Mini Review

Emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in different animal species

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**Abstract**

The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in animals such as horses, pet animals and productive livestock has raised questions of a probable human origin and in more general of host specificity of *S. aureus*. Particular clonal lineages are obviously specific for humans (e.g. ST15, ST25, ST45) and other for ruminants (e.g. ST151). MRSA associated with veterinary nosocomial infections (e.g. ST8 and ST254 in horses, ST22 in small animals) very likely have their origin in health care facilities. MRSA ST398 which became first known from widespread colonization in industrially raised pigs seems to have a limited host specificity and is able to colonize and to cause infections in various hosts. Mechanisms of host adaptation and their genomic background are poorly understood so far.

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*Staphylococcus aureus* and host specificity

*S. aureus* is not only a colonizer of the upper respiratory tract mucosa of all mammals investigated so far, it has also been found in natural populations of birds (Hajek et al., 1988), in industrially raised poultry (Witte et al., 1977), and probably also in snakes (Devriese and Hajek, 1980).

In the first decades after World War II, frequent clusters of human mastitis and subsequently infections in newborns on one side and outbreaks of mastitis in cows associated with mechanical milking and of infections in industrially raised chicken on the other led to the question of mutual transmission of *S. aureus* between humans and animals. At that time characterization of *S. aureus* isolates by means of phenotypical traits (phage typing, hemolysine types, coagulase types, staphylokinase etc.) suggested the existence of host-adapted so-called ecovars such as for humans, cattle, sheep, and chicken (Meyer, 1967; Hajek and Marsalek, 1969; Witte et al., 1977; Witte et al., 1978; Devriese, 1984; Theakston et al., 1990). These techniques have been useful for classifying bacterial isolates into convenient intraspecific subsets but provided little information about genetic relationships of these ecovars. Application of multilocus enzyme electrophoresis clearly separated isolates of ovine and bovine origin from those of human origin (Musser et al., 1990; Musser and Ma, 1990; Kapur et al., 1995).

Use of different methods of DNA-based molecular typing (e.g. macrorestriction patterns, PCR-based typing) revealed that among *S. aureus* from different mammalian host species clones with distinctive genetic background are responsible for the majority of infections within each host species (Musser et al., 1990), although distinct “bovine types” are often interspersed among the human genotype clusters suggesting that human-adapted MRSA were the evolutionary ancestors of *S. aureus* adapted to cattle in modern agriculture (Fitzgerald et al., 1997; Reinoso et al., 2004; Smith et al., 2005; Aires-de-Sousa et al., 2007; Zadoks et al., 2000; Musser and Ma, 1990).

Multilocus sequence typing (MLST) as a powerful method for bacterial population analysis has been widely applied for studying *S. aureus* from humans, in particular MRSA (Enright et al., 2000, 2002; Gomes et al., 2001), also for MRSA from animals, but much less for *S. aureus* isolates of animal origin in general.

MLST analysis of numerous methicillin-sensitive *S. aureus* (MSSA) isolates of human and animal origin revealed that some isolates derived from certain animal species (e.g. ruminants) were assigned to sequence types (ST151, ST771, ST130 and ST837) which are clearly different from common human lineages up to now (Rabello et al., 2007; Sung et al., 2008) and are lacking or only
Infections of humans by *S. aureus* ecovars regarded as animal adapted ones have been only exceptionally observed in the past (Meyer, 1967; Hájek and Marsálek, 1969), however, nasal colonization of milkers with *S. aureus* from cattle was observed (Hummel et al., 1978). That *S. aureus* adapted to cattle and sheep only infrequently colonize humans was shown in recent studies on *S. aureus* from two Asian countries for isolates from humans and from raw bulk milk (Hata et al., 2008; Hsieh et al., 2008).

On the opposite there are particular clonal lineages which are frequent among *S. aureus* colonizing and/or infecting humans that have not been reported from animal so far such as ST15, ST25, and ST45.

A number of other clonal lineages, however, are not restricted to particular hosts (extended host spectrum ecotypes--named EHSG--according to Walther et al. (2009a)). Thus *S. aureus* isolates of equine origin have been found to cluster preponderantly together with clonal lineage from humans such as ST1 and ST254.

Also MRSA-ST22-IV (Barnim epidemic strain; EMRSA-15) seems to be able to cause a wide range of infectious diseases in several mammalian species: In humans (Witte et al., 2008), in different small animal species, particularly in dogs and cats, but also in exotic animals like turtles and bats as well as in pet birds (Loeffler et al., 2005; Strommenger et al., 2006a; Walther et al., 2008, 2009a). Occasionally, this genotype was also found to be associated with isolates derived from pigs (Sergio et al., 2007) and horses (Sung et al., 2008; Walther et al., 2009b).

Phenotypic characterization of *S. aureus* of porcine origin isolated during the 1960s and 1970s did not allow a clear separation from human isolates in the past (Devriese, 1984). When typed by MLST they are assigned to the unrelated lineages ST9 and ST20 ([Gomes et al., 2001] and Witte, unpublished data). *S. aureus* ST9 is also known from occasional nasal colonization of humans (Grundmann et al., 2002).

A study from France on *S. aureus* from pigs, however, has described ST398 as specific for pigs (Armand-Lefevre et al., 2005), a clonal lineage, which has not been reported before and has raised wide attention when emerging as MRSA (Wulf and Voss, 2008; Grundmann et al., 2002; Armand-Lefevre et al., 2005).

As a consequence of MRSA colonization and infection in productive livestock, MRSA can also contaminate meat products and have been demonstrated after enrichment cultures (Normanno et al., 2007; van Loo et al., 2007a).

**MRSA**

MRSA has become a worldwide public health problem. Increasing prevalence of healthcare-associated MRSA (haMRSA) infections is most often based on wide dissemination of particular epidemic clonal lineages of the *S. aureus* population (Tiemersma et al., 2004; Morgan et al., 2000). Emergence and spread of haMRSA is usually associated with a number of risk factors which are typical for the nosocomial settings. There are also situations in which infections with MRSA exhibiting characteristics of haMRSA become apparent at hospital admission due to acquisition of an haMRSA during a previous stay in a nosocomial setting. These isolates represent hospital-associated community onset MRSA (haMRSA, Bartels et al., 2007). Since the late 1990s MRSA has emerged in many countries as a cause of invasive skin infections in the community independently from the healthcare setting in many countries around the world (Salgado et al., 2003; Tristan et al., 2007). There are widespread clonal lineages such as cMRSA ST8 ("USA300") (Tenover et al., 2006; Kennedy et al., 2008) in the USA or ST80 in Europe (Tristan et al., 2007; Witte et al., 2007b).

With respect to MRSA infections in the community, colonization and infections of domestic animals are of particular interest with regard to a mutual dissemination. The first communication on MRSA infections in domestic animals concerned mastitis cases in dairy cows in Belgium in 1972 (Devriese et al., 1972). Since that time there have been reports of sporadic cases of infections with MRSA in a variety of other domestic animal species such as horses, chickens, dogs, and cats (Hartmann et al., 1997; Gortel et al., 1999; Seguin et al., 1999). MRSA infections in horses associated with wide dissemination of a particular clonal lineage were documented in Canada. Since 2005 emergence of MRSA in domestic animal species was reported with increasing frequencies.

MRSA in horses: The first communication of postoperative wound infections in a Michigan veterinary hospital (Hartmann et al., 1997) was followed by reports from several countries about nosocomial infections in horses such as from Japan (Anzai et al., 1996), Northern America (Weese et al., 2005), United Kingdom (Baptiste et al., 2005), Austria (Cuny et al., 2006), Germany (Walther et al., 2006), and Ireland (O’Mahony et al., 2005). MRSA were associated with different kinds of infections, e.g. skin and soft tissue infections (SSTI), septic arthritis, bacteremia, osteomyelitis, ophthalmitis, and implant infections.

MRSA in pigs: MRSA CC398 are widely disseminated as nasal colonizers of pigs in all countries with high-density pig farming investigated so far, e.g. the Netherlands (Huijsdens et al., 2006), Denmark (Guardabassi et al., 2007), Germany (Meemken et al., 2008), Portugal (Pomba et al., 2009), Canada (Khanne et al., 2008), and the USA (Smith et al., 2008). In the Netherlands MRSA CC398 was found for 40% of the farms checked and for 80% of the animals (De Neeling et al., 2007). There are, however, also reports about infections such as exudative epidermitis (van Duijkeren et al., 2008).

MRSA in cattle: The first report on the emergence of MRSA in animals was from an outbreak of mastitis in cattle (De Vriese et al., 1972). More recent reports are from Pakistan (Farzana et al., 2004), Korea (Moon et al., 2007), and Hungary (Jubasz-Kaszanyitzky et al., 2007). As suggested by results from raw milk control programs in European countries,udder colonization and mastitis are obviously infrequent. In the Netherlands, MRSA colonization was also found in veal calves (Graveland et al., 2008).

MRSA in poultry: MRSA CC398 were recently also reported from infections in poultry flocks (Persoons et al., 2009; Nemati et al., 2008).

MRSA in companion animals: first reports on their emergence in dogs came from the United Kingdom (Rich et al., 2005). Cross transmission in veterinary hospitals seems likely, and the finding of MRSAST22, which represents the most frequent haMRSA in United Kingdom, suggested an origin from human hospitals (Loeffler et al., 2005). MRSA ST22 from wound infections of dogs were also reported from Germany (Strommenger et al., 2006a).

**Transmission of MRSA between different animal species and from animals to humans**

To address questions on transmission of MRSA between different animal species and from animals to humans (or vice versa), transmission studies have to be undertaken in farms and veterinary hospitals. Isolates originating from such studies must be investigated by highly discriminatory comparative molecular typing procedures in order to facilitate the unambiguous determination of origin, transmission and spread of particular lineages.

For nearly 3 decades phage typing was broadly applied in *S. aureus* epidemiological typing; however, due to continuous
dynamics within the *S. aureus* population, results became increasingly difficult to interpret, especially for newly emerging MRSA clones, which were not sufficiently discriminated by this method. By the early 1990s pulsed-field gel electrophoresis (PFGE) of genomic SmaI macrorestriction fragments has been introduced and still represents the gold standard with respect to discriminatory power (Murchan et al., 2003; Struelens et al., 2009). Clonal groups determined by cluster analysis of SmaI macrorestriction patterns are widely congruent with those defined by MLST (Enright et al., 2000; Grundmann et al., 2002). Despite its excellent discriminatory power PFGE has major drawbacks concerning reproducibility and portability of its results; moreover some lineages of special interest (e.g. ST398) are non typeable by the standard restriction enzyme SmaI most probably due to modification of the corresponding restriction sites (Waldron and Lindsay, 2006), an alternative is the use of the isoschizomer Cfr91.

MLST which is based on allelic polymorphisms within seven housekeeping genes (Enright et al., 2000) most reliably reflects the evolution of the population structure of *S. aureus* (Robinson and Enright, 2003; Feil et al., 2003). Fig. 1 shows a minimum spanning tree based on concatenated MLST sequences. However, the method is less useful for short-term epidemiological investigations due to its limited discriminatory power; moreover, sequencing of seven different genomic loci is quite expensive. Thus, the single locus based spa sequence typing, which is based on repeat polymorphisms within the X-region of spa, was introduced as an alternative (Harmsen et al., 2003). MLST types are expressed as ST numbers and spa types as t numbers. Discriminatory ability of spa typing is almost comparable to that of Smal macrorestriction analysis and grouping of related spa types by use of the BURP algorithm (Mellmann et al., 2007) results in clusters which are highly concordant to those obtained by MLST and eBURST analysis (Strommenger et al., 2006b). However, discordant grouping infrequently occurs and can be the result of large chromosomal recombination events containing the spa locus (e.g. in haMRSA ST239 (Robinson and Enright, 2004)). In addition, it has been shown that unrelated clonal lineages might contain similar spa types not separated by BURP, thus also leading to “false” group designation. This is for example the case for particular caMRSA lineages (caMRSA ST80 and caMRSA ST1) which are grouped along with several different MSSA lineages, as well as for caMRSA lineage ST30 which is grouped along with MRSA ST398 (Strommenger et al., 2008a). PCR for lineage-specific markers might be helpful in those cases for unambiguous assignment of isolates to particular clonal lineages and can already be performed in routine clinical bacteriology (Strommenger et al., 2008b). In Table 1 the most common spa types associated with colonization or infection in different animal species are summarized.

In the following MRSA assigned to clonal complexes and clonal lineages detected in both animals and humans are considered in more detail.

**MRSA assigned to clonal complex CC8 and horses**

The first MRSA strain detected in humans exhibited ST8, t008. One should, however, be reluctant to regard this “ancient” MRSA as the ancestor of all haMRSA isolated afterwards and showing

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**Table 1**

Dominant *spa* types of MRSA associated with different animal species.

<table>
<thead>
<tr>
<th>Species</th>
<th><em>spa</em> type</th>
<th>MLST</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pig</td>
<td>t011</td>
<td>ST398</td>
<td>de Neeling et al., 2007; Khanna et al., 2008; Köck et al., 2009b</td>
</tr>
<tr>
<td></td>
<td>t034</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t008</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t567</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t1254</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t1255</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t002</td>
<td>ST005</td>
<td>Khanna et al., 2008</td>
</tr>
<tr>
<td></td>
<td>t021</td>
<td>ST030</td>
<td>Pomba et al., 2009</td>
</tr>
<tr>
<td></td>
<td>t567</td>
<td>ST398</td>
<td>Nemati et al., 2008; Persoons et al., 2009</td>
</tr>
<tr>
<td>Poultry</td>
<td>t011</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t099</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t1456</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horse</td>
<td>t036</td>
<td>ST254</td>
<td>Moodley et al., 2006; Cuny et al., 2008; Walther et al., 2009b</td>
</tr>
<tr>
<td></td>
<td>t009</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t064</td>
<td>ST008</td>
<td>Walther et al., 2009b</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Minimum spanning tree for clonal complexes (CC) and clonal lineages (ST) of *S. aureus/MRSA* based on concatenated MLST sequences. (Data from www.mlst.net).
this typing pattern: findings of different types of SCCmec elements indicate convergent evolution. Besides ST8 other lineages of haMRSA assigned to CC8 are ST250, t008, t051, t194, as single locus variant and ST254, t009, ST239, t037/t030 as double locus variants.

MSSA ST8, t008 represent a substantial portion of isolates from natural nasal colonization of humans (Holtfreter et al., 2007). They have not been reported from horses so far, however, this might be due to neglecting MSSA from these animals. However, MRSA ST8, t008, SCCmecIV seem to be adapted to equine colonization in the veterinary hospital setting and is obviously also able to cause infections in horses. In parallel, frequent colonization of humans attending horses has been described (Weese et al., 2005, 2006). This lineage was also reported from horses in Ireland (Moodley et al., 2006). MRSA ST8, t064, SCCmecIV, detected among MRSA from horses in Germany (Walther et al., 2009b), is frequent among isolates from humans in the Copenhagen area in Denmark (Bartels et al., 2007).

MRSA ST259, t036, SCCmecIVd also seems particularly associated with horses: it was isolated from infections and colonization in equine hospitals in Germany (Friedrich and Friedrich, 2004; Walther et al., 2009b), Austria (Cuny et al., 2006, 2008) and United Kingdom (Moodley et al., 2006). MRSA ST259, t036, SCCmecIV is obviously not a derivative of haMRSA ST254, besides the different spa type (t009) it contains an SCCmecIVh which points to convergent evolution from a common ancestor. MRSA ST254, t009, was, however, also isolated from horses (Walther et al., 2009b).

MRSA ST254, t036 was also found as frequent colonizer of humans attending horses in an Austrian veterinary hospital (Cuny et al., 2008). Besides one case of colonization of a diabetic ulcer in a Vienna hospital, it was not represented among MRSA isolates from infections in humans in Germany typed from 2006 to 2008 (data bank of the German National Reference Centre for Staphylococci).

**Table 2**

Emergence of MRSA CC398 in livestock and other animals.

<table>
<thead>
<tr>
<th>Country</th>
<th>Species</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>Pigs</td>
<td>2005</td>
<td>Guardabassi et al., 2007</td>
</tr>
<tr>
<td>Singapore</td>
<td>Pigs</td>
<td>2005</td>
<td>Sergio et al., 2007</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Pigs</td>
<td>2006</td>
<td>de Neeling et al., 2007</td>
</tr>
<tr>
<td>Germany</td>
<td>Veal calves</td>
<td>2007</td>
<td>Graveland et al., 2008</td>
</tr>
<tr>
<td>Germany</td>
<td>Pigs, Dogs</td>
<td>2007</td>
<td>Witte et al., 2007a</td>
</tr>
<tr>
<td>Austria</td>
<td>Horses</td>
<td>2007</td>
<td>Cuny et al., 2008</td>
</tr>
<tr>
<td>Belgium</td>
<td>Horses</td>
<td>2007</td>
<td>Van den Eede et al., 2009</td>
</tr>
<tr>
<td>Canada</td>
<td>Chicken</td>
<td>2007</td>
<td>Nenati et al., 2008</td>
</tr>
<tr>
<td>USA</td>
<td>Pigs</td>
<td>2007</td>
<td>Khanna et al., 2008</td>
</tr>
</tbody>
</table>

**MRSA of clonal lineage ST1**

MRSA exhibiting ST1 (t355) became prominent as the first widely disseminated Panton-Valentine leucocidin (PVL)-positive caMRSA by the end of the 1990s (Naimi et al., 2001). Different from most of the other clonal lineages, S. aureus/MRSA of lineage ST1 contain the superantigen determinant seh, located on a mobile genetic element (Baba et al., 2002). PVL-positive MRSA ST1 are still infrequent caMRSA in Central Europe (Witte et al., 2007b). PVL-negative MRSA seem to be frequent haMRSA in South-Eastern Europe as evident from the results of the Seq.net initiative (Friedrich et al., 2008). MRSA ST1 had also been isolated from infections in horses in an Austrian veterinary university hospital. These isolates exhibited the same typing characteristics as MRSA from nosocomial infections (Cuny et al., 2008).

Most interestingly MRSA ST1 was also described from an outbreak of mastitis in cattle in Hungary (Juhasz-Kazanyitzky et al., 2007). These data suggest that MRSA ST1 can adapt to different mammalian hosts.

**What we can learn from genomics for more advanced diagnostics and molecular epidemiology?**

At present the genomes of eleven MRSA and MSSA clinical strains, of both, community and hospital origin plus two bovine strains have been deposited in the GenBank database. Of particular interest with respect to evolution and features characteristic for caMRSA are comparisons of genomes of caMRSA...
and haMRSA of the same clonal lineage as well as of their most probable MSSA ancestor.

About 78% of the genes are conserved, the remaining 22% comprise an “accessory genome” including genomic islands, pathogenicity islands, prophages, integrated plasmids, and transposons (for review see (Feng et al., 2008)). Comparisons of genomes as well as results from a microarray analysis on gene content (Lindsay et al., 2006) did not reveal conclusive differences in gene content with respect to epidemic haMRSA and their ancestors and only subtle genomic differences between caMRSA and their ancestors as e.g. caMRSA “USA300” and MRSA ST8 (Highlander et al., 2007). Of particular interest is furthermore a study on mutations affecting different genes regulating cell wall synthesis and arising during the course of an MRSA infection along with antibiotic therapy (Mwangi et al., 2007).

A more important characteristic of caMRSA strains is very likely the strong expression of small, phenol soluble proteins which interact with host defenses. These peptides have a remarkable ability to recruit, activate and subsequently lyse human neutrophils. Their role in bacteremia as well as in SSTI has been demonstrated just recently in murine models (Wang et al., 2007).

For MSSA and MRSA of human origin these findings underline the necessity of more detailed analysis of functional genomics for understanding epidemiology and pathogenic potential with respect to transcriptome shifts and protein expression.

Currently, multiple genome sequencing projects are under way, including analyses of one caprine and one avian S. aureus isolate (Ben Zakour et al., 2008a), and several isolates of porcine origin. These projects generate a large amount of data that will be available soon and presumably will provide novel insights into evolutionary and epidemiological aspects of host specialization of S. aureus. The advent of innovative ‘ultrafast’ sequencing technologies will undoubtedly spur this field of research.

However, a comparison of genomes from S. aureus from mastitis in cattle (ST151) to S. aureus from humans has shown that this bovine clone probably has evolved from a common ancestor by foreign DNA acquisition. Subsequent microarray studies on recent epidemic strains of bovine origin such as ST97 also revealed the presence of mobile genetic elements absent from S. aureus of human origin (Herron-Olson et al., 2007).

While genomics has provided impressive insights into the evolution of S. aureus, it has not yet provided many clues about host adaptation of the pathogen, since only limited data are available. To date, only a single S. aureus genome sequence from an animal source has been published (Herron-Olson et al., 2007). The sequenced strain (RF122) had been isolated from bovine mastitis and showed elevated virulence in a mouse model of mastitis (Guinane et al., 2008). By MLST, it was assigned to sequence type ST151 which is unrelated to human isolates. The genome of RF122 contained a number of unique features that had not been seen in other S. aureus genomes, including multiple genes of unknown function and several homologues of virulence genes from other Gram-positive bacteria, and the majority of these genes were located on mobile genetic elements, such as prophages and genomic islands. However, subsequent microarray-based comparisons of gene content revealed that these features were not present in other bovine isolates, and, hence, their role for host specificity remained unclear (Herron et al., 2002). Intriguingly, several genes that are considered important factors for colonization and virulence, including spa and clfA, were non-functional in the bovine isolate, suggesting that gene decay may be associated with host specialization (Herron-Olson et al., 2007). However, the specificity of these features for bovine isolates, or more generally, its association with S. aureus from particular host species, remains to be tested.

In another study, several isolates from cows, goats, and sheep were compared by using genomic hybridization to microarrays and whole-genome PCR scanning (Ben Zakour et al., 2008b). Interestingly, isolates from ovine and caprine mastitis were closely related phylogenetically (as revealed by MLST), and their genomes contained five ovine-caprine-specific regions including allelic variants of membrane protein genes and two regions where genes had been lost through genetic deletion events. In contrast, isolates of bovine origin were more diverse (Ben Zakour et al., 2008b).

Sung et al. (2008) compared S. aureus isolates that caused infection in cows, horses, goats, sheep and a camel with human S. aureus isolates from healthy carriers and community-acquired infections in the UK using a seven-strain S. aureus microarray. This comparative analysis of different S. aureus genomes suggested that only a small number of genes or gene combinations which contained allelic variation in genes encoding proteins of known and unknown function specific for ruminant strains may be responsible for host specificity. In principle, these proteins represent excellent targets for studies of the molecular basis of S. aureus host adaptation (Ben Zakour, et al., 2008b; Sung et al.,...
However, an in-depth analysis revealed that specific bovine S. aureus-associated genes were not found to be uniquely distributed among bovine S. aureus and, therefore, cannot be regarded as specific factors essential for bovine isolates (Kozytska et al., unpublished results). The genes within the pathogenicity island SaPlhovBeta (sab1888-1892) were generally associated with bovine isolates being consistently present in the majority of isolates from cattle but were absent from human clinical S. aureus isolates. The gene content was similar among clones that are closely related by MLST. These results suggest that bovine S. aureus strains are adapted to their host rather than specific expression of a particular set of genes found also in S. aureus strains from human origin than the occurrence of a definite set of genes specific for bovine isolates (Kozytska et al., unpublished results).

The study by Sung et al. (2008) revealed the absence of sak (staphylokinase, not only activating human plasminogen but also trapping anti-staphylococcal cationic peptides), scn (staphylococcal complement inhibitor) and chp (chemotaxis inhibitory protein). The chp and scn genes are part of an immune evasion cluster (IEC-1) in S. aureus, which also encodes staphylokinase (sak) and staphylococcal enterotoxin A (sea) (van Wamel et al., 2006). These genes are located on serogroup F phage(s) such as phi3 and are acquired by lysogenic conversion (Coleman et al., 1989). Acquisition or loss of this prophage might be a reflection of host adaptation. chp and scn are strictly specific for human complement proteins. There is obviously high substrate specificity for human proteins which are involved in innate immunity. In contrast to IEC-1, a second immune evasion cluster (IEC-2) is not human specific (Jongerius et al., 2007). This cluster encodes scb (staphylococcal complement inhibitor b), scc (staphylococcal complement inhibitor c), efb (extracellular fibrinogen-binding protein) and ecb (extracellular complement-binding protein). These proteins are four staphylococcal complement modulators that block convertases, the central protease complexes of the complement cascade. IEC-2 is present in the bovine S. aureus strain RF122. Efb and Ecb block complement activation not only in humans but also in several animal species. Although IEC-2 contains mobile elements and bacteriophage remnants the borders and nature of this cluster are unclear. It is suggested that horizontal gene transfer has played a role in its development (Jongerius et al., 2007).

The human fibrinolytic system is also used for bacterial spread, invasion and host colonization. In parallel with the staphylococcal-nase-dependent activation of plasminogen, the metalloprotease aureolysin contributes to the activation of the fibrinolytic system (Beaufort et al., 2008).

S. aureus has evolved several other mechanisms to resist the host immune system. For example resistance against the respiratory burst is mediated by production of oxidant scavengers like the staphyloxanthin carotenoid. Historically, staphyloxanthin has been known as the yellow pigment of S. aureus, its potent antioxidant properties were discovered just recently (Clauditz et al., 2006). S. aureus also resists against antimicrobial fatty acids by decreasing bacterial cellular hydrophobicity by the surface protein IsdA or by detoxifying fatty acids with FAME (fatty acid modifying enzyme) (Kraus and Peschel, 2008).

According to all the different resistance mechanisms the combination of virulence and immune evasion factors probably play an important role in host- and/or tissue tropism.

**Conclusion**

It has to be stated that particular clonal lineages of MRSA, such as ST1 and especially ST398, do not seem to exhibit pronounced host specificity with respect to colonization and infection. So far there are no data from comparative analysis of isolates assigned to the same lineage but originating from different hosts with respect to genome composition and function. Furthermore, an analysis of genome-wide single nucleotide polymorphisms will help to understand the exact role of evolution and its time course. Especially, acquisition of additional genes (as already shown for PVL-encoding lukS-lukF) or mutation(s) affecting regulatory networks of virulence-associated genes may lead to a further spread of MRSA widely disseminated among animals among the human community. In addition, such strains may become an external source of MRSA causing nosocomial infections (as already observed in the Netherlands (Wulf et al., 2008) and in China (Yu et al., 2008) for MRSA ST398).

An additional potential risk is borne by emergence and spread of transferable antibiotic resistance genes coding for so far unknown resistance mechanisms, e.g. the cfr-mediated broad methylation-based resistance which includes linezolid (Long et al., 2006). Plasmids containing cfr were first described in coagulase-negative staphylococci and have been found very recently in MSSA ST9 and MRSA ST398 (Kehrenberg et al., 2009). Accumulation of MRSA in animals and transfer to humans therefore has also an impact on regulations of antibiotic usage in animal husbandry. Prevention of further dissemination of MRSA with a zoonotic potential needs concerted action of veterinary infection control specialists and clinicians.

An essential prerequisite to this is tight surveillance based on a better understanding of evolution, reservoirs and routes of transmission and on reliable molecular diagnostic markers for discrimination of zoonotic MRSA from hospital- and from community-associated MRSA. Most desirable this should include markers informing about the patho-potential with respect to different kinds of disease in humans and in animals.

**References**


In fact, the study by de Neeling et al. (2009) indicates that the prevalence of MRSA in livestock and livestock handlers is high, highlighting the importance of understanding the role of these animals in the transmission of MRSA. The high prevalence of MRSA in livestock and handlers poses a significant risk for the spread of MRSA to humans, especially in settings where there is close contact between animals and humans. This study underscores the need for effective strategies to prevent and control MRSA transmission in livestock settings.

In conclusion, the study by de Neeling et al. (2009) provides valuable insights into the prevalence of MRSA in livestock and handlers, emphasizing the importance of implementing effective interventions to prevent and control MRSA transmission in these settings. The findings from this study highlight the need for continued research in this area to develop and implement effective strategies for control and prevention.
characterize the long-term evolution of Staphylococcus aureus populations based on spa polymorphisms. BMC Microbiol. 7, 98.


