

REVIEW ARTICLE

Reflection paper on MRSA in food-producing and companion animals: epidemiology and control options for human and animal health

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(Accepted 15 December 2009; first published online 9 February 2010)

SUMMARY

The scope of this reflection paper was to review the latest research on the risk of MRSA infection and colonization in animals. Attention focused on occurrence, risk factors for colonization and infection, and human contact hazard for livestock, horses, and companion animals. Whereas the clonal relationship between MRSA strains of CC398 is straightforward in livestock this is less obvious in horses. Small companion animals typically share MRSA strains that seem to exchange with a human reservoir. Management and therapeutic options have been suggested for livestock, horses, companion animals, as well as instructions on safety measures for persons in contact with animals. Conclusions were drawn with emphasis on future research activities, especially to confirm the apparent evolution of the organism and to demonstrate efficiency of control strategies.

Key words: CC398, companion animals, horses, livestock, MRSA, *Staphylococcus aureus*, ST398.

INTRODUCTION

An increased number of reports on methicillin-resistant *Staphylococcus aureus* (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 (reviewed in [1, 2]). This apparent extension of the host range of MRSA to different animal species demands a critical review on the factors associated with this emerging zoonotic bacterium from both the veterinary and public health point of view.

The scope of the present reflection paper is to review the latest research on the risk of MRSA infection

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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: (a) to assess the impact of the use of antimicrobials in livestock and companion animals on the risk of colonization or infection with MRSA, and (b) to provide advice on management options for animals related to the issue. In addition, the document 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.

STAPHYLOCOCCUS AUREUS

S. aureus causes a wide range of severe and economically important diseases in human and veterinary medicine [1, 3]. The bacterium is a colonizer of the skin and mucosae from which it can invade multiple organs. In livestock *S. 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 [4].

In humans, prevalence of *S. aureus* infection varies widely between European member states, among hospitals and inside hospitals. The reasons for the difference are probably 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 geographical location [5].

Human invasiveness

S. aureus is by far the most important pathogen in SSTI including SSIs. Life-threatening nosocomial infections such as pneumonia and septicaemia also occur. Treatment of invasive infections largely relies on antimicrobial agents (antimicrobials), in this respect penicillinase-stable β -lactams (isoxazolylpenicillins, cephalosporins) are of utmost importance for human medicine. Resistance to these agents drastically limits therapeutic options and is a worldwide

emerging problem [6]. It should be noted that in this document the applied definition of an antimicrobial does not include commonly used local antiseptics and disinfectants, e.g. chlorhexidine, alcohol, or soaps.

S. aureus can also produce toxins associated with food intoxications. Other rare but severe syndromes including toxic shock syndrome (TSS) have also been documented [7].

Epidemiological definitions of MRSA groups

S. aureus is intrinsically susceptible to β -lactam agents that inhibit cell-wall formation due to binding with proteins involved in the formation of peptidoglycan, as previously reviewed [8]. The mechanism of resistance to penicillinase-stable β -lactams including methicillin, isoxazolylpenicillins and cephalosporins in *S. aureus* (MRSA) is an altered target site due to an acquired penicillin-binding protein (PBP2a, also called PBP2') encoded by the gene *mecA*.

Different types of MRSA may be distinguished based on epidemiological groupings. This can be a simplistic approach since in some cases strains of MRSA have spread between the groups [7]. Thus it might be difficult to determine which epidemiological pattern a certain MRSA strain is associated with. The grouping is of relevance for the remainder 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.

Hospital-associated MRSA (HA-MRSA). These have been known as nosocomial pathogens for decades. MRSA are regarded as HA-MRSA when infections caused by them are likely to be acquired in healthcare settings when they emerge at least 48 h 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 [9].

Healthcare-associated community MRSA (HCA-MRSA). These are associated with outpatients with MRSA infection/colonization and previous hospitalization, such as residence in a nursing home, receiving home nursing, attending centres for dialysis and/or centres for diabetes were MRSA of hospital origin has been introduced [10].

Community-associated MRSA (CA-MRSA). These emerge in the community; affected patients lack the above-mentioned risk factors. Close contact in sport settings, schools, day-care centres, military settings and prisons, are considered risk factors.

Livestock-associated-MRSA (LA-MRSA). These refer mainly to the clonal spread of a certain MRSA strain (ST398, see below) that colonizes different food animal species (including horses) and may cause infections in humans.

Companion animals and horses may be colonized 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’) [7].

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 [1]. Thus, until the end of the 20th century both the scientific community and policy makers were convinced that animal husbandry was of little relevance to MRSA causing diseases in humans, but was rather a problem solely based on the antimicrobial use in human medicine [11]. The situation has now changed, with an increased number of reports on 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. This has recently been reviewed [1]. Sometimes distinct animal specific-lineages such as LA-MRSA have been involved [12, 13], but on many occasions human-associated MRSA genotypes have been identified [14]. A note of caution in assessing the impact of ‘animal’ MRSA in human infections is that the increased awareness of such organisms is likely to have influenced the concentration of studies dealing with MRSA in animals. Interpretation and comparisons over time and between studies should be carefully performed since different procedures and approaches (study design) may have influenced prevalences.

Zoonotic concerns

Persons in direct contact with MRSA-positive animals have been shown to have an increased risk of

carrying the same MRSA strains as the animals. This has been observed in small-animal healthcare, equine hospitals and livestock environments [7, 14]. Severe manifestations of LA-MRSA in humans have been documented, including a recent outbreak in a Dutch hospital [15, 16]. This emerging phenomenon represents a hazard that demands a bilateral management approach, taking both animals and humans as potential sources of MRSA.

Molecular typing

The *mecA* gene is located on the mobile staphylococcal chromosomal cassette (*SCCmec*), and six major types have been found (I–VI). *SCCmec* types I–III are the most common in HA-MRSA [6]. 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 *SCCmec* type IV, and also type V, while multiresistance is less common. These strains often carry an exotoxin Pantón–Valentine leukocidin (PVL) toxin; the pathogenicity of this toxin is still under debate [17]. HA- and CA-MRSA cannot be strictly separated because genotypic CA-MRSA are reported with increasing frequency in the health-care environment [6, 18]. LA-MRSA carry *SCCmec* types IV or V.

In addition to *SCCmec* 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 has the disadvantage of considerable variation of 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 *SmaI* restriction enzyme by traditional PFGE and results are therefore not interpretable [19]. 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 an upcoming 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 [19]. The aforementioned and other techniques are under evaluation to increase the discriminative power especially with regard to MRSA ST398 [20].

Throughout this document and unless otherwise specified, 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 [5].

EPIDEMIOLOGY AND ECOLOGY OF MRSA

Occurrence in livestock

The first report of MRSA in livestock was a case of bovine mastitis in Belgium [21]. Although molecular-typing methods were not available, biotyping strongly suggested a human origin. Four decades later, investigations have found cattle also to be colonized by LA-MRSA, with 88% of farms positive in Dutch veal-calf rearing units [22]. 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 [23]. In general, the occurrence of MRSA in bovine mastitis isolates is well studied and its prevalence seems to be very low [24].

In 2005, a high prevalence of LA-MRSA was found in Dutch pigs in slaughterhouses [25]. This study was undertaken following high colonization rates of pig farmers and relatives without known risk factors for MRSA [13]. Other reports have confirmed these findings in different countries, e.g. Denmark [26], Germany [27], Canada [28] and Belgium [29], and the predominant *spa* types found were t108, t034, and t011, all close relatives within CC398. The *SCCmec* 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 methicillin (MSSA) [30]. In a recent Canadian study [28] an endemic HA-MRSA (US100) strain was found in pigs in addition to CC398. Of the cited porcine studies, the highest percentage of positive farms (living animals, not slaughterhouse) was found in Belgium with 34/50

fattening pig farms studied being positive (68%). Recent investigations from Asia have demonstrated that pig farms also can act as a reservoir for other sequence types of MRSA, e.g. ST9 in China [31] and Malaysia [32].

In poultry, a Belgian study revealed a new *spa* type t1456 within CC398 to be present in 2/14 randomly selected broiler farms (14.3%), but it was not found in 10 layer farms [33]. Similarly, Nemati *et al.* [34] found 5/39 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 provided elsewhere [5].

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 [35]. A second report showed LA-MRSA to be present in Belgian bovine clinical and subclinical mastitis isolates [23]. Thus far, the LA-MRSA strains in the living animal have not been reported to possess PVL [29, 36]. On the contrary, in CC398 from predominantly healthy persons, a prevalence of 9.4% (3/32) of the PVL toxin was reported [19] although an Asian subclone was suggested for these isolates [37]. Other MRSA clones harbouring PVL have nevertheless been found in living animals [7].

Risk factors for colonization and infection in livestock

A causal relationship between the use of antibacterial drugs and MRSA has been demonstrated in human medicine for different antimicrobial compounds, e.g. quinolones, glycopeptides and β -lactams, in a recent meta-analysis [38]. It is probable that similar conditions apply also to animals, particularly as LA-MRSA are often co-resistant to several other antimicrobials as indicated below.

An antimicrobial 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 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 [39].

Since most LA-MRSA are resistant to tetracyclines (and trimethoprim) [40], an association between the use of antimicrobials in pig farming [39] and the widespread occurrence of MRSA has been hypothesized [16, 25]. Monitoring of antimicrobial consumption in The Netherlands [41] and Denmark [42] has revealed an increased use of tetracyclines during the last 5 years. So far there has been only one report demonstrating an association between the occurrence of MRSA in livestock and the use of antimicrobials. Van Duijkeren *et al.* [36] 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 found no such association [43]. The isolation of LA-MRSA in the case report of dermatitis in swine [35] 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 [44].

S. aureus infections in veterinary medicine are seldom treated with β -lactamase-resistant penicillins. The exception is intramammary use of isoxazolylic penicillins, amoxicillin combined with clavulanic acid and cephalosporins for dairy cows. Despite this practice for several decades, the prevalence of MRSA in bovine *S. aureus* isolates has hitherto been low or absent [45].

A lower prevalence of MRSA was found in sows compared to 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 (56%) farms [29]. 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 [36]. Piglets in 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 [25].

Human contact hazard related to livestock

Epidemiological studies in The Netherlands have indicated that contact with veal calves or pigs was significantly associated with CC398 [13, 46]. In The Netherlands, farmers of swine and veal calves are now considered a defined risk group, and are screened upon admission to hospitals [16].

The occupational hazard for LA-MRSA colonization through (the intensity of) pig contact has been confirmed in Belgian farmers [29], regional German investigations [27] and at an international veterinarian conference in Denmark [47]. Markedly, in two of the studies, current hygiene measures (e.g. wearing a mask) were not found to be protective for MRSA carriage [29, 47]. These findings were in contrast with conclusions drawn from a Canadian study on horse units [48]. Veterinary practitioners are at risk for MRSA, which is clearly demonstrated in countries with a low overall MRSA prevalence like Denmark [49].

Infections of humans with LA-MRSA have been described since 2004 [13], with an increasing frequency in The Netherlands [46] and Denmark [50]. Examples of severe infections are an aggressive soft tissue infection of a pig-inflicted bite wound [15] and endocarditis [51]. An outbreak in a surgical ward at a Dutch hospital has also been described [16].

Occurrence in horses

The first report on the isolation of MRSA in horses was published in the 1990s; 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 [52, 53]. To date, MRSA has been isolated from horses in Europe, Asia and North America [53-60]. Wound and post-operative infections with MRSA tend to be most common [1, 61].

Weese *et al.* [62] found that 5.3% of horses at a Canadian veterinary teaching hospital and 4.7% of horses on farms in Canada and the USA [63] were colonized with MRSA. Cuny *et al.* [12] reported 24 MRSA infections in 768 clinical samples from horses at a veterinary teaching hospital in Austria and an estimated infection rate of 4.8 MRSA cases/1000 equine admissions. In a recent study investigating 110 horses presenting at a Belgian equine clinic 10.9% of the horses carried MRSA. All isolates in this latter study were LA-MRSA (non-typable by PFGE using

SmaI digestion) and belonged to *spa* types t011 and t1451 [59]. In the Netherlands, the percentage of MRSA isolates found in equine clinical samples at the Veterinary Microbiological Diagnostic Center of Utrecht University increased from 0% in 2002 to 37% in 2008. MRSA of *spa* type t064, belonging to MLST ST8 and *spa* types t011 and t2123, both belonging to the livestock-associated MLST ST398, predominated [64]. In Sweden, one of 300 horses admitted to four equine clinics carried MRSA CC398 *spa* type t011 [65]. In an equine clinic in Belgium MRSA CC398 *spa* type t011 were isolated from various infections of 13 hospitalized horses [66]. Busscher *et al.* [67] did not find any MRSA in 200 healthy horses in the community in The Netherlands, similarly no MRSA was detected in nasal samples of 300 healthy horses from 14 farms in Slovenia by Vengust *et al.* [68]. MRSA colonization was also not identified in 497 healthy horses on farms in Atlantic Canada [69].

Risk factors for colonization and infection in horses

Antimicrobial administration within 30 days before admission to a veterinary teaching hospital has been demonstrated to be a risk factor for MRSA colonization in horses [70]. Administration of ceftiofur or aminoglycosides during hospitalization was a risk factor associated with nosocomial MRSA colonization of horses [62].

Weese & Lefebvre [70] 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 ICU and admission to a service other than the surgical service were risk factors for community-associated colonization. Weese *et al.* [62] 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 23/1000 admissions and that of nosocomial MRSA infection was 1.8/1000 admissions, with an incidence density of 0.88/1000 patient-days. Residence on a farm that housed more than 20 horses was a factor significantly associated with MRSA colonization [63]. In a retrospective multicentre study investigating MRSA infections in 115 horses, previous hospitalization and treatment with gentamicin were associated significantly with CA-MRSA, whereas infected

incision sites were associated significantly with HA-MRSA [61].

Human contact hazard related to horses

Occupational or recreational exposure to horses has been incriminated as a risk factor for human MRSA colonization [71]. Nasal carriage was significantly higher in veterinary practitioners (3.9%) than in persons not professionally exposed to animals (0.7%) or in healthy persons in the Danish community (<1%). Exposure to horses was found to be a risk factor [49]. 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 [48].

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 [58, 63, 64, 72, 73]. In Austria ST254, *spa* type t036, *SCCmec* type IV predominated in horses followed by ST398 (t011, *SCCmec*IV) and ST1 (t127, *SCCmec*IV) [72]. In Canada the majority of equine isolates are ST8 (t008, *SCCmec*IV) classified by PFGE as Canadian MRSA-5. The predominance of this clone in horses and horse personnel in Canada suggests that this human-origin clone is horse-adapted [2]. In The Netherlands most equine MRSA are either ST398 *spa* type t011 or ST8 *spa* type t064 [64]. 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 [74]. 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 [71]. Screening of personnel during an outbreak of MRSA infections of horses at a veterinary teaching hospital showed that persons in close contact with horses were more often MRSA-positive than those without [64].

Occurrence in companion animals

In 1988 Scott *et al.* [75] 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 then the number of reports on infections and colonization with MRSA from companion animals has increased [1]. The transmission of a PVL-positive MRSA strain between humans and a dog has been reported [76]. The available evidence suggests that humans are the source of infection or colonization of companion animals and thus a probable ‘humanosis’ exists, but animals can act as carriers and pass the infecting strain to humans in contact [77]. Molecular-typing methods support the hypothesis that MRSA of human origin have adapted to companion animals. Clonal complexes tend to be those predominating in people in the region [2].

Healthy animals can be colonized for variable periods of time without developing clinical disease [78], but the overall prevalence of the colonization remains low in dogs and cats [1, 57, 79–83]. 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. A recent study concluded on the lack of transmission of MRSA between apparently healthy dogs in a rescue kennel in the absence of risk factors (e.g. infected MRSA animal) [84].

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 methicillin-susceptible *S. aureus* (MSSA), *S. intermedius/pseudintermedius* and coagulase-negative staphylococci [85]. *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 STIs including abscesses, dermatitis, post-operative wound infections, and intravenous catheter or surgical implant infections [1, 55, 57, 73, 83, 86, 87–90]. Morris *et al.* [91] 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 [55, 83] [92]. A recent study compared MRSA and MSSA infection outcomes in dogs and cats and reported a high survival rate in both groups, probably because of the high frequency of non-invasive infections.

Risk factors for colonization and infection in companion animals

Little information is available 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 [55, 93].

Studies on risk factors other than antimicrobials for MRSA infections in companion animals are scarce. Owners from MRSA-positive households or health-care workers constitute possible risk factors for this companion animal humanosis [55, 76, 93, 94].

MRSA infections in small animals have also been associated with exposure to medical hospitals, extensive wounds, prolonged hospitalization and immunosuppression [87]. 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 [93]. Invasive procedures, including the presence of foreign material such as suture material, orthopaedic implants, urinary catheters, central venous lines and chest drains appear to be associated with the persistence of MRSA infections [88, 95]. Other identified risk factors associated with SSIs 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 anaesthesia, emergency *vs.* daytime surgery, surgical tissue handling, number of persons present in the operating room, and total length of hospital stay [95]. Small-animal ICUs may be at particular risk for periodic outbreaks of colonization and disease as reported by Weese *et al.* [96].

Transmission of MRSA infection between dogs apparently can be associated with contamination of the floor in a veterinary clinic (Y. Abbott and F. C. Leonard, personal communication). Thus, in veterinary medicine cleanliness of floors appears to be as important as hand-touch sites in the control of human MRSA infections.

Human contact hazard related to companion animals

Several studies have examined the prevalence of MRSA in veterinary hospitals in the UK [58, 81, 82]. These studies have shown that veterinary staff and

their pets have a higher prevalence of MRSA, although they are mostly asymptomatic carriers. A recent study by Moodley *et al.* [49] showed that MRSA carriage was significantly ($P < 0.02$) higher in veterinary practitioners (3.9%) than in 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 having involvement with companion animals such as dogs and cats have been suggested for many years, and evidence for this hazard has increased during recent years [1, 7, 76, 94]. Larger epidemiological studies are required to provide more information on specific risk factors.

CURRENT MANAGEMENT AND THERAPEUTIC OPTIONS

As discussed above, 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. non-use of antimicrobials that are a last resort for treatment or decolonization 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.

LIVESTOCK

Reduction of antimicrobial selective pressure in livestock

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 and to evaluate a possible benefit, 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 vs. layer), and the regimens applied needs to be documented in detail (dose, duration, formulation, treatment interval).

Prevention of transmission of MRSA between and within livestock farms

Given the efficient transmission of LA-MRSA throughout the production chain as shown for swine [36], one way to reduce the dissemination of MRSA from farm to farm would be to improve sanitary control measures 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 MRSA-negative herds could be considered.

The stand-alone period is a cornerstone in reducing 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 (chlorhexidine), and thermal (burning, steaming, cold) cleansing.

Reduce carriers in MRSA-positive livestock farms

Control options for colonized livestock animals

Non-antimicrobial management

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

Means of decontaminating 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 infection control measures including hygiene (biosecurity) on the occurrence of MRSA, especially in pig farms [29, 47]. 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 because the amount of target animals is high, likely to evoke resistance towards the antimicrobials used.

Control options for infected livestock 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 prevent further spread. Culling of infected animals is a further option in extreme cases.

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 [97].

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 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 livestock 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 [35] 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 [34]. 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 regarded as critically important antimicrobials (CIAs) for the treatment of MRSA infections in human medicine [98]. In veterinary medicine these antimicrobials have no maximum residue limit (MRL), they are therefore not allowed and should not be used in animals intended for food production (Council Regulation EC No. 470/2009). In addition there are ethical concerns about their use in veterinary medicine.

Prevention of transmission of MRSA strains in livestock

Because of the high colonization frequency in healthy animals and the relatively few documented infections, control options suggested in an earlier section entitled '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 [99] have been extrapolated in line with general principles for control of bacterial infections as developed.

- Identification and isolation of animals to minimize the risk of zoonotic transmission.
- Use contact precautions such as protective outerwear, e.g. overalls, aprons or coats and boots or overshoes that are not worn elsewhere.

- Protective outerwear and all items handled during the treatment of 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 must 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 colonized 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 eliminated MRSA without antimicrobial treatment. On farm A colonization was eradicated, while only two (3%) colonized horses remained on farm B at the end of the study [60]. The authors concluded that the infection control programme 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 re-infection from other horses, people and the environment [100]. However, we do not know if this applies to other MRSA types. Antimicrobial therapy should therefore, if applied, be reserved for persistent colonizations or for those cases where other control measures are impossible.

Applying topical antimicrobials to the nares of horses seems unpractical, although nebulization (e.g. with amikacin) might be an alternative [60]. 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 [14]. Local treatment with antiseptics such as glycerol, chlorhexidine, or povidone iodine can be used in wound infections. Studies on the efficacy of such compounds in MRSA-infected horses are not currently available.

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 commonly used 'routine' antimicrobials. 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, e.g. 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, e.g. by the British Small Animal Veterinary Association (BSAVA) [99] 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 outerwear, e.g. 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 a 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 programme. 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 [1].

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 [14, 64, 100]. Environmental transmission may be of greater importance in stables than in hospitals [1] as 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 [99] is also applicable to horse practices.

COMPANION ANIMALS

Given the available evidence that MRSA found in companion animals share the same genetic background as MRSA strains common in human infections, experience gained from MRSA-control in 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 [101]. 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-colonization is prevented [83]. In one recent study, MRSA carriage in all healthy carrier dogs was transient and resolved without antimicrobial decolonization therapy in the regularly cleaned and disinfected environment [84]. This may constitute an important factor for MRSA control but long-term studies are needed to confirm this, particularly within a home environment.

Antimicrobial treatment of colonized companion animals

Given the potential for MRSA selection including additional resistance markers, antimicrobial therapy could be questioned except for cases with persistent colonizations 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 antimicrobials 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 colonized dog with a combination of ciprofloxacin and rifampin and another with rifampin and doxycycline have been described [75, 76, 94]. Decolonization with antimicrobials may involve a risk of selection of MRSA strains resistant to the agent applied. Of note 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 [83]. Fusidic acid resistance was also reported in an MRSA isolate from a seal [58].

Topical agents used in humans for decolonization are mupirocin and fusidic acid alone or in combination with other topical agents such as chlorhexidine or bacitracin. Systemic antimicrobials used include cotrimoxazole (trimethoprim + sulfonamides), rifampicin, and doxycycline, in general given by the oral route [102, 103].

As for livestock and horses, the use of antimicrobials in pets that are critical for MRSA treatment in humans 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 [85]. 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 [104]. 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 [105]. Whenever topical therapy alone is used, close monitoring progression of local disease or development of bacteraemia and systemic disease is required [105].

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 [85]. 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 comorbidity [85]. Local antimicrobial therapy may be an option in certain cases [89], while in some patients systemic antimicrobial 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 and colleagues [90] described treatment of 11 MRSA infections in dogs: six occurred after surgical treatment, two as complication of wounds, and three 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-sulfadiazine, ciprofloxacin, enrofloxacin and clindamycin) based on culture and susceptibility testing clinically cured infection in 9/11 dogs. Clindamycin could be a potential candidate for MRSA skin, soft tissue and bone infections. However, Rich *et al.* [106] 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, 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 [107]. Additionally, a number of compounds for human use to combat the growing resistance problems are in development, including novel glycopeptides (dalbavancin, telavancin, oritavancin), and next-generation cephalosporins (ceftobiprole, 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 regarded as CIAs for human MRSA infections (e.g. glycopeptides, oxazolidinones, tigecycline, 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, e.g. by

BSAVA [99]. Stringent household infection control practices, in particular frequent hand hygiene and avoiding high-risk contact are important factors to minimize the risk of becoming 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 [95]. Protocols for asepsis prior to and during placement of the catheter should exist. ICUs may be at particular risk for periodic outbreaks of colonization and disease, but can be curtailed by barrier precautions, and hand hygiene [96].

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 allows for implementation of additional control options. Concerns have been raised about dogs involved in hospital visitation programmes such as therapy pets [108].

PERSONS IN CONTACT WITH LIVE ANIMALS

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

Cooperation between the medical and veterinary professions is a vital requirement not only to identify human carriers but also to implement effective control measures. Owners, farmers and their household 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 [48], although knowledge and compliance with protective behaviour that helps to reduce the risk of zoonotic transmission in general could substantially be improved among veterinarians [48, 109]. Clearly, for all people having contact with the living animal, appropriate hygiene and covering wounds and skin lesions are the two cornerstones in minimizing 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, e.g. in consulting rooms, animal units, and on farms. The use of disposable aprons, gloves, masks, and eye protection are appropriate especially for contact with suspected wounds, body fluids or other contaminated materials.

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 β -lactam agents. In human medicine there is evidence that the use

of a variety of antimicrobials is a major risk factor for colonization 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 spread 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, e.g. fattening pigs, veal calves and broilers.
- Both efficient transmission of CC398 between farms and high within-herd prevalence have been documented in many countries worldwide.
- As with human medicine, antimicrobial consumption must be considered a driving force in the emergence and spread of CC398, and additional studies confirming this hypothesis are urgently needed.
- Molecular studies support the hypothesis that co-selection by non- β -lactam 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 colonized and infected by specific lineages of MRSA, of which CC398 is one.
- Case studies suggest equine hospitals to be at high risk, and post-surgical 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 colonization, 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), in order to evaluate the compliance with 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 need to document the long-term carriage of MRSA, and find efficient ways to decolonize animals and to clear different animal husbandry settings.
- Blind, randomized controlled trials as well as a pro-active surveillance of MRSA in different animal species is required to follow-up evolution and to provide evidence with regard to efficient and affordable control strategies.

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 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.

Persons 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 the spread of MRSA between animals needs to consider humans in contact with animals.

ACKNOWLEDGEMENTS

The authors sadly report that one of the co-authors, Professor Fritz Ungemach, passed away on 20 December 2009. The information contained in this publication does not necessarily reflect the opinion or the position of the European Medicines Agency.

DECLARATION OF INTEREST

None.

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