*	both
Bleomycin	Binding to the gene product	*ble*	both
Fosfomycin	Metallothiol-transferase	*fosD*	both
Fusidic acid	Ribosome protective protein	*fusB, fusC*	both
Lincosamides	Nucleotidylation	*Lnu*(A), *lnu*(B)	both
Lincosamides + streptogramin A	Efflux (ABC porter)	*sal*(A)	animals
Lincosamides + pleuromutilins + streptogramin A	Efflux (ABC porter)	*vga*(A), *vga*(A)v, *lsa*(E)	both
		vga(B)	humans
		vga(C)	animals
Macrolides	Efflux	*mef*(A)	both
	Phosphorylation	*mph(C)*	humans
Macrolides + streptogramin B	Efflux (ABC transporter)	*msr*(A)	both
Macrolides + lincosamides + streptogramin B	Methylation of target site (23 S rRNA)	erm(A), *erm*(B), *erm*(C), *erm*(F), *erm*(T), *erm*(43),	both
		erm(33), *erm*(44), *erm*(45)	animals
Mupirocin	Target replacement	*mupA* (syn. *ileS2*)	both
		mupB	humans
Phenicols	Acetylation	*cat*	both
	Efflux (MFS porter)		both
Phenicols, lincosamides, oxazolidinones, pleuromutilins, streptogramin A	Target site demethylation (23 S rRNA)	*cfr*	both
Streptogramin A	Acetylatipon	*vat*(A), *vat*(C)	humans
		vat(B)	both
Streptogramin B	Enzymatic inactivation	*vgb*(A)	both
Streptothricins	Acetylation	*sat4*	both
Tetracyclines	Efflux (MFS porter)	*tet*(K), *tet* (L)	both
	Target protection	*tet*(M), *tet*(O)	both animals
Oxazolidinones + phenicols	Ribosome protective protein	*optrA*	animals
Oxazolidinoses + phenicols + tetracyclines	Ribosome protective protein	*poxtA*	animals

(*continued on next page*)

Table 1 (*continued*)

Antibiotic class	Resistance mechanism	Genes	Association with isolates of human and/or animal origin (reported so far)
Trimethoprim	Target replacement	*dfrA, dfrD, dfrG, dfrK*	both
Glycopeptides	Target modification	*vanA*	humans

Based on previous reviews: Argudin et al., 2017; Wendlandt et al., 2015; Schwarz et al., 2021; Mlynarczyk-Bonikowska et al., 2022; Kruger-Haker et al., 2023.

Gram-negative bacteria such as *E. coli* and *Proteus vulgaris* (Shen et al., 2013). With low prevalence, *cfr* was observed in linezolid-resistant CoNS from humans worldwide (Mendes et al., 2014). Although *cfr*-mediated resistance became at first known in *M. sciuri* of bovine origin from Germany (Schwarz et al., 2000), in the following years there were only a few reports on its occurrence in CoNS of animal origin from European countries (Argudin et al., 2015). In contrast, a study from China reported that up to 5% of CoNS isolates from pigs, chickens, and ducks contained *cfr* (Wang et al., 2015). A study on veal calfes raised in Luxemburg revealed that the emergence of *cfr* containing CoNS in these animals was associated with florfenicol use. Staphylococci possessing *cfr* were not detected in veal calf famers and their household members. However, the latter was the case in pig farms. Furthermore, *cfr* containing CoNS were detected in 2,3% of German veterinarians participating in a longitudinal study on nasal staphylococcal colonization and in 3 of their 263 family members. Among these isolates was also *S. epidermidis* attributed to clonal complex CC2, which is widely disseminated in hospitals (Cherifi et al., 2013). More recently the emergence of *cfr* containing LA-MRSA CC398 was reported from Portugal (Leao et al., 2022). The acquisition of *cfr* by LA-MRSA CC1 from pigs was recently observed in Italy (Iurescia et al., 2023). The *cfr* gene was plasmid-located and transferable to *S. aureus* in vitro (Cuny et al., 2017). A recent study presented evidence for transmission of plasmid-located *cfr* transmission *from S. epidermidis* CC2 to *S. aureus* attributed to different clonal lineages in a French hospital (Cortes et al., 2022). As to be expected, *cfr* was also found in single isolates of livestock-associated MSSA and MRSA attributed to clonal complexes CC9 and CC398 of pig origin in Germany (Kehrenberg et al., 2009), and later also in LA-MRSA in China (Wang et al., 2012) and in LA-MRSA CC9 in Thailand (Chanchaithong et al., 2019). Concomitant occurrence on the same pig farm of LA-MRSA CC398 and NAS which contained *cfr* located on nearly identical Tn558 mobile genetic elements was recently reported from Korea (Lee and Yang, 2023), which suggests transmission under suitable conditions. Besides a report from China (Wang et al., 2015) observations of nasal colonization of humans exposed to livestock with *cfr* containing LA-MRSA remained just as sparse (Ruiz-Ripa et al., 2021) as case reports on infections in humans with occupational livestock exposure (Gales et al., 2015; Cuny et al., 2017). In humans, the first clinical isolate documented to carry the *cfr* gene, was a methicillin-resistant *Staphylococcus aureus* (MRSA) strain isolated from a patient with respiratory infection in Colombia in 2005 (Toh et al., 2007). In this isolate *cfr* was contained by the chromosome, unfortunately the isolate was not typed. The first outbreak by MRSA carrying the *cfr* gene was reported in 2008 and involved 15 patients admitted in the intensive care unit of a hospital from Madrid, Spain (Morales et al., 2010). Of particular concern was the attribution to epidemic hospital-associated MRSA ST125 (Gopegui et al., 2012). Later, *cfr* was reported to be contained by epidemic HA-MRSA ST22 from Ireland (Shore et al., 2016) and by CA-MRSA ST8 (USA 300) in Ireland and in the United States (Shore et al., 2010; Locke et al., 2014). Despite these reports on *cfr* containing staphylococci from different geographical regions, linezolid resistance obviously remained infrequent among clinical staphylococcal isolates from humans so far: in 2021 less than 0, 9% among 65.462 CoNS and none among 104.896 *S. aureus* in Germany (Markwart et al., 2021; Robert Koch-Institut, 2023a). Furthermore, linezolid resistant *S. aureus* was not observed in nasal swabs from 3891 adult persons in Germany (Holtfreter et al., 2016). The same applies to NAS from nasal swabs taken from 363 humans living in a German municipal community (Cuny and Witte, 2017) and to CoNS from nasal swabs from humans in a German community in an area with high density of livestock farms (Marincola et al., 2021). In the veterinary sector in Germany plasmid-coded linezolid resistance in MRSA was detected in only 0.5% of 4000 food and livestock samples (Lienen et al., 2022). This corresponds to data from the investigation of isolates from diseased pigs collected in the German National Resistance Monitoring Program GERM-Vet from 2007 to 2019 (Kruger-Haker et al., 2023).

Linezolid resistance mediated by *cfr* in MRSA of both human and animal origin is obviously also rare in the Netherlands as evident from a study based on an analysis of 332 deposited sequenced genomes (Schouls et al., 2022). Data based on phenotypical linezolid resistance might be biased as *cfr* is not always sufficiently expressed, and the minimum inhibitory concentrations of linezolid of the corresponding isolates ae below the breakpoints for clinical resistance (Li et al., 2018). On the other hands, mutations in *cfr* may result in phenotypic susceptibility (Lee and Yang, 2023). Nevertheless, outbreaks of nosocomial infections with *cfr* containing *S. epidermidis* are still reported and need attention (Wessels et al., 2018); (Dortet et al., 2018). Taken together these data suggests that the emergence of *cfr* gen mediated resistance is directly associated with selective pressure by antibiotic usage in veterinary and human medicine. Based on the current situation, questioning the use of florfenicol and of pleuromutilins in veterinary medicine is by no means justified, however regular surveillance of susceptibility of indicator pathogens is advisable. Consumption of phenicols and of pleuromutilins together in veterinary medicine in Germany represented about 5% of all antibiotics and remained stable from 2011 until 2020 (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit and Bundesinstitut für Risikobewertung, (2021)). In human medicine the consumption of linezolid in German hospitals was 1.2% in relation to the total daily doses of all antibiotics (Robert Koch-Institut, 2023b). As increased linezolid consumption in singular hospitals was reported prior to the emergence of linezolid resistant *S. epidermidis* in hospitals (Mulanovich et al., 2010), antibiotic stewardship in hospitals is important. In human medicine retapamulin, a semisynthetic pleuromutilin, is licensed as a 1% ointment in the United States as well as in Europe for topical treatment of mild impetigo and infected minor wounds due to MSSA or S. pyogenes. It is an important alternative for treating impetigo with mupirocin and fusidic acid resistant *S. aureus* (review by Hall et al., 2022). Its activity is affected by the *cfr* mediated resistance mechanism (Candel et al., 2011). As is known from the example of fusidic acid, topical use of an antibiotic especially selects for resistance (Heng et al., 2013). Therefore, topical use of retapamulin might contribute to an increased spread of *cfr*.

8. Conclusions

S. aureus has impressive abilities to function as a versatile colonizer and multihost conditional pathogen which evolves and adapts to new hosts. Obviously human activities play a central role in host switching events. Historically, it began with the domestication of animals and continued in recent times with industrialized agriculture including intensive livestock farming. Due to farming practices associated with the use of antibiotics, improved sanitation and feed supplements, livestock became an ideal reservoir for bacteria like *S. aureus* but also non-aureus staphylococci with new resistance properties, that can spread into the community with a significant risk to the human population. With regard to antimicrobial resistance, intensive farming has been repeatedly questioned during the past 25 years. Therefore, research on changes that are still economically viable should be strengthened. Furthermore,

associated with urbanization the importance of pets as close companions grew. So far, prevention of spread of multi-resistant nosocomial bacterial pathogens mainly focused on human medicine but should consider veterinary hospitals in an integrative manner. Host-switching may be associated with the emergence of subpopulations with pronounced capacity for dissemination ("epidemic virulence") among humans, livestock and companion animals. This underlines the critical role of surveillance in the early identification of emerging clones originating from host jumps by interdisciplinary programmes, coordinated between human and veterinary medicine as well as agriculture and the environmental sector ("One Health"). Such kind of integrated surveillance is important for taking preventive measures in a rational and efficient way.

CRediT authorship contribution statement

Witte Wolfgang: Writing – original draft. **Werner Guido:** Writing – original draft. **Layer-Nicolaou Franziska:** Writing – original draft. **Cuny Christiane:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

All authors declare no conflict of interest.

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