The impact of zoonotic MRSA colonization and infection in Germany

MRSA als Erreger von Zoonosen in Deutschland

Summary

Methicillin-resistant Staphylococcus aureus (MRSA) causes colonization and infection both in animals and humans. In Germany, cases of MRSA colonization among humans, which affect 0.5–1.5% of the general population and 1.0–2.5% of patients at hospital admission, are still mostly associated with previous healthcare contact and defined epidemic clonal lineages. However, MRSA is also distributed in livestock production in Germany, mostly without causing infections in the animals. These MRSA predominantly belong to the clonal complex (CC) 93, but also to CC9 and CC97. Zoonotic transmission of MRSA CC93 from livestock to humans occurs predominantly in people with occupational livestock contact. Spread of MRSA CC398 to household members of these persons is also frequently observed, but dissemination in the general population is limited so far. However, especially in areas with intensive livestock husbandry, about 20–38% of MRSA CC398 cases among humans cannot be epidemiologically linked to direct livestock contact, indicating other transmission pathways. MRSA CC398 currently causes about 2% of all human MRSA infections (wound infections, pneumonia, sepsis) in Germany, but up to 10% in regions characterized by a high density of livestock-farming. The burden of MRSA in companion animals was demonstrated to range between 6–9.4% within wound samples obtained from dogs, cats and horses, respectively. In contrast to livestock and horses, MRSA distributed in pet animals are mostly associated with MRSA clonal lineages that are also prevalent in human healthcare facilities. Overall, zoonotic exchange of MRSA between humans and animals has relevant impact on the epidemiology of MRSA in Germany.

Keywords: S. aureus, MRSA, zoonosis, MedVet-Staph

Zusammenfassung

Methicillin-resistente Staphylococcus aureus (MRSA) verursachen Besiedlungen und Infektionen bei Menschen und Tieren. In Deutschland ist die Mehrzahl der MRSA-Fälle beim Menschen, die 0,5–1,5 % der Allgemeinbevölkerung und 1,0–2,5 % der Patienten bei Krankenhausaufnahme betreffen, mit vorhergehendem Kontakt zu Einrichtungen des Gesundheitswesens assoziiert. Meist handelt es sich um Besiedlungen durch definierte, epidemisch auftretende MRSA-Genotypen. Zugleich wird MRSA jedoch verbreitete in der landwirtschaftlichen Nutztiertierzucht gefunden, meist ohne Infektionen bei den Tieren auszulösen. Unter diesen Nutztier-assozierten MRSA überwieg der klonale Komplex (CC) 398 neben CC9 und CC97. Zoonotische Übertragungen von MRSA CC398 führten zur nasalen Besiedlung von Berufsgruppen mit Nutztierkontakt und deren Haushalts-
MRSA among the human population in Germany

Among healthy humans in the general population, MRSA colonization is still rarely found in Germany. In three recent studies, MRSA was detected in 0.5–1.5% of the population in the German federal states of North Rhine-Westphalia and Lower Saxony (Cuny et al., 2009; Bisdorf et al., 2011; Köck et al., 2012b). However, the prevalence of MRSA is different in defined risk populations: Investigations performed among patients at hospital admission indicated that 0.8–2.2% are colonized (Becker et al., 2006; Köck et al., 2009a; Grabe et al., 2010; Pohle et al., 2012; Popp et al., 2012; Herrmann et al., 2013). Most of these patients are associated with classical nosocomial risk factors for MRSA carriage such as previous healthcare contact or antibiotic pre-treatment (Köck et al., 2009a; Köck, 2013). Moreover, point-prevalence studies revealed that about 1–3% of nursing home residents in Germany were colonized with MRSA (Köck et al., 2011a). In 2012, the proportion of MRSA among all S. aureus isolated from blood cultures in Germany was 16.9% (data “Antibiotika Resistenz Surveillance”; https://ars.riki.de; date of retrieval: 27.12.2013). However, in high risk areas of healthcare institutions, such as intensive care units, this proportion was 24.7% in hospitals participating in a nationwide surveillance system (“SARI” surveillance project; data for 2012; http://sari.eu-burden.info; date of retrieval: 27.12.2013). Molecular typing of MRSA isolates is mainly performed to detect epidemiological transmission pathways and to monitor the occurrence of clones which are associated with virulence factors or resistance patterns that have a special relevance for public health (Goering et al., 2013). In Germany, a limited number of MRSA clonal lineages as defined by multilocus sequence typing (MLST) and/or S. aureus protein A gene (spa) types accounts for the vast majority of MRSA cases among humans (Schaumburg et al., 2012a). This includes MRSA belonging to MLST clonal complexes (CC) 22 (sequence type [ST] 22, mainly spa type t032) and CC5 (ST225, mainly t003) which were identified in 51% and 31% of 156 German hospitals, respectively. These epidemic CCs accounted for 55% and 33% of all 1357 MRSA isolates typed in 2011 in the national reference laboratory (Layer et al., 2012). This demonstrates that “classical” healthcare-associated (HA-)MRSA clones are still predominant.

MRSA among livestock in Germany

Initially, MRSA colonization of livestock was reported from the Netherlands and France (Armand-Lefèvre et al., 2005; Voss et al., 2005), where the term “livestock-associated” (LA-)MRSA was introduced to describe this epidemiological subgroup of MRSA (Wagenaar et al., 2009).

Staphylococcus aureus is a major pathogen for both humans and animals. The variety of infections (including those of skin and soft-tissues, endocarditis, pneumonia, osteomyelitis and mastitis) that is caused by S. aureus is classically treated with beta-lactams such as broad-spectrum penicillins (e.g. amoxycillin/clavulanic acid and flucloxacinil) or first and second generation cephalosporins (e.g. cefazolin and cefuroxime). However, infections due to methicillin-resistant S. aureus (MRSA) are clinically not treatable by these agents due to less effective binding of beta-lactams to their targets in the bacterial cell wall. In contrast to human healthcare, where alternative antimicrobial agents like vancomycin, oxazolidinones or daptomycin are available to cure patients with MRSA infections, in animals, the use of these substances is not licensed and should be avoided to prevent development of resistance to these substances.

Although early studies indicated rather distinct staphylococcal ecovars in different animal species and in humans (Cuny et al., 2013a), modern typing techniques revealed that for S. aureus/MRSA there is a significant overlap of genotypes found in humans and animals, which indicates zoontic exchange across boundaries. Hence, such S. aureus/MRSA strains have been designated as “extended host-spectrum genotypes” (EHSG) (Walther et al., 2009).

In this review, we summarize data elucidating zoontic transmission pathways for S. aureus/MRSA and the evidence for EHSG molecular types of MRSA that are found among humans, livestock and companion animals. This review includes the most recent results (2010–2013) of the “MedVet-Staph” research consortium (www.medvet-staph.net), which is funded by the German Ministry for Education and Research (BMBF), and discusses them in the perspective of international findings.
In 2008, a survey on the occurrence of MRSA on 1600 breeding farms and 3473 piglet production farms (including “farrow-to-weaner”, “farrow-to-grower” and “farrow-to-finish” farms) was performed in 24 EU and two non-EU countries. In this survey, dust samples were analysed yielding MRSA in a mean of 22.8% of pig holdings in EU countries. Germany was among the countries with the highest MRSA rates in Europe: 43.5% of 46 rearing farms tested (mean EU-value 14%) and 41.3% of 155 production units tested (mean EU-value 26.9%) were affected (European Food Safety Authority, 2009a). Logistic regression analysis showed that MRSA was associated with the herd size (OR 5.4; CI 2.7–11.2; p < 0.05) and the production type of wean-to-finish farms (OR 4.0; CI 1.6–10.4; p < 0.05) (Alt et al., 2011). Assessing the prevalence of MRSA in livestock holdings is also depending on the methods applied. When nasal swabs of individual animals instead of dust samples are tested, the prevalence of MRSA on farm-level in pig holdings is higher and reaches 70–92% (Köck et al., 2009b; Blaha and Sundrum, 2011). Moreover, studies assessing the colonization dynamics of MRSA CC398 in pigs found that in addition to the nares, facial shedding of MRSA CC398 is frequent, which makes stool an additional screening specimen for the detection of MRSA (Szabo et al., 2012).

In pig units in all European countries, MRSA belonging to the CC398 clonal lineage were predominant (93% of all MRSA). Associated with MRSA CC398, several spa types including t011, t034, t108 and others were detected. Besides MRSA CC398, isolates belonging to ST132/CC133 (t1403) were found (European Food Safety Authority, 2009a). ST5/CC5 (t002), ST8/CC8 (t008), ST9/CC9 (t1430) and ST12/CC123 (t1403) were found (European Food Safety Authority, 2009a) (Tab. 1). When testing a non-representative set of MRSA CC398 isolates, phenotypic resistance to tetracycline (100%), erythromycin/clindamycin (70%), gentamicin (14%), ciprofloxacin (8%) and trimethoprim/sulfamethoxazole (4%) was found (Argudin et al., 2011). Genotypically, antimicrobial resistance was determined by the presence of blaz (beta lactamase, 94%), aac(6’)-Ie-aph(2)”-la (gentamicin, kanamycin, tobramycin, 37%), tet(M) (tetracycline, 100%) alone or in combination with the genes tet(K) (51%) and tet(L) (22%) (Argudin et al., 2011). Genes conferring macrolide/lincosamide resistance [erm(A), ermA(B), erm(C)] were present in 35%, 32% and 41%, respectively. Trimethoprim resistance was mediated by the following genes, alone or in combination: dfr5 dfrD (1%), dfrK dfrG (2%), dfrC (21%) and dfrK (39%) (Argudin et al., 2011). Noteworthy, in single cases, the plasmid-borne dfr gene causing a transmissible, multidrug resistance phenotype (PhLOPSA) including oxazolidinone resistance was found (Argudin et al., 2010). MRSA CC398 isolates are usually associated with agr group I and SCCmecV or IVa (Argudin et al., 2010). Recent studies revealed a variety of novel transferable resistance genes and mobile genetic elements in MRSA CC398 (Kadlec et al., 2012b). Exemplarily, the genes vga(C), apmA, erm(T) and dfrK were detected. Small plasmids carrying these genes were completely sequenced and compared to the sequenced parts of larger plasmids previously identified in S. aureus. The results showed that these small plasmids are likely not the precursors of the vga(C)-, apmA- and dfrK-segments found to be integrated into the larger plasmids (Kadlec et al., 2012a). The novel gene vga(E) for pleuromutilin-lincosamide-streptogramin A resistance was identified for the first time in MRSA CC398 (Schwendener and Penret, 2011; Hauschild et al., 2012). Another novel ABC transporter gene, Isa(E), that also confers pleuromutilin-lincosamide-streptogramin A resistance and the novel spectinomycin resistance gene spa were identified in MRSA CC398 and methicillin-susceptible S. aureus (MSSA) CC9 strains (Wendlandt et al., 2013a, c). These two genes represented part of multi-resistance gene clusters of enterococcal origin, which have been acquired by MRSA CC398 and CC9 (Li et al., 2013; Wendlandt et al., 2013b).

Regarding the origin of the MRSA CC398 clonal lineage, it has been suggested by a phylogenetic model based on single nucleotide polymorphism (SNP) analysis that MRSA CC398 originate from human MSSA, that were transferred to livestock animals where they acquired methicillin- and tetracycline resistance, but lost an important virulence factor, the so-called immune evasion cluster (IEC) encoded on a β-haemolysin-converting phage (qIII). Hence, it was indicated by this model, that MRSA CC398 occurring among humans are mostly zoonotically transferred LA-MRSA CC398 which are less adapted to the human host (since they do not carry the IEC which facilitates escaping the human immune response system) (Verkaik et al., 2011; Price et al., 2012). However, the accuracy and validity of this model, which contains a collection of only 89 S. aureus CC398 isolates derived from very divergent, epidemiologically unrelated areas (animals and humans from 19 countries), to describe the actual epidemiological situation is unknown. For example, a study in which animals and humans in several livestock production sectors in Belgium were sampled, found MSSA CC398 isolates among 6 of 149 humans and in 22/141 MSSA isolates from animals (Vandendriessche et al., 2014). MSSA CC398 isolates were all resistant to tetracycline due to possession of tet(M) alone or in combination with tet(K) and tet(L). MSSA CC398 with spa type t571, which carry the macrolide-lincosamide-streptogramin B resistance gene erm(T) were found in human patients who lacked direct contact with livestock (Vandendriessche et al., 2011). Moreover, three porcine isolates contained rem-

**TABLE 1: MLST clonal complexes (CC) and spa types commonly associated with MRSA recently isolated from pigs and livestock in Germany**

<table>
<thead>
<tr>
<th>Animal species</th>
<th>CC (spa type)*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs</td>
<td>(22,022,032, t329, t545, t557, t1407, t1292), (5,002,003, 01045, 01246, 01007), (398,0101, 01043, 011688, 01008, 01009, 01024, 01036), (9,011430)</td>
<td>Vincze et al., 2014</td>
</tr>
<tr>
<td>Cats</td>
<td>(22,0106, 0102, 01002, 01032, 01613, 01346, 017982), (9,0002, 01003, 01045), (0,0008), (398,0101, 01599, 01278)</td>
<td>Vincze et al., 2014</td>
</tr>
<tr>
<td>Horses</td>
<td>(398,0101, 016867, 0110643), (8,01009, 012131), (12127, 00503)</td>
<td>Vincze et al., 2014</td>
</tr>
<tr>
<td>Pigs</td>
<td>(398,0101, 01034, 0108, 011250, 011451, 012510), (97,013992, 015487, 010007), (9,011430)</td>
<td>European Food Safety Authority, 2009a</td>
</tr>
<tr>
<td>Veal calves</td>
<td>(398,0101, 01034), (8,0009)</td>
<td>Hartung und Käsbor, 2012</td>
</tr>
<tr>
<td>Turkey</td>
<td>(398,0101, 01034, 01517, 01456, 012330), (398,01430), (0,0002)</td>
<td>Hartung und Käsbor, 2012, Richter et al., 2012</td>
</tr>
</tbody>
</table>

* MLST CCs sorted in order of importance/frequency for the species in the respective reference; predominant spa types(s) indicated in bold
nant DNA indicating the partial excision of SCCmec from these strains. Hence, these findings indicate that MSSA precursors from which MRSA CC398 could re-emerge or MSSA that originate from “mec-lost” MRSA CC398 are present in the livestock environment. These MSSA CC398 are missed by current microbiological monitoring programs focussing on the detection of MRSA and the extent of this zoonotic burden of *S. aureus* is almost not evaluated. Hence, further studies are warranted to describe and better understand (micro-)evolutionary adaptive processes of *S. aureus* CC398.

Within the framework of national monitorings, dust samples were not only collected from pig farms, but also from other livestock holdings in Germany in 2009 and 2010. In turkey production units, MRSA was detected in 22/112 dust samples tested (19.6%). Typing results showed that MRSA CC398 accounted for 90% of the isolates; 10% were associated with *spa* types t1430 and t002 (Hartung and Käsbohrer, 2012). However, in a regional study, 90% of turkey flocks were MRSA-positive; besides MRSA CC398, t002 was detected in in 5/18 holdings tested (Richter et al., 2012). MRSA was rarely found in laying hens and in broiler flocks (1.4% and 0.7%, respectively) (Hartung and Käsbohrer, 2011). In veal calf holdings MRSA was found in 58/296 dust samples (19.6%); all except one isolate (t009) were associated with CC398 (Hartung and Käsbohrer, 2012). When tested at the abattoir, nasal swabs of veal calves were MRSA positive in 35.1% (Hartung and Käsbohrer, 2011). In contrast, bulk milk samples from dairy herds were tested positive for MRSA only in 4.1–4.7% (2009–2010) (Hartung and Käsbohrer, 2011; Kreausukon et al., 2012).

The data described above were assessed on conventional livestock farms. One investigation tested the occurrence of MRSA in alternative breeding systems belonging to the “Neuland”-initiative in Germany. Cuny et al. did not detect MRSA when testing 178 nasal swabs of pigs from 25 alternative holdings (Cuny et al., 2012). However, other studies have also detected MRSA in organic pig herds in Germany, although its prevalence (MRSA was detected in 11/42 [26%] of the organic herds tested) was overall lower compared with conventional farms, where MRSA was found in 24/26 (92%) of the pig holdings (Blaha and Sundrum, 2011). Exemplarily, differences to conventional livestock farms could be explained by divergent stocking densities on the farm, differences in the conditions of farming (origin of animals, housing conditions), or differences in the density of antibiotic use.

Despite the high rate of colonization with MRSA among livestock, infections in animals are rarely observed or detected. Clinical and subclinical cases of mastitis in cows or exudative epidermitis in swine have been described (van Duijkeren et al., 2007; Feßler et al., 2010; Spohr et al., 2011). When analysing *S. aureus* isolates collected between 2004 and 2007 from various pathological lesions of pigs at necropsy, MRSA accounted for 43% of all *S. aureus* isolates identified (Meemken et al., 2010). Hence, the role of MRSA as causative agents of infections among livestock is not well assessed.

**MRSA in food items in Germany**

Since 2008 the occurrence of MRSA in food items in Germany is monitored in annual, representative surveys. In 2011, MRSA was detected in 27.7% of chicken meat samples from retail. This proportion of contaminated samples has increased since 2008 where 13.2% of the meat samples contained MRSA (Hartung and Käsbohrer, 2011). In beef and game, MRSA contamination was detected in 8.1% and 4.8% of the samples, respectively. Raw milk cheese contained MRSA in 1.6%; in cheese made of pasteurised milk MRSA was not
TABLE 2: MRSA colonization among persons with occupational livestock contact

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Occupation (exposed to)</th>
<th>n</th>
<th>MRSA colonization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia-Graells et al. (2013)</td>
<td>NL, DK, B</td>
<td>Farmer (swine)</td>
<td>15</td>
<td>100%</td>
</tr>
<tr>
<td>Cuny et al. (2009)</td>
<td>D</td>
<td>Farmer (swine)</td>
<td>113</td>
<td>86%</td>
</tr>
<tr>
<td>Köck et al. (2012a)</td>
<td>D</td>
<td>Farmer (swine)</td>
<td>35</td>
<td>77%</td>
</tr>
<tr>
<td>Van Den Broek et al. (2009)</td>
<td>NL</td>
<td>Farmer (swine)</td>
<td>139</td>
<td>24%</td>
</tr>
<tr>
<td>Richter et al. (2012)</td>
<td>D</td>
<td>Farm workers (Turkeys)</td>
<td>59</td>
<td>37%</td>
</tr>
<tr>
<td>Graveland et al. (2011)</td>
<td>NL</td>
<td>Farmer (cattle)</td>
<td>51</td>
<td>38%</td>
</tr>
<tr>
<td>Dorado-Garcia et al. (2013)</td>
<td>NL</td>
<td>Farmer (cattle)</td>
<td>NA</td>
<td>30%</td>
</tr>
<tr>
<td>Cuny et al. (2009)</td>
<td>D</td>
<td>Veterinarian (swine)</td>
<td>18</td>
<td>45%</td>
</tr>
<tr>
<td>Paterson et al. (2013a)</td>
<td>UK</td>
<td>Veterinarian (cattle)</td>
<td>307</td>
<td>2.6%</td>
</tr>
<tr>
<td>Verkade et al. (2013)</td>
<td>NL</td>
<td>Veterinarian (swine/cattle)</td>
<td>137</td>
<td>44%</td>
</tr>
<tr>
<td>Gilbert et al. (2012)</td>
<td>NL</td>
<td>Slaughterhouse worker (swine)</td>
<td>341</td>
<td>3.2%</td>
</tr>
<tr>
<td>Morcillo et al. (2011)</td>
<td>ES</td>
<td>Slaughterhouse worker (swine)</td>
<td>25</td>
<td>8%</td>
</tr>
<tr>
<td>Van Cleef et al. (2010a)</td>
<td>NL</td>
<td>Slaughterhouse worker (swine)</td>
<td>249</td>
<td>5.6%</td>
</tr>
<tr>
<td>Mulders et al. (2010)</td>
<td>NL</td>
<td>Slaughterhouse worker (poultry)</td>
<td>466</td>
<td>5.6%</td>
</tr>
<tr>
<td>Boost et al. (2013)</td>
<td>CN</td>
<td>Butcher (swine)</td>
<td>300</td>
<td>5.6%</td>
</tr>
<tr>
<td>Bisdorf et al. (2011)</td>
<td>D</td>
<td>„Occupational livestock contact“</td>
<td>190</td>
<td>24%</td>
</tr>
</tbody>
</table>

NA = information not available

Among MRSA from food items, MRSA CC398 was predominant. However, in some samples a significant proportion of MRSA isolates also belonged to other MRSA clonal lineages: When testing MRSA from chicken abattoirs and meat, 16–17% of all isolates were not associated with CC398, but belonged mainly to CC9 (spa type t1430). Similarly, 4/32 MRSA isolates from chicken and turkey meat products were associated with CC9 and CC5, respectively (Feßler et al., 2011). MRSA from wild boar meat was associated with other than CC398 in 35% (mainly CC8, CC45 and CC72). In beef, MRSA contamination was due to isolates belonging to CC1 and CC9 in 15% (Hartung and Käsbohrer, 2011, 2012, 2013).

Comparing data of MRSA contamination in food items at retail with data for MRSA contamination on other steps of the farm-to-fork chain indicates that the slaughter process has a substantial influence on the contamination rate of carcasses (Lassok and Tenhagen, 2013). Exemplarily, in the fresh pork production chain, contamination rates were highest (64.7%) in nasal swabs and lower (6.0%) on carcasses, meat at processing (4.2%), and final products (2.8%) (Beneke et al., 2011). In contrast, it was found that surfaces of chicken and turkey carcasses, were MRSA contaminated in 48.3–60% (Hartung and Käsbohrer, 2011, 2012, 2013). Hence, optimizing the slaughter process is essential to limit MRSA contamination. Qualitative models simulating MRSA contamination in pig slaughter demonstrated that independent from the degree of MRSA contamination at the beginning of the slaughter process, low contamination rates between 0.5–1.2% can be achieved when controlling specific production steps (Vossenkuhl et al., 2014).

As classical staphylococcal enterotoxins (SEA-SEE) are rarely (< 1%) detected in MRSA from food items, the risk of staphylococcal food poisoning is considered low (Bundesinstitut für Risikobewertung, 2009; European Food Safety Authority, 2009b). Until now, outbreaks of food poisoning due to MRSA have been rarely reported, but they were not caused by MRSA CC398 (Jones et al., 2002). The risk associated with the ingestion of uncooked meat and handling of raw meat in the kitchen for MRSA colonization of consumers, is more difficult to estimate. Whether meat or thawing liquid that are contaminated in higher degrees (as suggested by the detection of MRSA in thawing liquid without enrichment technique; Cuny et al., 2011b), are a source of transmission to people handling food in the kitchen, is unknown. Against the background that food items are usually contaminated with low amounts of bacteria and the fact that MRSA CC398 has not emerged in the general population so far, European and German national public health authorities consider the risk to be limited (Bundesinstitut für Risikobewertung, 2009; European Food Safety Authority, 2009b). The role of MRSA as a food-borne pathogen has recently been reviewed (Wendlandt et al., 2013d). Although MRSA of different clonal lineages can be present in/on food intended for human consumption, the authors concluded on the basis of the published literature that this does not equate to MRSA being considered a food-borne pathogen.

Zoonotic MRSA cases

Burden of MRSA CC398 colonization among humans

Sporadic MRSA CC398 infections in the human population in Germany were first described by Witte et al., but the incidence of colonization and infections due to this MRSA clone was considered low at that time (Witte et al., 2007). However, in 2006, an assessment of the MRSA prevalence in the Dutch-German border region indicated that among 23 566 patients admitted to 39 hospitals, 1.6% carried MRSA, 17% of which were MRSA CC398 (Köck et al., 2009a).

Many international studies have assessed MRSA colonization in persons with occupational livestock contact, such as farmers, veterinarians or abattoir staff (Tab. 2) (Cuny et al., 2009; Van Den Broek et al., 2009; Mulders et al., 2010; Van Cleef et al., 2010a; Bisdorf et al., 2011; Graveland et al., 2011; Morcillo et al., 2011; Gilbert et al., 2012; Köck et al., 2012a; Richter et al., 2012; Boost et al., 2013; Dorado-Garcia et al., 2013; Garcia-Graells et al., 2013; Paterson et al., 2013a; Verkade et al., 2013).

A study among epidemiological field workers suggested that MRSA colonization was easily acquired in swine holdings (17% of field workers MRSA positive when tested directly after leaving the stables), but rather not persistent (94% of these MRSA negative when re-tested the following day) (Van Cleef et al., 2011b). This result was not confirmed for farmers with daily routine exposure to MRSA colonized animals. In one longitudinal cohort study in which nasal samples were derived from Dutch, Danish and Belgian swine farmers over a six-month period, 87% of the farmers were colonized in all eight samples obtained, 13% were intermittent carriers (Garcia-Graells et al., 2013).
In Germany, 35 farmers (swine holdings) provided nasal screening samples on three consecutive days before a planned holiday (of at least 7 days without pig contact) and again on three consecutive days after return from the holidays (before first contact to the animals). While 77% of these farmers were at least intermittent carriers of MRSA, 59% of those colonized before their holidays were still colonized after return (Köck et al., 2012a).

The number of MRSA-infections resulting from colonization due to occupational livestock exposure is mostly unknown. One study has described that a follow-up of all MRSA cases (n = 109) occurring in 2008–2009 in Northern Denmark revealed that 26/109 cases (24%) were associated with MRSA CC398. In 18 of 109 cases, occupational exposure was identified as the source for MRSA and in 16 of these 18 cases (89%), this exposure was contact with pig holdings. Infections were detected in 3/16 cases of occupation-related MRSA CC398 exposure (tonsillitis, impetigo) (Omland and Hoffmann, 2012).

Although, direct animal exposure is considered to be the most effective way of MRSA CC398 transmission from livestock to humans, some studies indicated that also indirect exposure is a relevant pathway to acquire colonization. Preliminary results of a longitudinal study indicate that 12.8% of household contacts of MRSA-positive veterinarians were also colonized with MRSA; 77.8% of which carried the same strain (based on spa typing) (Hermes et al., 2012). Table 3 summarizes further studies assessing MRSA colonization among household contacts of farmers or veterinarians (Cuny et al., 2009; Van Den Broek et al., 2009; Graveland et al., 2011; Dorado-Garcia et al., 2011; Garcia-Graells et al., 2013; Garcia-Graells et al., 2013).

For cases of MRSA colonization in hospitals it has been described in a case-control study (cases = patients colonized with MRSA CC398 vs. controls = patients colonized with other MRSA clonal lineages), that patients colonized with MRSA CC398 were significantly associated with “direct contact with cattle” (OR 8.6; 95% CI 1.7–42.9) and “direct contact with pigs” (OR 20.5; 95% CI 7.8–64.4). The risk factor “chronic illness and need for long-term nursing care” was found mainly among persons with MRSA other than CC398 (OR 0.07; 95% CI 0.008–0.5). However, in this study 38/100 and 75/100 patients colonized with MRSA CC398 reported no contact with pigs and cattle, respectively. This might indicate that there are further routes of MRSA CC398 transmission. This is also suggested by other studies showing that only 11/30 patients with MRSA CC398 in a Dutch hospital (26%) had direct livestock contact (Wulf et al., 2012). National Dutch surveillance data demonstrated that for 352/1738 persons (20%) with MRSA CC398 for whom case-tracing information was available, contact with livestock was not reported (Lekkerkerk et al., 2012). In Northern Denmark, 10/26 MRSA CC398 cases (38%) were not due to occupational livestock contact (Omland and Hoffmann, 2012).

Overall, these findings indicate that in about 20–38% of MRSA CC398 cases among humans, colonization cannot be traced back directly to livestock. For these cases, the transmission routes are unknown.

An aspect that has to be considered in this context is the emission of MRSA from livestock farms. Investigations have proved that MRSA is emitted from livestock holdings via air and manure. Ground samples taken in distances of 300 m downwind of stables were tested positive for MRSA and air samples contained MRSA in concentrations of 2–14 colony forming units (cfu/m³) in 150 m distance downwind of a livestock farm (Friese et al., 2012; Schulz et al., 2012). This data was confirmed in a study assessing emission of MRSA from turkey and broiler barns, where MRSA was detected in the air (50 m 33 cfu/m³; 150 m 11 cfu/m³) and on the soil (Friese et al., 2013).

Based on the results of one Dutch study where the results of multivariate model indicated that living in rural, livestock-dense areas in The Netherlands was independently associated with MRSA carriage (Feingold et al., 2012), it was feared that such emissions could be a relevant factor facilitating spread of LA-MRSA in the general population. However, the results of this model might be criticized as they are not based on a prospective, population-based study, but on retrospective analysis of pooled, less controlled data sets. In addition, other studies from the same areas in The Netherlands did not confirm these findings (Van Cleef et al., 2010b). In addition, an epidemiological study from Pennsylvania, USA, which reported an increased risk of MRSA carriage among humans living in proximity to crop field applications of pig manure, raised attention (Casey et al., 2013). However, molecular typing of MRSA isolates from the same study region indicated these cases were not due to MRSA CC398 (Casey et al., 2014). For Germany, population-based investigations in rural areas have found that the prevalence of MRSA CC398 was 1% among those persons who did not report to have direct livestock contact. These persons had the following risk factors associated with MRSA CC398 carriage: Being a household member of another person with direct livestock exposure (OR 3.8) and private visits on livestock farms (OR 3.2) (Bisdomorf et al., 2011). Living in the vicinity of farms was not a risk factor for MRSA carriage (if there was no direct contact to livestock) (Bisdomorf et al., 2011).

Hence, currently there is no convincing data suggesting that the quantities of bacterial emissions are efficient to cause colonization of persons passing stables or living in the neighbourhood of stables. However, similar to contamination of food items, this transmission pathway is not excluded. Recently, some studies reported the emergence of MSSA CC398 associated with spa type i571 among humans in Europe and the USA (Valentin-Domeil et al., 2011; van der Mee-Marquet et al., 2011; Vendendriesche et al., 2011; Mediavilla et al., 2012). Although related to LA-MRSA CC398 there is currently no hint that this specific subclone within the CC398 clonal lineage is associated with livestock (Uhlemann et al., 2012).

### Table 3: MRSA colonization among household member of persons with occupational livestock contact

<table>
<thead>
<tr>
<th>Study</th>
<th>Occupation of directly exposed person</th>
<th>MRSA in directly exposed person</th>
<th>MRSA in household members</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia-Graells et al. (2013)</td>
<td>Farmer (swine)</td>
<td>100%</td>
<td>86%,7%,19%</td>
<td>DK, NL</td>
</tr>
<tr>
<td>Van Den Broek et al. (2009)</td>
<td>Farmer (swine)</td>
<td>49%</td>
<td>6%</td>
<td>NL</td>
</tr>
<tr>
<td>Graveland et al. (2011)</td>
<td>Farmer (cattle)</td>
<td>38%</td>
<td>16%</td>
<td>NL</td>
</tr>
<tr>
<td>Dorado-Garcia et al. (2013)</td>
<td>Farmer (cattle)</td>
<td>23%</td>
<td>13%</td>
<td>NL</td>
</tr>
<tr>
<td>Cuny et al. (2009)</td>
<td>Farmer (swine)</td>
<td>86%</td>
<td>4.6%</td>
<td>D</td>
</tr>
<tr>
<td>Cuny et al. (2009)</td>
<td>Veterinarian (swine)</td>
<td>45%</td>
<td>9%</td>
<td>D</td>
</tr>
</tbody>
</table>
In Germany, it was recently demonstrated that MSSA t571 is very infrequent and represents less than 0.5% of human MSSA infections and cases of colonization (Cuny et al., 2013b).

Human burden of infections due to MRSA CC398

In several case reports, human infections due to MRSA CC398 have been described indicating that this clonal lineage is able to cause severe infections in the human host. This included cases of mastitis, endocarditis, wound infections, pneumonia, ear infections/mastoiditis and sepsis (Huijsdens et al., 2006; Witte et al., 2007; Pan et al., 2009; Van Hoecke et al., 2009; Schijffelen et al., 2010; Camoez et al., 2013).

A European-wide study assessing the molecular epidemiology of S. aureus from blood cultures collected in 2006–2007, found spa types associated with CC398 only in methicillin-susceptible strains (Grundmann et al., 2010). A study performed three years later (2009) demonstrated that in The Netherlands the incidence of S. aureus bacteraemia was 19.3/100,000 inhabitants. Among 1520 cases of S. aureus bacteraemia, 14 were MRSA (MRSA/S. aureus = 0.9%), 23% of which were MRSA CC398 (van Cleef et al., 2013). In another study performed in 17 European countries in 2007, MRSA CC398 represented between 0% and 11.9% of all MRSA isolated in the respective countries from screening and clinical specimens. This proportion was highest in the Netherlands (11.9%), Belgium (4.7%), Denmark (1.6%) and Austria (1.4%). A close correlation between the proportion of MRSA CC398 and pig- as well as cattle density were reported (Van Cleef et al., 2011a). For Germany, this study demonstrated that in 2007, MRSA CC398 accounted for 0.7% of 1293 MRSA isolates typed in a national reference laboratory, but for 4.3% of 866 isolates typed in a regional reference laboratory located in an area characterized by a high density of livestock (Van Cleef et al., 2011a). Hence, this investigation pointed towards the importance of regional differences when describing the burden of MRSA CC398 infections among humans.

Recently, a multi-centre study has compared the molecular epidemiology of MRSA collected in 33 laboratories in Germany in two study periods (2004/5 and 2010/11). During this time, the proportion of MRSA CC398 on all MRSA isolates increased from 0.3% to 5.4% (OR 22.67, 95% CI 8.51–85.49, P < 0.0005). MRSA CC398 isolates were predominantly found in regions in Northwest Germany where livestock production is performed (Schaumburg et al., 2012a).

In these regions, another study collected 14 036 MRSA isolates from patients in 39 hospitals and 745 general practices (www.eursafety.eu) and subjected these isolates to spa typing (Köck et al., 2013). In this
study, it was found that spa types t011 and t034, both associated with MRSA CC398, represented 10% and 6% of all MRSA, respectively. In 2008, MRSA CC398 (including t011, t034 and other closely related spa types) accounted for 14% (221/1615) of all MRSA from screening specimens (i.e. nasopharyngeal swabs) (Köck et al., 2013). This proportion increased to 29% in 2012 (334/1150) (P < 0.001). A similar significant increase was found for MRSA from superficial wounds (7% to 10%, P = 0.04). Overall, the mean proportion of MRSA CC398 on MRSA from screenings (2008–2012) was 23%. Among MRSA from clinical specimens, MRSA CC398 accounted for a mean of 8% of isolates from blood cultures (n = 194), 11% from deep wound swabs or tissues (n = 331) and 14% from deep respiratory fluids (n = 346), respectively (Köck et al., 2013). This study has also assessed the occurrence of LA-MRSA genotypes other than CC398, which were detected in livestock and meat samples: However, MRSA associated with spa types t1430 (0.14%), t3992 (0.01%), t002 (1%) and t007 (0.01%) were rarely detected among humans (Köck et al., 2013).

Overall, comparison of molecular typing data demonstrates the necessity to survey regional differences. This is shown in Figure 2 which summarizes data from three regional and national studies on the occurrence of MRSA CC398 in samples from humans.

As shown in Figure 2, two studies suggested that MRSA CC398 was more prevalent in screening samples than in clinical specimens. This seems atypical as MRSA clonal lineages are rather equally represented among colonization and infection related isolates (von Eiff et al., 2001). To assess potential reasons that could explain this issue, a retrospective case-control study was performed among patients at an university hospital including 447 patients in whom MRSA of other than the CC398 clonal lineage were detected (= controls; MRSA non-CC398) and 149 patients with MRSA CC398 (= cases) (Köck et al., 2011b). For all patients, basic demographic data (age, sex, length of hospital stay [LOS]), medical procedures (based on OPS codes) and primary as well as secondary diagnoses (based on ICD 10-GM code) were assessed. This study observed major differences between MRSA CC398 and non–CC398 patients. Patients with MRSA CC398 were younger (mean age 53 vs. 59 years), had a shorter LOS (8 vs. 13 days) and were less frequently treated on intensive care units (12% vs. 17%). Moreover, the mean number of diagnoses coded for MRSA CC398 patients was 2.8 (95% CI 2.5–3.1) compared with 4.1 (95% CI 3.8–4.3) in the non–CC398 group (P < 0.001) and significant differences regarding the type of diagnoses were found. In addition, mean number and types of medical procedures performed in the two patient groups was divergent (MRSA CC398 patients: n = 6.8 procedures [CI 95% 5.1–8.6] vs. non–CC398 patients: 11.8 [CI 95% 10.4–13.2] procedures; P < 0.001) (Köck et al., 2011b).

Hence, it was shown that hospital inpatients currently affected by MRSA CC398 in Germany are younger and more healthy compared with patients affected by other (classical nosocomial) MRSA clones. This can help to explain the differences in the occurrence of MRSA CC398 among screening and clinical isolates. Moreover, this could also impact on the probability of transmission of MRSA CC398 in the hospital setting. Although two nosocomial outbreaks of MRSA CC398 in human healthcare facilities have been described (Wulf et al., 2008; Verkade et al., 2012), mathematical models published by a Dutch group indicated that, based on outbreak data, MRSA CC398 compared with non–CC398 was 5.9-times less transmissible (Relative Risk = 0.27) (Bootsma et al., 2010; Wassenberg et al., 2011). Since until now, no data have been published that would suggest that MRSA CC398 is “biologically” less effectively transmitted from humans to humans, such “host”-specific factors, as demonstrated for the patient structure, could contribute to these findings.

**MRSA colonization and infection among companion and wildlife animals**

In a large nationwide study performed in Germany (2010–2012), 5229 samples from animals suffering from wound infections (n = 3479 wound swabs from dogs; n = 1146 from cats; n = 604 from horses) were collected by > 1000 veterinarians (Vincze et al., 2014). It was found that *S. aureus* (both MSSA and MRSA) is a major pathogen causing wound infections in companion animals, since 5.8% of the canine, 12.2% of the feline and 22.8% of the equine samples were positive. Overall, MRSA was detected in 3.6% of the wound swabs from dogs, in 5.7% of the swabs from cats and 9.4% of the equine samples. The MRSA proportion of *S. aureus* was 62.7%, 46.4% and 41.3% in isolates from specimens of dogs, cats and horses, respectively. Molecular typing of the MRSA isolates from companion animals revealed that there were differences with regard to the genetic background: Canine and feline MRSA isolates were mostly associated with spa types t003 (MLST CC5) and t032 (MLST CC22), while MRSA CC398 (spa types t011, t6867) predominated among equine isolates (Tab. 1) (Vincze et al., 2014).

This recent investigation confirms findings from several case-reports and studies showing that the rate of MRSA infections in horses is high. Cuny et al. reported that in a horse clinic in Austria the incidence of MRSA infections was 4.8 cases/1 000 admissions (Cuny et al., 2006). Moreover, in accordance with Vincze et al. (2014), other studies have also suggested a change in the epidemiology of MRSA derived from horses in Germany. While strains belonging to CC8 were frequent causes of equine infections ten years ago (Walther et al., 2009), isolates belonging to CC8 were more frequent in more recent (outbreaks of) infections (Cuny et al., 2010). The reason for this observation is unclear. In outbreak reports, a high nasal colonization rate of staff in horse clinics was found, which could facilitate transmission to horses and subsequent infections. However, a Belgian study revealed that 11% of all horses already carried MRSA when admitted to a clinic (Van den Eede et al., 2009). In consequence, the pathways responsible for the spread of MRSA in horse clinics, the asymptomatic colonization of horses, clinic staff and horse owners are not well investigated yet and preventive concepts are lacking.

For pet animals (dogs and cats) in Germany the results of Vincze et al. were surprising as previous studies did not yield high nasal MRSA colonization rates among dogs (Walther et al., 2012a). However, the above cited investigation shows that they are mostly infected by the same MRSA strains circulating in human healthcare facilities (CC22 and CC5). This is in accordance with previous findings (Walther et al., 2008). Interestingly,
a further study by Vincze et al. revealed that MSSA of canine and human origin belong to classical human S. aureus lineages, too (Vincze et al., 2013). Hence, transmission between humans and pets (or vice versa) is likely. Since (as described above) the overall prevalence of MRSA CC5 and CC22 in the German human population is low, human-to-animal transmission seems to be probable mainly for pet owners who have an increased risk of MRSA colonization (e. g. contact with healthcare settings). However, studies assessing the exact transmission routes are missing. The basic fact that humans are major sources for MRSA in pet animals (or the opposite way) is also underpinned by various studies, mostly from the US, demonstrating that also in these countries, MRSA clonal lineages prevalent in the human community are those that are most frequent among pets (David and Daum, 2010). The likelihood of transmission in households has been described in a case-report: Among 49 patients with community-acquired MRSA infections who all lived in a household together with pets, MRSA was also found in at least one pet animal in 8.2% (Ferreira et al., 2011). However, the high probability of zoonotic transmission can be explained by the close contact pets have with their owners: A recent study from Germany has demonstrated that dogs usually live directly in their owners’ flats or houses (89%), are allowed to sit on the sofa (68.5%) and are allowed to lick their owners’ hands (93.5%) or faces (53%). Of all pet owners (n = 108), 40% allowed the family dog to lie in their beds (Walther et al., 2012a).

Compared with data about MRSA colonization of livestock veterinarians, there is less data assessing this issue among veterinarians treating pets. Of 128 participants attending a conference for small and hobby animals, MRSA colonization was found in 1.6%. Colonization with methicillin-resistant S. pseudintermedius (which is very infrequent among humans, but prevalent in companion animals) was found in 3.9% (Paul et al., 2011). In an Australian study it was demonstrated that veterinarians with contact to horses had very high MRSA colonization rates (21.4%) compared with a control group (0.9%). In this study, veterinarians treating cats and dogs were also more frequently colonized than the control group (4.9% vs. 0.9%) (Jordan et al., 2011). This was confirmed in a study from the UK where veterinarians and pet owners who had contact with a pet animal which suffered from an MRSA infection, were colonized with MRSA in 12.3% and 7.5%, respectively (Loeffler et al., 2010).

Drug-resistant S. aureus including MRSA carried by humans may pose also a risk to endangered wildlife populations as reported for great apes and their sanctuary personnel during the course of reintroduction programs (Schaumburg et al., 2012b). Although no MRSA were observed, human associated drug-resistant S. aureus lineages have also been found to be transmitted to primates (Schaumburg et al., 2013).

Importance of MRSA isolates with novel mec homologs
While methicillin-resistance in MRSA is usually conferred by the mecA gene, a new homolog of mecA has recently been described. This homolog is named mecC (or before that mecA<sub>LGA251</sub>). Phenotypically, strains harbouring mecC are oxacillin or cefoxitin resistant as expected for MRSA. However, the performance of cefoxitin-based tests to detect mecC-MRSA seems to be better compared with oxacillin (Skov et al., 2014). Skov et al. conclude that the lower ability of oxacillin to detect mecC-MRSA isolates most likely results from higher affinity of the mecC-encoded PBP2avar for oxacillin (i. e. lower MICs) vs. cefoxitin (Kim et al., 2012). The occurrence of mecC is of major importance as conventional diagnostic MRSA confirmatory assays after phenotypic resistance testing are either based on PCR-detection of mecA or on the detection of the modified penicillin binding protein PBP2a by anti-PBP2a monoclonal antibodies. These conventional tests are negative for MRSA harbouring mecC (Kriegeskorte et al., 2012; Becker et al., 2013; European Food Safety Authority et al., 2013). Initially, mecC was detected in an MRSA isolate (LGA251) obtained from a bulk milk sample in England. Retrospective data analysis revealed further isolates in cattle and humans in England and Denmark with the earliest isolate found in 1975 (Garcia-Alvarez et al., 2011; Shore et al., 2011; Paterson et al., 2014). The MRSA isolates that are mecC positive are usually associated with the clonal lineage CC130 (ST130, ST1245, ST1526, ST1764, ST1944, ST1945; spa types t843, t1535, t1736, t6220, t6293, t7485, t7734, t7946, t7947), and the lineages CC425 (ST425; spa types t742, t6292, t6300, t6386), CC705 (ST151; spa type t529) and CC1943 (ST1943, ST1946; spa types t978, t7945) (Garcia-Alvarez et al., 2011). Investigations into the prevalence of mecC found it in bulk milk from 10/465 farms in England and Wales (2.15%) and 0/625 farms in Scotland. Seven isolates belonged to ST425, three were associated with CC130 (Paterson et al., 2013b). Besides livestock animals (cows and sheeps), mecC positive MRSA have been detected in several wild-living animals (Paterson et al., 2014) and in companion animals (cats, dogs and guinea pigs) (Walther et al., 2012b). Of note, also coagulase-negative staphylococci (S. sciuri, S. stepanovicii and S. xylosus) harboring mecC seem to be widely distributed among wildlife animals (Loncaric et al., 2013).

The occurrence of mecC positive MRSA in samples from humans has been assessed in several investigations. In nasal screenings of cattle veterinarians in the UK where 7/307 veterinarians were colonized with MRSA (3.6%), none of the seven MRSA harboured mecC (Paterson et al., 2013a). In Denmark, where a mandatory notification system documents all cases of humans MRSA colonization, mecC positive MRSA represented 1.9% (21 of 1097) of all MRSA derived from humans in 2010 and 2.8% (36 of 1294) in 2011 (Petersen et al., 2013). In the UK 9/2,010 (0.45%) of isolates obtained in 2011/2012 were associated with mecC (Paterson et al., 2013b) and in Switzerland mecC was not detected in >500 S. aureus isolates derived between 2005 and 2011 (Bassett et al., 2013).

In Germany, Schaumburg et al. showed that mecC was rare in two collections of MRSA isolates from humans both in 2004/5 and 2010/11. Among 3,207 isolates, only 2 were positive for mecC (0.06%) (Schaumburg et al., 2012a). This is in agreement with results from a further study in which isolates derived between 2006 and 2011 were included (11/12,691 isolates; 0.09%) (Cuny et al., 2011a). MRSA isolates associated with mecC among human patients in Germany mostly belonged to CC130 (Cuny et al., 2011a), and spa types t843, t978, t1535, t1773 and t7189 (Kriegeskorte et al., 2012). With the exception of edinB (Epidermal Cell Differentiation Inhibitor-B), 16 isolates tested mostly did not contain classical virulence factors associated with human infection. However, one
isolate contained three pyrogenic toxin superantigen (PTSAg) genes (tst1, sec, sel) and another (978) harboured eight PTSAg genes (tst1, sec, seg, sei, sel, sen, seo, seu) (Sabat et al., 2012).

**Conclusion**

MRSA colonization and infections among humans and animals is caused by a variety of different MRSA clonal lineages; many (or most) of them are extended-host-spectrum genotypes.

In Germany, humans are still mostly colonized by classical HA-MRSA clones that are predominant in hospitals, nursing homes and other healthcare facilities. These cases of MRSA seldomly occur among persons in the community without defined risk factors (e. g. previous hospitalization, presence of catheters) (Kock et al., 2009a) and are, originally, not epidemiologically linked to animals. Recent research results indicate that infection among pets (dogs, cats) is caused by the same spectrum of MRSA genotypes circulating in human healthcare facilities, which ostensibly suggests zoonotic infection of pets via contact to humans. This raises the question how to contain MRSA spread and development of invasive diseases in companion animals. Preventive concepts to contain MRSA (e. g. decolonization therapies, efficient hospital hygiene concepts in veterinary clinics) are mostly missing nowadays. Moreover, concepts aiming to prevent “to-and-fro” transmission between pets and humans living the same households are lacking and should be evaluated.

Zoonotic transmission also occurs between livestock and humans, mainly involving cases of MRSA CC398. Many studies have demonstrated that there are two well-characterized risk groups of humans: (i) persons with direct livestock exposure (such as farmers, veterinarians, slaughterhouse personnel) and (ii) individuals living in the same household with the former. As intensive livestock production is concentrated in some geographical areas, the extent of zoonotic MRSA colonization and infection of humans is regionally divergent. Healthcare facilities in the respective regions need to account for this additional MRSA burden including costs caused by the required testing, isolation and decolonisation procedures, which are currently not well covered by the healthcare system. However, there is human colonization with MRSA CC398, which seems unrelated to direct livestock contact. Increasing evidence suggests that this involves about 20–38% of MRSA CC398 cases among humans. In these cases, the origin of MRSA CC398 is unknown. Potential transmission pathways include dissemination in healthcare facilities, community spread by contact, spread via emissions from livestock holdings or food-related “uptake” (e. g. contamination of hands and subsequently nares by handling of uncooked food items). However, these alternative transmission routes have not been well confirmed or quantified. It was not evaluated, whether efforts limited to promoting reduction of antibiotic use or fostering animal health, although important, will be effective to contain the spread of MRSA CC398 among livestock. One may be doubtful regarding this issue, because *S. aureus* is a physiological colonizer of livestock and selective pressure leading to upsurge of MRSA is caused by commonly administered antibiotics such as tetracycline or small-spectrum beta-lactam.

Hence, there is a need for developing more targeted preventive concepts (not only to contain MRSA but also other antibiotic resistant pathogens such as enterobacteria resistant to third-generation cephalosporines or carbapenems). A first step could be to establish monitoring programs assessing antibiotic resistance in farm environments, which focus on all, not only classical animal or food-borne pathogens. Concepts for a better control of trading pathways or setting up healthy nucleus herds not colonized with the respective antibiotic resistant bacteria, could be further steps. The proportion of the recently described mecC-MRSA and mecC–harbouring coagulase negative staphylococci seems rather low in humans and animals. However, those strains appear to be widely distributed in Europe with a broad diversity of host species including livestock, companion animals and wildlife. In addition, the divergent molecular nature of mecC hampers its detection in diagnostics and epidemiological studies. In consequence, it is warranted to closely monitor the occurrence of phenotypic meticillin-resistance in staphylococci from animals and humans in order not to miss emergence of mecC or other new mec homologs. This requires to include detailed genotypic characterization of isolates with non-mecA related beta-lactam resistance.

In conclusion, cases of MRSA are no longer limited to the human health-care system. There are manifold transmission routes between humans and different kinds of animal hosts including farming, companion and wildlife animals. Thus, livestock and related fields are nowadays part of the MRSA problem necessitating concerted efforts in human and animal health care, public health service and research.

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