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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

REFLECTION PAPER ON MRSA IN FOOD PRODUCING AND COMPANION ANIMALS IN THE EUROPEAN UNION: EPIDEMIOLOGY AND CONTROL OPTIONS FOR HUMAN AND ANIMAL HEALTH

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CVMP RECOMMENDATIONS

Following SAGAM's review on the impact of use of antimicrobials in livestock and companion animals on the risk of colonization or infection with meticillin-resistant *Staphylococcus aureus* (MRSA), the CVMP has prepared the following recommendations:

MRSA is resistant to virtually all beta-lactam agents and in addition in many cases co-resistant to a number of other antimicrobials. Recently clonal spread of a certain MRSA strain (CC398) has been reported in high prevalence mainly in intensive animal production systems. In addition, companion animals may act as carriers for a variety of typically human MRSA clones. All the major lineages of MRSA strains in companion animals, horses and in livestock are able to infect animals and humans.

By analogy with the epidemiology documented in human medicine, it could be assumed that antimicrobial consumption is one of the driving forces in the emergence and spread of animal associated MRSA. However, control of livestock and companion animal associated MRSA is not an issue limited to controlling the use of antimicrobials but needs to be addressed in its context. Use of antimicrobials is one risk factor but there are other factors in particular related to hygiene and trade that need to be considered.

Due to the multiresistant character of MRSA, there are several antimicrobial classes that may increase the risk of spread of MRSA. Therefore, to be effective to control the emergence of MRSA, measures to reduce the use of antimicrobials cannot be limited to any specific class but routine use of antimicrobials is to be regarded as a risk factor. Any measures to be taken should consider all antimicrobials with the aim to eliminate unnecessary use or replace use with other strategies.

Further studies are required to document the long-term carriage of MRSA, and to find effective ways to decolonize animals and to clear the organism from different animal husbandry settings. The clonal nature of the Livestock Associated MRSA (LA-MRSA) theoretically presents opportunities for vaccine development but further research would be required. Use of antimicrobials for decolonisation seems to be of limited value.

Appropriate wound management without antimicrobials will be sufficient for many MRSA infections. If antimicrobial treatment is necessary, based on the severity of the infection, there is a need to manage the risk of emergence of further resistance in the strain of MRSA infecting the animals to avoid subsequent spread of resistance to animals and humans. Due to the multiresistant nature of MRSA it may be difficult to find approved veterinary medicinal products for the condition. Last resort human medicines for MRSA treatment such as e.g. glycopeptides, oxazolidones, tigecycline and streptogramins have no maximum residue limit (MRL) and therefore they are not allowed to be used in animals intended for food production (Council Regulation (EEC) No 2377/90). In addition there are ethical concerns about their use in veterinary medicine.

Based on the conclusions above the following recommendations are made;

- Adherence to the principles of prudent use remains a key measure to manage risks for spread of MRSA in accordance with:
    - The Codex code of practice to minimize and contain antimicrobial resistance (CAC/RCP 61-2005[1]),
    - OIE Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine[2],
    - Federation of Veterinarians of Europe: Antibiotic Resistance & Prudent use of Antibiotics in Veterinary Medicine.

  as discussed in the CVMP strategy on antimicrobials 2006-2010 and status report on activities on antimicrobials (EMEA/CVMP/353297/2005[3]). Special consideration should be given to improving controls related to group and flock medication of food producing animals and routine perioperative treatment of companion animals and horses when implementing these guidelines.

- Monitoring of the consumption of antimicrobials in the EU is needed to identify and target action towards sources of unnecessary use of antimicrobials. This will also allow for evaluation of the effectiveness of measures taken in this respect.

- Development of non-antimicrobial control measures should be encouraged.

- In case of antimicrobial treatment of MRSA infections, the risk of emergence of further resistance in the strain of MRSA infecting the animals should be considered. Use in animals of last resort medicines for MRSA treatment in humans should be avoided. Any use of such molecules in companion animals and horses should take into account the public health risk involved and should therefore involve discussions with public health practitioners.

- CVMP bases its opinions on authorisation of veterinary medicinal products on an assessment that the benefits of a product outweigh its risks. If the Committee receive applications for authorisation of products containing molecules used as last resort medicines for MRSA treatment in humans, the CVMP will pay special attention in this assessment to the need to ensure the continued efficacy of such molecules in human medicine.

The Committee recommends that these conclusions be communicated to all relevant stakeholders, including National Competent Authorities (through the Heads of Medicines Agencies), marketing authorisation holders and other interested parties of the CVMP.

1 http://www.ipfsaph.org/servlet/BinaryDownloaderServlet/codex10213_CXP_061e.pdf.pdf?filename=\kopool_data\codex_0\en_cxp_061e.pdf&refID=codex10213

2 Terrestrial Animal Health Code (2007): chapter 3.9.3 http://www.oie.int/eng/normes/mcode/code2007/en_chapitre_3.9.3.htm

3 http://www.emea.europa.eu/pdfs/vet/swp/35329705.pdf

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MANDATE

The Scientific Advisory Group on Antimicrobials (SAGAM) was mandated to give advice to the CVMP on the recent developments with regard to the occurrence of meticillin-resistant *Staphylococcus aureus* (MRSA) in animals. Following a request from the European Commission (DG SANCO) it was agreed that SAGAM should work in collaboration with the EFSA Panel on Biological Hazards, who is working in parallel with its self-tasking mandate to assess the public health significance of meticillin-resistant *Staphylococcus aureus* (MRSA). The EFSA opinion (Scientific Opinion of the Panel on Biological Hazards on a request from the European Commission on Assessment of the Public Health significance of meticillin resistant *Staphylococcus aureus* (MRSA) in animals and foods. *The EFSA Journal* (2009) 993, 1-29) will be referred to as appropriate in this reflection paper.

To avoid overlap between the groups, the present reflection paper focuses on the epidemiology, ecology and control of MRSA in living food producing and companion animals with particular emphasis on the impact of the use of antimicrobial agents in veterinary medicine.

The joint opinion from SAGAM/CVMP and EFSA will be presented in collaboration with ECDC as an "umbrella document" linking this reflection paper to the EFSA opinion.

INTRODUCTION

An increased number of reports on MRSA in livestock (in particular in swine) have been recently published. MRSA has also been found in companion animals and horses, and transmission between humans and colonized animals has been reported (Leonard and Markey, 2008). This evolution of MRSA in different animal species demands for a critical review on the factors associated with this emerging zoonotic bacterium, from the veterinary and public health point of view.

OBJECTIVE

The scope of the present reflection paper is to review the latest research on the risk of MRSA infection and colonization in animals in order to provide a preliminary risk profile for animal use of antimicrobials in relation to this risk. The document considers all food producing and companion animal species. The major public health significance is focused on direct contact with living animals and not on animal-derived food products.

The specific aims of the document are:

- To assess the impact of use of antimicrobials in livestock and companion animals on the risk of colonization or infection with MRSA.
- To provide advice on management options for animals related to the issue.

The document provides a scientific base for CVMP when considering possible actions to recommend and implement. It identifies those areas where the available information is absent or too small to allow reflections, and indicates areas for future research and data collection to focus on.

BACKGROUND

Staphylococcus aureus

Staphylococcus (*S.*) *aureus* causes a wide range of severe and economically-important diseases in human and veterinary medicine (Leonard and Markey, 2008;Safdar and Bradley, 2008). The bacterium is a colonizer of the skin and mucosae from which it can invade multiple organs. In livestock *Staphylococcus aureus* is an important cause of mastitis, skin and soft tissue infections (SSTI) and to lesser extent infections of the locomotory system. Surgical site infections (SSI) in which *S. aureus* is isolated have been increasingly reported in small companion animals and horses (Hermans et al., 2008).

In humans, prevalence of *Staphylococcus aureus* infection varies widely between European Member States, among hospitals and inside hospital. The reasons for the difference are likely due to the level of screening, isolation and monitoring of patients and staff in hospitals, with the Dutch having the most pro-active system over the last decades. There is a shortage of quality data investigating infection and/or carriage rates in the community, but occurrence appears to vary substantially with geography (Scientific Opinion of the Panel on Biological Hazards on a request from the European Commission on Assessment of the Public Health significance of meticillin resistant *Staphylococcus aureus* (MRSA) in animals and foods. *The EFSA Journal* (2009) 993, 1-29).

Human invasiveness

S. aureus is by far the most important pathogen in SSTI including surgical site infections. Life-threatening nosocomial infections such as pneumonia and septicaemia also occur. Treatment of invasive infections largely relies on antimicrobial agents, and penicillinase stable beta-lactams (isoxazolylpenicillins, cephalosporins) are of utmost importance for human medicine. Resistance to these agents drastically limits therapeutic options and is a worldwide emerging problem (de Lencastre et al., 2007).

S. aureus can also produce toxins associated with food intoxications. Other rare but severe syndromes including toxic shock syndrome (TSS) have also been documented (Morgan, 2008).

Epidemiological definitions of MRSA groups

Staphylococcus aureus is intrinsically susceptible to beta-lactam agents that inhibit cell wall formation due to binding with proteins involved in the formation of peptidoglycan (Haesebrouck et al., 2009). The mechanism of resistance to penicillinase-stable beta-lactams including meticillin, isoxazolylpenicillins and cephalosporins in *S. aureus* (MRSA) is an altered target site due to an acquired penicillin-binding protein (PBP 2a, also called PBP 2') encoded by the gene *mec*A.

Different types of MRSA may be distinguished based on epidemiological groups. This can be a simplistic approach since in some cases strains of MRSA have spread between the groups (Morgan, 2008). Thus it might be difficult to determine which epidemiologic pattern a certain MRSA strain is associated with. The grouping is of relevance for the remaining of this document although only MRSA related to animals will be discussed. It should be noted that virulence may differ between strains within groups and that toxin producing strains may be found in any of the groups.

1.a) *Hospital Associated MRSA* (HA-MRSA) are known as nosocomial pathogens for decades. MRSA are regarded as HA-MRSA when infections caused by them are likely to be acquired in health care settings when they emerge at least 48 hours after admission in patients having particular risk factors such as prolonged hospital stay, care in intensive care units (ICUs), prolonged antibiotic treatment, surgical interventions, and/or close contact with MRSA-positive individuals (Salgado et al., 2003).

1.b) *Health Care Associated community MRSA* (HCA-MRSA) is associated with outpatients with MRSA infection/colonisation and previous hospitalization, such as residence in a nursing home, receiving of home nursing, attending centers for dialysis and/or centers for diabetes were MRSA of hospital origin has been introduced (Bartels et al., 2007).

2) *Community Associated MRSA* (CA-MRSA) emerge in the community, and patients affected lack the above mentioned risk factors. Close contact in sport settings, schools, day care centers, military settings and prisons, is among others considered a risk factor.

3) *Livestock Associated MRSA* (LA-MRSA) refers mainly to the clonal spread of a certain MRSA strain (ST398, see below) that colonise different food animal species (including horses) and may cause infections in humans.

Companion animals and horses may be colonised with a variety of strains due to their close contact with humans. Thus these species may act as carriers of MRSA originating from humans (a so called "humanosis") (Morgan, 2008).

Emergence in animals

During the period 1970-2000, MRSA has been sporadically isolated from animals, in particular cows, small companion animals, and horses. With the exception of some equine isolates, the nature of these cases suggested a human origin and no epidemics have been reported (Leonard and Markey, 2008). Thus, until the end of the 20th century both the scientific community and policy makers were convinced that MRSA in human medicine had nothing to do with animal husbandry but was a problem solely based on the antimicrobial use in human medicine (Anonymous, 1998). The situation has now changed, with an increased number of reports on LA-MRSA in livestock, especially swine and veal calves. MRSA has also been reported in companion animals and horses, as well as transmission between humans and animals (Leonard and Markey, 2008). Sometimes distinct animal specific-lineages such as LA-MRSA have been involved (Cuny et al., 2006;Voss et al., 2005), but in many occasions human associated MRSA genotypes have been isolated (Weese, 2008).

Zoonotic concerns

Persons in direct contact with MRSA-positive animals have shown to have an increased risk of carrying the same MRSA strains as the animals. This has been documented in small animal health care, equine hospitals and livestock environments (Morgan, 2008;Weese, 2008). Severe manifestations of LA MRSA in humans have been documented, including a recent outbreak in a Dutch hospital (Declercq et al., 2008;Wulf et al., 2008a). This emerging phenomenon represents a hazard that demands a bilateral management approach, taking both the animals and humans as potential sources of MRSA.

Molecular typing

The *mec*A gene is located on the mobile staphylococcal chromosomal cassette (SCC*mec*), and six major types have been found (I to VI). SCC*mec* types I-III are the most common in HA-MRSA (de Lencastre et al., 2007). These strains often carry additional plasmids or transposons enhancing the spread of resistance to two or more unrelated classes of antimicrobials (multiresistant). CA-MRSA typically harbour the smaller and possibly more mobile SCC*mec* type IV but also type V, while multiresistance is less common. These strains often carry an exotoxin - Panton Valentine Leukocidin toxin (PVL) - but the pathogenicity of this toxin is still under debate (Appelbaum, 2007). HA and CA-MRSA cannot be strictly separated because genotypic CA-MRSA are reported with increasing frequency in the health care environment (David et al., 2008;de Lencastre et al., 2007). LA-MRSA carry SCC*mec* types III, IV or V.

In addition to SCC*mec* typing which is relatively new and was discussed above, two important molecular typing techniques for differentiation of MRSA are pulsed field gel electrophoresis (PFGE) and multilocus sequence typing (MLST). In contrast to MLST, PFGE is less expensive but has the disadvantage of considerable variation of the results between laboratories. MLST and PFGE can assist in ascertaining if strains are clonally-related, but not all strains are typable with these methods. For example the typical LA-MRSA strain which belongs to sequence type (ST) 398 resists digestion by the *Sma*I enzyme by traditional PFGE and results are not interpretable (van, I et al., 2007). Some reports call these strains untypable or non-typable MRSA (UT or NT-MRSA). Recent evolutions in the genome can alter the MLST profiles, and strains approaching a certain type are defined as belonging to a clonal complex (CC). *Spa* typing is the third important genotyping method which can differentiate strains that are indistinguishable by PFGE or MLST. ST398 belongs to CC398, and examples of *spa* types found are t108, t011, t034 (van, I et al., 2007).

Throughout this document and unless otherwise specified, livestock associated MRSA (LA-MRSA) is the preferred term used as a synonym for UT-MRSA, NT-MRSA, MRSA ST398, and MRSA CC398.

The term colonization or carriage as used in the document refers to an individual person or animal that tests positive for MRSA in swabs from nares or throat (or other body sites) due to multiplication and settlement of MRSA not causing clinical symptoms (Scientific Opinion of the Panel on Biological Hazards on a request from the European Commission on Assessment of the Public Health significance of meticillin resistant *Staphylococcus aureus* (MRSA) in animals and foods. *The EFSA Journal* (2009) 993, 1-29).

EPIDEMIOLOGY & ECOLOGY OF MRSA

LIVESTOCK

Occurrence of MRSA

The first report of MRSA in livestock was a case of bovine mastitis in Belgium (Devriese et al., 1972). Although molecular typing methods were not available, biotyping strongly suggested a human origin of the isolate. Two decades later, investigations have found cattle also to be colonized by LA-MRSA, with 88% positive farms among Dutch veal calves rearing units studied (Graveland et al., 2008). Only occasional reports exist on dairy farms but in one study in Belgium, up to 15% of lactating cows in herds with a previous history of MRSA were positive (Vicca.J et al., 2008). In general, the occurrence of MRSA among bovine mastitis isolates is well studied and its prevalence seems to be very low (Hendriksen et al., 2008).

In 2005, a high prevalence of LA-MRSA was found in Dutch pigs in slaughterhouses (de Neeling et al., 2007). This study was undertaken following high colonization rates of pig farmers and relatives without known risk factors for MRSA (Voss et al., 2005). Other reports have confirmed these findings in different countries like Denmark (Guardabassi et al., 2007), Germany (Meemken et al., 2008), Canada (Khanna et al., 2008) and Belgium (Denis et al., 2008), and the predominant *spa* types found were t108, t034, and t011, all close relatives within CC398. The SCC*mec* element predominantly found was IV. In 2002, the isolation of this clone from pigs was reported in France for the first time, but the isolate was susceptible to meticillin (MSSA) (Armand-Lefevre et al., 2005). In a recent Canadian study (Khanna et al., 2008) an endemic HA-MRSA (US100) strain was found in pigs in addition to CC398. Among the cited porcine studies, the highest percentage of positive farms (living animals, not slaughterhouse) was found in Belgium with 34 out of 50 fattening pig farms studied being positive (68%).

In poultry, a Belgian study revealed a new *spa* type t1456 within CC398 to be present in 2 out of 14 randomly selected broiler farms (14.3%), but it was not found in 10 layer farms (Persoons et al., 2009). Similarly, Nemati et al. ((Nemati et al., 2008)) found 5 out of 39 Belgian broiler farms (12.8%) to be positive for LA-MRSA (CC398).

A detailed overview on the occurrence in food producing animals and derived products is given in the accompanying EFSA document (Scientific Opinion of the Panel on Biological Hazards on a request from the European Commission on Assessment of the Public Health significance of meticillin resistant *Staphylococcus aureus* (MRSA) in animals and foods. *The EFSA Journal* (2009) 993, 1-29).

To date, clinical infections with LA-MRSA in food producing animals have been described twice. The first report described a case of post-weaning dermatitis with 20% mortality in swine from the Netherlands, in which *spa* type t011 was found (van Duijkeren et al., 2007). A second report showed LA-MRSA to be present among Belgian bovine clinical and subclinical mastitis isolates (Vicca.J et al., 2008). So far, the LA-MRSA strains in the living animal have not been reported to possess PVL (Denis et al., 2008;van Duijkeren et al., 2008). On the contrary, in CC398 from predominantly healthy persons, a prevalence of 9.4% (3/32) of the PVL toxin was reported (van, I et al., 2007) although an Asian subclone was suggested for these isolates (Yu et al., 2008). Other MRSA clones harbouring PVL have nevertheless been found among living animals (Morgan, 2008).

Risk factors for colonisation and infection

Antimicrobial use

A causal relationship between the use of antimicrobial drugs and MRSA has been demonstrated in human medicine for different antimicrobial compounds in a recent meta-analysis (Tacconelli et al., 2008). It is probable that similar conditions apply also to animals, in particular since LA-MRSA are often co-resistant to several other antimicrobial agents as indicated below.

From January 1st 2006, antimicrobial growth promoters (AMGP) are no longer authorised for use in the European Union. Antimicrobials for animals are prescription only veterinary medicines. A therapeutic regimen in the strict sense requires a diagnosis. However, many treated animals are not sick at the initiation of the antimicrobial regimen. First, prevention of mainly respiratory and digestive disorders can be done by treating the animals in a known risk period during the production cycle. In addition, healthy animals sharing the same space (barn) with diseased individuals may be treated. Many experts consider preventive therapy necessary in the modern livestock industry. Such practices are common in the majority of intensively reared animals like broilers, fattening pigs and veal calves. Of a particular concern is that in preventive therapy, deviations from approved posology including underdosing and prolonged duration of treatment are common, and treatment is often initiated without diagnosis (Timmerman et al., 2006).

Since the vast majority of LA-MRSA are tetracycline (and trimethoprim) resistant (Kadlec and Schwarz, 2009), an association between the use of antibiotics in pig farming (Timmerman et al., 2006) and the widespread occurrence of MRSA has been hypothesed (de Neeling et al., 2007;Wulf et al., 2008a). Monitoring of antimicrobial consumption in the Netherlands (MARAN-2006) and Denmark (DANMAP-2006) has revealed an increased use of tetracyclines during the last five years. So far there is only one report demonstrating an association between the occurrence of MRSA in livestock and the use of antimicrobial agents. Van Duijkeren et al. (van Duijkeren et al., 2008) found the number of colonized pigs in farms applying oral group treatments, often with tetracyclines, to be higher compared to farms with no such use of antimicrobials. On the other hand, preliminary results from another ongoing porcine study, no such association was found (Broens et al., 2008). The isolation of LA-MRSA in the case report of dermatitis in swine (van Duijkeren et al., 2007) was preceded by unsuccessful therapy with different antimicrobial classes including cephalosporins (ceftiofur and cefquinome), macrolides, and potentiated sulphonamides. Additional genetic resistance markers, including the multidrug resistance gene *cfr*, could speed up the emergence of MRSA ST398 due to co-selection (Kehrenberg et al., 2009).

S. aureus infections in veterinary medicine are seldom treated with beta-lactamase resistant penicillins. The exception is intramammary use of isoxazolylpenicillins, amoxicillin combined with clavulanic acid and cephalosporins for dairy cows. Despite this practice for decades, the prevalence of MRSA among bovine *S. aureus* isolates has hitherto been absent or fairly low.

Other risk factors

A lower prevalence of MRSA was found among sows compared with piglets and finishers in a Belgian survey. In addition, this survey revealed a marked difference in the number of MRSA positive animals between open (94%) and closed farms (56%) (Denis et al., 2008). This is in line with a Dutch survey which indicated transmission of LA-MRSA within the production chain, e.g. from multiplier to finisher farms (van Duijkeren et al., 2008). Piglets in these multiplier farms can be colonized by different routes or vectors, and longitudinal studies are needed to indicate if the environment, e.g. feed or dust or the sows are the primary source of colonization (de Neeling et al., 2007).

Human contact hazard

Epidemiological studies in the Netherlands have indicated that contact with veal calves or pigs was significantly associated with CC398 (van Rijen et al., 2008;Voss et al., 2005). In the Netherlands,

farmers from swine and veal calves are now considered a defined risk group which is screened upon admission to hospitals (Wulf et al., 2008a).
The occupational hazard for LA-MRSA colonization through (the intensity of) pig contact has been confirmed in Belgian farmers (Denis et al., 2008), regional German investigations (Meemken et al., 2008) and at an international veterinarian conference in Denmark (Wulf et al., 2008b). Remarkably in two of the studies, and in contrast with conclusions drawn from a Canadian study on horse units (Anderson et al., 2008), current hygiene measures (e.g. wearing a mask) were not found to be protective for MRSA carriage (Denis et al., 2008;Wulf et al., 2008b). Veterinary practitioners are at risk for MRSA, which is clearly demonstrated in countries with a low overall MRSA prevalence like Denmark (Moodley et al., 2008).
Infections of humans with LA-MRSA have been described since 2004 (Voss et al., 2005), with an increasing frequency in the Netherlands (van Rijen et al., 2008) and Denmark (Lewis et al., 2008). Examples of severe infections are an aggressive soft tissue infection of a pig inflicted bite wound (Declercq et al., 2008) and endocarditis (Ekkelenkamp et al., 2006). An outbreak in a surgical ward at a Dutch hospital also has been described (Wulf et al., 2008a).

HORSES

Occurrence of MRSA

The first report on the isolation of MRSA in horses was published in 1996; from 1989 to 1991 MRSA was isolated from 13 mares with metritis in Japan. The source was thought to be a stallion on a stud farm which 10 of the mares had visited. PFGE showed that the isolates had indistinguishable patterns (Anzai et al., 1996;Shimizu et al., 1997). To date, MRSA has been isolated from horses in Europe, Asia and North America (Baptiste et al., 2005;Hartmann et al., 1997;Middleton et al., 2005;Moodley et al., 2008;O'Mahony et al., 2005;Shimizu et al., 1997;Van den et al., 2009;Weese et al., 2005;Witte et al., 2007). Wound and postoperative infections with MRSA tend to be most common (Leonard and Markey, 2008).
Weese et al. (Weese et al., 2006c) found that 5.3 % of horses at a Canadian veterinary teaching hospital and 4.7 % of horses on farms in Canada and the USA were colonized with MRSA. Cuny et al. (Cuny et al., 2006) reported 24 MRSA infections among 768 clinical samples from horses at a veterinary teaching hospital in Austria and an estimated infection rate of 4.8 MRSA cases per 1000 equine admissions. In a recent study investigating 110 horses presented at a Belgian equine clinic 10.9 % of the horses carried MRSA. All isolates in this latter study were LA-MRSA (non-typeable by PFGE using *SmaI* digestion) and belonged to spa types t011 and t1451 (Van den et al., 2009). In Sweden, one of 300 horses admitted to four equine clinics carried MRSA CC398 spa type t011 (SVARM-2007). In an equine clinic in Belgium MRSA CC398 spa type t011 were isolated from various infections of 13 hospitalized horses (Hermans et al., 2008). Busscher at al. (Busscher et al., 2006) did not find any MRSA among 200 healthy horses in the community in the Netherlands, nor Vengust et al. (Vengust et al., 2006) in nasal samples of 300 healthy horses from 14 farms in Slovenia.

Risk factors for colonisation and infection

Antimicrobial use

Antimicrobial administration within 30 days before admission to a veterinary teaching hospital was a risk factor for MRSA colonization in horses (Weese and Lefebvre, 2007). Administration of ceftiofur or aminoglycosides during hospitalization was a risk factor associated with nosocomial MRSA colonization of horses (Weese et al., 2006c).

Other risk factors

Weese and Lefebvre (Weese and Lefebvre, 2007) evaluated factors associated with MRSA colonization of horses at the time of admission to a veterinary teaching hospital. Previous colonization of the horse, presence of colonized horses on the farm, admission to the neonatal intensive care unit and admission to a service other than the surgical service were risk factors for community-associated colonization. Weese et al. (Weese et al., 2006c) found that horses colonized at admission at a horse clinic were more likely to develop clinical MRSA infection than those not colonized at admission. The

overall incidence rate of nosocomial MRSA colonization was 23 per 1,000 admissions, and that of nosocomial MRSA infection was 1.8 per 1,000 admissions, with an incidence density of 0.88 per 1,000 patient days. Residence on a farm that housed more than 20 horses was a factor significantly associated with MRSA colonization (Weese et al., 2005).

Human contact hazard

Occupational or recreational exposure to horses has been incriminated as a risk factor for human MRSA colonization (Weese et al., 2006a). Nasal carriage was significantly higher among veterinary practitioners (3.9 %) than among persons not professionally exposed to animals (0.7 %) or among healthy persons in the Danish community (< 1%). Exposure to horses was found to be a risk factor (Moodley et al., 2008). Colonization with MRSA was found in 10.1 % of veterinary personnel attending an international equine veterinary conference. An increased risk of being colonized was associated with having treated a horse diagnosed with MRSA or having been personally diagnosed with MRSA in the past year. Hand washing between infected patients and hand washing between farms was protective (Anderson et al., 2008).

Several studies report that MRSA isolates from horses and people working with horses are indistinguishable and differ from MRSA isolates from humans in the general population (Cuny et al., 2008;O'Mahony et al., 2005;Seguin et al., 1999;Weese et al., 2005). In Austria ST254, spa type t036, SCC*mec* type IV predominated in horses followed by ST398 (t011, SCC*mec*IV) and ST1 (t127, SCC*mec*IV) (Cuny et al., 2008). In Canada the majority of equine isolates are ST8 (t008, SCC*mec*IV). In the Netherlands most equine MRSA are either ST398 spa type t011 or ST8 spa type t064 (van Duijkeren E., personal communication). From 2000 to 2002, 27 persons were found colonized with MRSA at a Canadian veterinary teaching hospital and 10 horse farms. Only one person, a veterinarian working at the clinic, had clinical infection, and the same strain was isolated from two horses he had cared for (Weese, 2004). Human skin infections were also reported from three persons working in a foal nursery and MRSA-isolates from the humans and the foal were indistinguishable by PFGE (Weese et al., 2006a).

COMPANION ANIMALS

Occurrence of MRSA

In 1988 Scott et al. (Scott et al., 1988) reported the first companion-animal related outbreak of MRSA in a rehabilitation geriatric ward where the ward cat was colonized and was implicated as reservoir for re-infection. Infection control measures and removal of the cat led to rapid resolution of the outbreak. Since, the number of reports on infections and colonisation with MRSA from companion animals has increased (Leonard and Markey, 2008). The transmission of a PVL positive MRSA strain between humans and a dog has been reported (van Duijkeren et al., 2004). The available evidence suggests that humans are the source of infection or colonisation of companion animals and thus a probable 'humanosis' exists, but animals can act as carriers and pass the infecting strain to humans in contact (Strommenger et al., 2006).

Healthy animals can be colonized for variable periods of time without developing clinical disease (Weese, 2005a), but the overall prevalence of the colonization remains low among dogs and cats (Abbott et al., 2006;Abraham et al., 2007;Hanselman et al., 2008;Leonard and Markey, 2008;Loeffler et al., 2005;Middleton et al., 2005;Weese et al., 2006b). Potential differences with the human epidemiology of the disease, particularly the dynamics of colonization in companion animals (e.g. shedding, type of contacts and duration of colonization) may exist and are inadequately identified.

Little is known about the prevalence of MRSA infections in companion animals. MRSA infections cannot be recognized from their clinical presentations alone because they resemble those caused by meticillin-susceptible *S. aureus*, *S. intermedius/pseudintermedius* and coagulase-negative staphylococci (Lloyd et al., 2007). *S. aureus* can give rise to a wide diversity of suppurative infections in animals. In line with that, MRSA have been isolated from diverse skin and soft tissue infections including abscesses, dermatitis, post-operative wound infections, and intravenous catheter or surgical implant infections (Baptiste et al., 2005;Bender et al., 2005;Duquette and Nuttall, 2004;Leonard et al., 2006;Leonard and Markey, 2008;Middleton et al., 2005;Owen et al., 2004;Seguin et al., 1999;Tomlin et al., 1999;Weese et al., 2006b). Morris *et al.* (Morris et al., 2006) reported that MRSA were significantly more frequently associated with deep pyoderma in dogs than other strains of *S. aureus*. Less frequently MRSA has been isolated from lower urinary tract infection, pneumonia, and chronic rhinitis (Baptiste et al., 2005;Gortel et al., 1999;Weese et al., 2006b).

Risk factors for colonisation and infection

Antimicrobial use

Little information is available to date on the risk of antimicrobial usage with regard to MRSA infection or colonization in companion animals. According to case reports quoted above, many animals infected or colonized with MRSA have been treated with antimicrobials prior to the diagnosis. Fluoroquinolone administration has been identified as a risk factor for MRSA infections in dogs and cats (Baptiste et al., 2005;Faires and Weese, 2008).

Other risk factors

Studies on risk factors other than antimicrobials for MRSA infections in companion animals are scarce. MRSA positive households or healthcare workers owners constitute risk factors for this companion animal humanosis (Baptiste et al., 2005;Faires and Weese, 2008;van Duijkeren et al., 2004;van Duijkeren et al., 2005).

MRSA infections in small animals have also been associated with exposure to medical hospitals, extensive wounds, prolonged hospitalization and immunosuppression (Duquette and Nuttall, 2004). In a retrospective case-control study at three veterinary referral hospitals significant risk factors for the acquisition of a MRSA infection compared to a MSSA infection was the presence of a urinary catheter or a joint infection (Faires and Weese, 2008). Invasive procedures, including the presence of foreign material such as suture material, orthopedic implants, urinary catheters, central venous lines and chest drains appear to be associated with the persistence of MRSA infections (Gaschen, 2008;Leonard et al., 2006). Other identified risk factors associated with surgical site infections in general, but highly

relevant in particular for staphylococci infections, include: improper surgical site clipping and aseptic preparation before surgery, duration of surgery, duration of anesthesia, emergency versus daytime surgery, surgical tissue handling, number of persons present in the operating room, and total length of hospital stay (Gaschen, 2008). Small animal intensive care units may be at particular risk for periodic outbreaks of colonization and disease as reported by Weese et al (Weese et al., 2007).
Transmission of MRSA infection between dogs apparently can be associated with contamination of the floor in a veterinary clinic (Abbott Y. and Leonard F.C., personal communication). Thus, in veterinary medicine cleanliness of floors appear to be as important as hand-touch sites in the control of human MRSA infections.

Human contact hazard

Several studies have examined the prevalence of MRSA in veterinary hospitals in the United Kingdom (Hanselman et al., 2008;Loeffler et al., 2005;O'Mahony et al., 2005). These studies have shown that veterinary staff and their pets have a higher prevalence of MRSA, although they mostly are asymptomatic carriers. A recent study by Moodley et al. (Moodley et al., 2008) showed that MRSA carriage was significantly ($P<0.02$) higher among the veterinary practitioners (3.9%) than among the participants not professionally exposed to animals (0.7%). The results from this study indicate that veterinary professionals are at risk of MRSA carriage and thus should be informed about this emerging occupational health risk and educated about preventive measures.
MRSA infections in owners with involvement of their companion animals like dogs and cats have been suggested for many years, and evidence for this hazard has increased during recent years (Leonard and Markey, 2008;Morgan, 2008;van Duijkeren et al., 2004;van Duijkeren et al., 2005). Larger epidemiological studies are required to provide more information on specific risk factors.

CURRENT MANAGEMENT AND THERAPEUTICAL OPTIONS

As discussed previously, exposure to antimicrobials is a risk factor for acquisition and spread of MRSA in humans and most probably also in animals. Strategies for prevention and management of MRSA in animals should therefore as far as possible not rely on the use of antimicrobials. Further, such strategies include consideration of the overall use of antimicrobials.

If, for animal welfare reasons, antimicrobial treatment is necessary in individual cases, the risk of emergence of further resistance in the strain of MRSA colonizing the animals needs to be managed, in particular considering zoonotic aspects. Options to manage the risk are e.g. not to use of antimicrobials that are last resort for treatment or decolonisation of MRSA in humans, contact isolation of the animal during treatment, and monitoring the effects of treatment on resistance in the strain through selective culture and susceptibility tests, should MRSA be re-isolated.

Of importance, in the present document the applied definition of ‘antimicrobial agent’ does not include commonly used local antiseptics and disinfectants, like e.g. chlorhexidine, alcohol, or soaps.

LIVESTOCK

Reduction of antimicrobial selective pressure

A reduction of the selective pressure by avoiding routine mass medication could be a major potential control measure. An additional benefit of this measure would be to preserve the efficacy of the current antimicrobials for veterinary and human use.

To confirm a reduction of antimicrobial consumption, detailed information on the applied therapies is necessary, with respect for animal species and the route of administration. Preferably the indication, the production system (e.g. broiler versus layer), and the regimens applied needs to be documented in detail (dose, duration, formulation, treatment interval).

Prevention of transmission of MRSA between and within farms

Given the efficient transmission of LA-MRSA throughout the production chain as shown for swine (van Duijkeren et al., 2008), one way to reduce the dissemination of MRSA from farm to farm would be to improve biosecurity between herds and during transport. The piglet suppliers form a first target for this approach, which then might be gradually implemented throughout the food chain. Prevention of trade from MRSA-positive to –negative herds could be considered.

The stand-alone period is a corner stone to reduce the persistence of bacterial organisms between production cycles. Research on disinfection measures in different production types are needed in view of the current MRSA situation, primarily in pigs, veal calves and broilers. Conversion of the current stable structures might be considered for a more efficient disinfection via mechanical, physical (drying), chemical (e.g. chlorhexidine), and thermal (burning, steaming, and cold) cleansing.

Reduction of carriers in MRSA-positive farms

Control options for colonized animals

Non-antimicrobial management
Sanitary control measures can gradually be implemented in affected livestock, and be conceptually based on other applied eradication programs in livestock. Given the amount of MRSA positive animals in many production types, culling of colonized animals may have economical repercussions.

Means to decontaminate colonized animals through e.g. chlorite bathing could be experimentally studied. LA-MRSA is transmissible between different animal species and between animals, farmers, and other potential sources, and these transmission and re-infection routes need to be documented, including their relative importance for the epidemiology of LA-MRSA, to allow preventive measures to be taken.

Strict implementation of hygienic measures might be difficult on livestock farms. In addition there is an apparent inefficiency of current biosecurity measures on the occurrence of MRSA, especially in pig farms (Denis et al., 2008;Wulf et al., 2008b). These observations urgently warrant further specific research.

Antimicrobial treatment in colonized animals
Decolonization procedures, such as those that are used in individual human patients, in the living animal are logistically difficult to apply to numerous living animals. Such procedures are expensive and likely to evoke resistance towards the antimicrobial agents used, because the amount of target animals is high.

Control options for infected animals

Non-antimicrobial management
All other diagnoses need to be excluded prior to defining a bacterial infection. Affected animals need to be immediately separated from healthy animals to stop further spread. Culling of infected animals is a further option.

Destruction of milk from animals with MRSA mastitis is a prerequisite for avoiding transmission. An option in exceptional cases would be premature drying-off of the infected quarter. The most stringent measure in modern dairy systems is culling of these affected cows. Common procedures to control contagious mastitis need to be followed as recommended in guidelines (NMC-2009, A Practical Look at Contagious Mastitis, http://nmconline.org/contmast.htm).

Local treatment with antiseptics such as glycerol, chlorhexidine, or povidone iodine might be considered in wound infections. It should be noted that studies on the efficacy of such compounds in MRSA-infected livestock are not available.

The clonal nature of the LA-MRSA may offer potential for vaccine development. The efficacy for prevention of colonization also needs to be investigated. Exploration of the efficacy and safety of this and similar measures could be extended to prevention of colonization.

Antimicrobial treatment of infected animals

Before any antimicrobial treatment of MRSA infections in livestock is considered, the risk for development of further resistance needs to be taken into account. The benefit/risk ratio for antimicrobial treatment needs to be compared with alternatives.

In individual animals where antimicrobials are deemed necessary, the choice of the antimicrobial should always be based on susceptibility testing. Every effort should be made to ensure efficacious treatment by ascertaining an appropriate concentration at the site of the infection.

One report described cases of porcine dermatitis caused by LA-MRSA (CC398), which failed to be cured after empiric therapy with cephalosporins, macrolides and potentiated sulphonamides. Fluoroquinolones were in this case clinically successful (van Duijkeren et al., 2007) but there was no microbiological follow up.

In different countries, different clones of MRSA are predominant, and antimicrobial susceptibilities may also vary. Most isolates of LA-MRSA are resistant to tetracyclines (including doxycycline) and trimethoprim (Nemati et al., 2008). During antimicrobial therapy the clinical response needs to be monitored to ensure that further resistance has not developed.

Antimicrobials such as vancomycin, linezolid and teicoplanin are critical for MRSA treatment in human medicine. In veterinary medicine these antimicrobials have no maximum residue limit (MRL), therefore they are not allowed and should not be used in animals intended for food production (Council Regulation (EEC) No 2377/90). In addition there are ethical concerns about their use in veterinary medicine.

Prevention of transmission of MRSA strains among livestock

Because of the high colonization frequency in healthy animals and the relatively few documented infections, control options suggested in the last paragraph under the heading: *Prevention of transmission of MRSA between and within farms* are applicable.

In addition, control options given below in a more specified form for horses and small companion animals can be extrapolated here, in line with general principles for control of bacterial infections as developed (BSAVA-2009, www.bsava.com).

- Identification and isolation of animals to minimize the risk of zoonotic transmission
- Use contact precautions such as protective outwear like overalls, aprons or coats and boots or overshoes that are not worn elsewhere, gloves and masks.
- Protective outwear and all items handled during the treatment of an MRSA positive animals (e.g. boards to drive livestock), should be regarded as potentially contaminated
- Hand hygiene, e.g. through alcohol gel pouches is essential but need to be performed correctly.
- Proper cleaning and disinfection of contaminated environments, including transport vehicles. Special attention should be paid to dust in stables.
- Owners should be informed about the risks and required precautions.

HORSES

Control options for colonised horses

Non-antimicrobial management

A Canadian study describes a case where active screening and strict implementation of infection control protocols resulted in a rapid decrease in number of colonized horses on two farms. At farm A 17% of the horses and 10% of the farm personnel were colonized and at farm B 43% of the horses and 17% of the farm personnel were colonized with Canadian MRSA-5 which is known to be ST8. The majority of horses became MRSA-negative without antimicrobial treatment. On farm A colonisation was eradicated, while only 2 (3%) colonized horses remained on farm B at the end of the study (Weese and Rousseau, 2005). The authors concluded that the infection control program was, at least in part, responsible for the decline in colonization (no control group was investigated) and that antimicrobial therapy is not required for eradication of colonization and control of MRSA on horse farms.

Antimicrobial treatment in colonized horses

Information on the antimicrobial treatment of colonized horses is scarce. Colonization with CMRSA-5 is often transient in adult horses, and colonization can be eliminated if proper measures are taken to prevent reinfection from other horses, people and the environment (Weese et al., 2004). However, we do not know if this applies to other MRSA types. Antimicrobial therapy should therefore, if applied, be reserved for persistent colonisations or for those cases where other control measures are impossible.

Applying topical antimicrobials to the nares of horses seems unpractical, although nebulisation (e.g. with amikacin) might be an alternative (Weese and Rousseau, 2005). Safety and efficacy of this therapy needs to be further evaluated before it can be recommended. Oral or parenteral administration could be used, but data on their efficacy are scarce.

Control options for infected horses

Non-antimicrobial management

A fast and accurate diagnosis is essential for the management of MRSA infections. Therefore, all post-operative infections need to be cultured routinely. In addition, non-healing wounds, and infections not responding to antimicrobial therapy should be suspected. Failure to detect MRSA at an early stage can lead to suboptimal treatment of patients and to late identification of an outbreak, facilitating the spread of MRSA (Weese, 2008). Local treatment with antiseptics such as glycerol, chlorhexidine, or povidone iodine can be used in wound infections. However, studies on their efficacy in MRSA infected horses are not available to date.

Antimicrobial treatment in infected horses

When considering antimicrobial therapy of animals infected with MRSA, the risk for further development of resistance in the infecting strain needs to be considered. The choice of the antimicrobial should always be based on susceptibility testing. Many equine MRSA are still susceptible to routine antibiotics. However, in different countries different clones of MRSA are predominant and also antimicrobial susceptibilities may vary between isolates. During antimicrobial therapy the clinical response should be monitored carefully. Studies comparing the efficacy of different antimicrobial strategies in infected horses are lacking, but are urgently needed.

The efficacy and safety of antimicrobials that are critical for MRSA treatment in human medicine like vancomycin, linezolid and teicoplanin have not been assessed in horses and similarly to livestock there are ethical concerns about using them in veterinary medicine. Therefore the use of these antimicrobials is not advisable.

Prevention of transmission of MRSA strains between horses

Guidelines on the management of MRSA in veterinary practices have been developed by the British Small Animal Veterinary Association (BSAVA-2009, www.bsava.com) and are applicable also to equine hospitals. It is recommended that patients diagnosed with or suspected of MRSA infections are isolated in order to minimize the risk of nosocomial and zoonotic transmission. MRSA-infected animals should be nursed using barrier nursing precautions and staff contact should be limited to what is essential. Infected horses should only be handled using contact precautions such as protective outwear like overalls, aprons or coats and boots or overshoes that are not worn elsewhere, gloves and masks. MRSA-infected wounds should be covered with clean bandages if possible. Personnel must avoid contaminating themselves. All items handled during the treatment of an MRSA positive patient should be regarded as potentially contaminated, e.g. electric shavers.

Transmission of the organism on the hands is thought to be an important route of transmission within human and veterinary hospital settings. Therefore, hand hygiene should be an essential part of any infection control program. Hand washing should be carried out between patients. Alcohol gel pouches for wearing on uniforms can be used as a rapid and convenient method of hand sanitizing (Leonard and Markey, 2008).

Proper cleaning and disinfection of contaminated environments is also highly recommended, because widespread contamination of the environment of a veterinary hospital environment has been reported (Weese et al., 2004;Weese, 2008). Environmental transmission may be of greater importance in stables than in hospitals (Leonard and Markey, 2008). Horse stables are often very dusty.

Routine screening of all horses before admission in order to identify colonized or infected animals could help to prevent the spread of MRSA, but is costly. Screening of hospitalized horses which have been in contact with MRSA positive horses or personnel is recommended.

Owners of infected horses need to be informed about the risks of MRSA and the precautions they should take. Furthermore the recommendation from BSAVA that owners visiting their infected animal should not visit other patients at the clinic is also applicable to horses practices.

COMPANION ANIMALS

Given the available evidence that MRSA found in companion animals share the same genetical background as MRSA strains common in human infections for this reason experience from human medicine is likely to be applicable to companion animals.

Control options for colonized companion animals

Non-antimicrobial management

Routine decolonization therapy is not recommended in humans or animals that have mucosae colonized with MRSA (http://www.ccar-ccra.com/english/pdfs/R06-716_barton_9745.pdf). At present there is no evidence of the effectiveness of various procedures to decolonize companion animals. Non-antimicrobial management may include baths with e.g. chlorhexidine which may help to decontaminate the coat but does not address other colonized sites such as oropharynx.

Persistent colonization has not yet been reported in companion animals, and some pets appear to eliminate MRSA carriage spontaneously if re-colonisation is prevented (Weese et al., 2006b). This may constitute an important factor for MRSA control but long term studies are needed to confirm this.

Antimicrobial treatment of colonized companion animals

Given the potential for MRSA selection including additional resistance markers, antimicrobial therapy could be questioned unless in cases with persistent colonisations or for those cases where other control measures are impossible, Antimicrobial therapy may be considered in individual MRSA colonized animals as an option to control transmission of MRSA between animals or from animals to humans. In addition, strategic control programmes could include decolonization in specific circumstances.

As yet, no antimicrobial drugs for veterinary medicine have been adequately studied and approved for local or systemic application intended to decolonize MRSA carrier animals.

Case reports of successful eradication therapy in one MRSA colonised dog with a combination of ciprofloxacin and rifampin and another with rifampin and doxycycline have been described (van Duijkeren et al., 2004;van Duijkeren et al., 2005). Decolonisation with antimicrobials may involve a risk of selection of MRSA strains resistant to the agent applied. Noteworthy is a report on high level mupirocin resistance (>256 mg/l) of *S. aureus* isolated in two cases of post-operative infections in dogs and in one case of lower urinary tract infection in a cat (Weese et al., 2006b). Fusidic acid resistance was also reported in an MRSA isolate from a seal (O'Mahony et al., 2005).

Topical agents used in humans for decolonisation are mupirocin and fusidic acid alone or in combination with other topical agents such as chlorhexidine or bacitracin. Systemic antimicrobials used include cotrimoxazole (trimethoprim + sulphonamides), rifampicin, and doxycycline, in general given by the oral route (Coia et al., 2006;Ulvatne, 2003).

As for livestock and horses, the use of antimicrobials in pets of antimicrobials that are critical for MRSA treatment in human is controversial, due to the risk for development of resistance against those agents. In some countries veterinary use of some antimicrobials, including mupirocin is limited to exceptional conditions or prohibited by law.

Control options for infected companion animals

Non-antimicrobial management

In some cases of wound infections in systemically healthy animals, meticulous local wound management may avoid the need for local or parenteral antimicrobial therapy (Lloyd et al., 2007). This was the case described in a report on a dog with a wound MRSA infection that had been treated with marbofloxacin and resolved after stopping antimicrobial therapy, debridement of the wound and administration of anti-inflammatory steroids (van Duijkeren et al., 2003). Superficial infections such as uncomplicated wound or incision infections can be treated with a variety of topical agents, including silver sulfadiazine, or a combination of 1% silver sulfadiazine and 0.2% chlorhexidine digluconate (Weese, 2005b). Whenever topical therapy alone is used, close monitoring progression of local disease or development of bacteraemia and systemic disease is required (Weese, 2005b).

Antimicrobial treatment of infected companion animals

As the clinical manifestations of MRSA infections in animals are variable, no single treatment protocol is suitable for all animals. The treatment must be tailored to the individual patient (Lloyd et al., 2007). When choosing a treatment plan, the risk for development of resistance in the MRSA infecting strain needs to be considered. In addition, several factors should be taken into account: i) the susceptibility profile of the MRSA isolated from the animal patient ii) the severity of the infection and presence of systemic disease (fever, leukocytosis) iii) the patient's underlying disease or any co-morbidity (Lloyd et al., 2007). Local antimicrobial therapy may be an option in certain cases (Owen et al., 2004), while in some patients systemic antibiotic therapy may be required. The decision of treatment or eventual animal euthanasia should take into account available national veterinary guidelines for infection control. Information on treatment and outcome of MRSA infections in companion animals is scarce.

Tomlin *et al.* (Tomlin et al., 1999) described treatment of 11 MRSA infections in dogs: six occurred after surgical treatment, two as complication of wounds, and 3 in dogs with recurrent pyoderma secondary to primary diseases such as atopic dermatitis, demodicosis and hypothyroidism. Wound and surgical treatment as well as oral antibiotic treatment (trimethoprim-sulphadiazine, ciprofloxacin, enrofloxacin and clindamycin) based on culture and susceptibility testing clinically cured infection in 9 of 11 dogs. Clindamycin could be a potential candidate for MRSA skin, soft tissue and bone infections. However, Rich *et al.* (Rich et al., 2005) identified inducible resistance to clindamycin which could compromise success of therapy.

MRSA sepsis is rare in companion animals. Antimicrobial therapy of these patients is challenging as some MRSA strains may not be susceptible to any of bactericidal agents which can be administered intravenously (e.g. cephalosporins, aminoglycosides, and fluoroquinolones) which would generally be chosen. Treatment options for human invasive MRSA infections currently include vancomycin, linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin but adequate data to support the use of these compounds in companion animals are not available. Resistance to new antimicrobials (linezolid, daptomycin, tigecycline) has also been reported (Moreillon, 2008). Additionally, a number of compounds for human use to combat the growing resistance problems are in development, including novel glycopeptides (dalbavancin, telavancin, and oritavancin), and next-generation cephalosporins (ceftobiprole and ceftaroline), which demonstrate excellent *in vitro* activity against MRSA, vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA).

Veterinary use of antimicrobials that are last resort for human MRSA infections (e.g glycopeptides, oxazolidones, tigecycline, and streptogramins) is undesirable as it will increase the risk for emergence and spread of resistance.

Prevention of transmission of MRSA between companion animals

Guidelines for control and prevention of MRSA infection in small animals have been prepared by the British Small Animal Veterinary Association (BSAVA) (www.bsava.com). Stringent household infection control practices, in particular frequent hand hygiene and avoiding high risk contact are important factors to minimize the risk of getting colonized. In the event of rare situations where MRSA infections are uncontrolled in people in the household and the entire family is undergoing eradication therapy, kennelling the pet, preferably using contact isolation to other pets, for weeks is a reasonable option. This may allow the clearance of colonization and avoid cross-contamination. Little is known about the nature and length of colonization in companion animals. Further studies are required to reach conclusions.

Use of latex gloves and protection measures such as masks and eye protection may be helpful provided they are appropriately used and changed between patients. For instance, it is recommended to rub the hands with alcohol immediately after the gloves are removed. Hand hygiene and disinfection of surfaces and equipment should be carried out between all patients. Finally, additional barrier precautions must be considered based on the conditions present in the hospital.

Additional simple strategies can effectively reduce the risk of nosocomial infections – including MRSA- in small animal patients. First, limitation of the extrinsic risk factors is the most logical approach: i) invasive procedures should be restricted, ii) surgical interventions should be designed to avoid the many risk factors for surgical site infections, iii) indwelling urinary catheters should be removed as soon as the patient's condition allows it, iv) the consequences of antibiotic use in dogs and cats with indwelling urinary catheters should also be evaluated, and v) proper care of intravenous and urinary catheters is essential to prevent complications (Gaschen, 2008). Protocols for asepsis prior to and during placement of the catheter should exist. Intensive care units (ICU) may be at particular risk for periodic outbreaks of colonization and disease, but can be curtailed by barrier precautions, and hand hygiene (Weese et al., 2007).

In veterinary hospitals, animals with suspected MRSA infections (animals with non-healing wounds, with non-antibiotic responsive infections or with nosocomial infections), animals from known MRSA-positive households, or those belonging to healthcare workers should be screened for MRSA colonization. The implementation of the “search-and-destroy” strategy as successfully applied in human medicine by certain Northern European countries could possibly be applied in small animal hospitals, given that the time for MRSA detection and the length of hospital stay allow implementing additional control options. Concerns have been raised about dogs involved in hospital visitation programs such as therapy pets (Enoch et al., 2005).

PEOPLE IN CONTACT WITH LIVE ANIMALS

There is a need for educational programmes for veterinarians to be organised by the competent authorities taking the regional differences in occurrence of MRSA in the hospital, community, and animal husbandry into account. Such programs should include information to farmers and owners of infected animals.

Co-operation between medical and veterinary professions is a vital requirement not only to identify human carriers and to implement effective control measures. Owners, farmers and their house hold contacts (possibly including children, elderly, and immunosuppressed people) are at risk after exposure to an infected/colonized MRSA animal. Basic hygienic measures have been shown to be protective in practice (Anderson et al., 2008), although knowledge and compliance to protective behaviour that help reduce the risk of zoonotic transmission in general could substantially be improved among veterinarians (Wright et al., 2008). Clearly, for all people having contact with the living animal, appropriate hygiene and covering wounds and skin lesions are the two corner stones in minimising the spread of MRSA between individuals, including the transmission from animals to humans and vice versa. Essential are correct hand washing, alcohol-based hand sanitizers and their availability in e.g. consulting rooms, animal units, and on farms. Especially for contact with suspected wounds, body fluids or other contaminated materials, the use of disposable aprons, gloves, masks, and eye protection are appropriate.

Surveillance of veterinary staff, farmers or owners for MRSA carriage is controversial and it is an issue that requires confidentiality. Ethical and privacy concerns needs to be considered during the preparation of further guidelines.

SUMMARY ASSESSMENT

Conclusions on ecology and epidemiology

GENERAL

- MRSA is resistant to virtually all beta-lactam agents. In human medicine there is evidence that the use of a variety of antimicrobial agents is a major risk factor for colonisation and infection.
- While in companion animals the MRSA strains are evolutionarily related to different typical human associated MRSA clones, this is not the case for the clonally spreading MRSA CC398 found in food producing animals.
- All the major lineages of MRSA strains in companion animals, horses and in livestock are able to infect animals and humans. Severe infections have been described.

LIVESTOCK

- The recently discovered MRSA strain, CC398, has emerged in the livestock production chain pre-harvest, mainly in intensified production systems like fattening pigs, veal calves and broilers.
- Both efficient transmission of CC398 between farms and high within-herd prevalence have been documented in multiple Member States and also outside Europe.
- As with human medicine, antimicrobial consumption is considered a driving force in the emergence and spread of CC398.
- Molecular studies support the hypothesis that co-selection by non-betalactam agents probably contributes to the high prevalence of CC398.
- Monitoring of antimicrobial consumption in veterinary medicine is lacking in most countries. Such monitoring is required to provide additional evidence for the causal relationship with the occurrence of MRSA CC398.

HORSES

- Horses can be colonised and infected by specific lineages of MRSA, of which CC398 is one.
- Case studies suggest equine hospitals to be at a high risk, and postsurgical infections can lead to epidemics within such settings.
- Studies indicate that antimicrobial use is a risk factor for MRSA carriage in horses, which agrees with the evidence from MRSA epidemiology in human medicine.

COMPANION ANIMALS

- Intensive contact of humans with companion animals results in the exchange of typically human MRSA clones.
- MRSA contamination can lead to colonisation, to infection especially after surgery, and to cross-transmission between owners, veterinary personnel and other companion animals.
- Studies indicate that antimicrobial use is a risk factor for MRSA carriage in companion animals, which agrees with the evidence from MRSA epidemiology in human medicine.

Conclusion on control and therapeutic options

GENERAL

- Based upon extrapolations from human medicine, biosecurity and reduction of antimicrobial selection pressure are cornerstones in constraining the spread of MRSA in animal husbandry.
- Biosecurity and infection control measures depend on the animal species and specific settings.
- Hygiene measures such as hand disinfection and adequate wound management are essential.
- For surveillance purposes, records for antimicrobial consumption need to be detailed, including e.g. information of the animal species and regimen applied (e.g. dose and route of administration), to evaluate the compliance to and effect of antibiotic policies.
- Limitation of veterinary use of critical and new agents for MRSA infections in humans needs to be considered. No MRLs are set for such substances and they cannot be used for food producing animals. Their use in companion animals and non-food producing horses is also questionable, due to the risk for development of resistance against these agents and subsequent spread of resistant bacteria to humans.
- Studies have to document the long-term carriage of MRSA, and find efficient ways to decolonize animals and to clear different animal husbandry settings.

LIVESTOCK

- The extensive use of antimicrobials for prevention of disease appears to be an important risk factor for the spread of MRSA although data are still sparse.
- Taking into account the occurrence of CC398 in different Member States the multi-faceted approach is advisable whereby infection control strategies and surveillance are integrated.
- Biosecurity measures that disrupt the spread to, within and between farms need to be documented and investigated for their efficacy and long term effect. A focus on avoiding transmission via trade is advisable.

HORSES AND COMPANION ANIMALS

- Well controlled hygiene and quarantine measures are needed to clear hospital epidemics.
- Strategies that effectively reduce the risk of hospital acquired infections, including MRSA, need to be applied. One component of such strategies would be to limit the prophylactic use of antimicrobials related to surgery.

PEOPLE IN CONTACT WITH LIVE ANIMALS

- Close collaboration between human and veterinary experts, coupled with appropriate education is necessary to develop adequate management guidelines.
- Risk mitigation measures to limit spread of MRSA between animals needs to consider humans in contact with animals.

ABBREVIATION KEY

BSAVA	British Small Animal Veterinary Association
BSI	blood stream infections
CA	community associated (acquired)
CC	clonal complex
CI	confidence interval
CNS	coagulase negative staphylococci
CVMP	Committee for Medicinal Products for Veterinary Use
DANMAP	Danish Integrated Antimicrobial resistance Monitoring and Research Programme
GISA	glycopeptide intermediate resistant *Stapylococcus aureus*
HA	hospital associated (acquired)
HGT	horizontal gene transfer
ECDC	European Centre for Disease Control and Prevention
EE	exudative epidermitis
EFSA	European Food Safety Authority
ET	enterotoxigenic
HCA	health care associated community acquired
ICU	intensive care unit
LA	livestock-associated
MARAN	Monitoring of Antimicrobial Resistance and antibiotic usage in Animals in The Netherlands
MLS_B	macrolides, lincosamides, streptogramins B
MLST	multilocus sequence typing
MRL	maximum residue limit
MRSA	meticillin-resistant *Staphylococcus aureus*
MS	Member State
MSSA	meticillin-susceptible *Staphylococcus aureus*
NMC	National Mastitis Council
NT	non-typable
OR	odd's ratio
PA	pet-associated
PBP	penicillin-binding protein
PFGE	pulsed field gel electrophoresis (macrorestriction analysis)
PVL	Panton-Valentine leukocidin
SAGAM	CVMP Scientific Advisory Group on Antimicrobials
SE	staphylococcal enterotoxin
SEl	staphylococcal enterotoxin-like (superantigens)
spa	staphylococcal protein A
SSI	surgical site infections
SSTI	skin and soft tissue infections
SCC*mec*	staphylococcal cassette chromose *mec*
ST	sequence type
SVARM	Swedish Veterinary Antimicrobial Resistance Monitoring
TSST	toxic shock syndrome toxin
UT	untypeable
VRSA	vancomycin resistant *Staphylococcus aureus*

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