



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 February 2011
EMA/CVMP/SAGAM/736964/2009
Committee for Veterinary Medicinal Products (CVMP)

Reflection paper on meticillin-resistant *Staphylococcus pseudintermedius*

Agreed by SAGAM (Scientific Advisory Group on Antimicrobials)	2 June 2010
Adoption CVMP for release for consultation	15 September 2010
End of consultation (deadline for comments)	30 November 2010
Scientific content agreed by SAGAM	4 January 2011
Adoption by CVMP	12 January 2011



CVMP recommendations for action

There is a sudden emergence of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) in dogs and cats mainly due to clonal spread. Due to the multiresistant characteristics of these bacteria they constitute a new prominent risk to animal health. Although most infections could be controlled without antimicrobials there are severe cases, that might be life threatening, for which only few, if any, effective veterinary approved antimicrobials are available for treatment.

MRSP itself is not a direct concern for human health, but it causes an indirect risk to humans, as treatment of MRSP in methicillin-resistant *Staphylococcus aureus* (MRSA) carrying animals may lead to additional resistances in MRSA, which has zoonotic potential. That could compromise efficacy in case of treatment of MRSA in humans. In addition, a possibility of transfer of genetic material coding for additional resistances exists. Measures to be taken should consider risks both to animal and human health.

Routine use of antimicrobials is a risk factor for spread of MRSP. There are several antimicrobial classes that may increase the risk. Therefore it would be beneficial to reduced total antimicrobial usage. The recommendations below have been prepared following the CVMP Scientific Advisory Group on Antimicrobials (SAGAM) review on the recent developments with regard to the occurrence of MRSP in animals:

- Unnecessary use of antimicrobials should be avoided.
- Whenever possible, use of antimicrobials should be substituted by other strategies. In addition to the use of antimicrobials there are other factors, in particular related to hygiene and travel that need to be considered to limit dissemination of MRSP. Appropriate wound management without antimicrobials will be sufficient for many MRSP infections.
- Adherence to the principles of prudent use remains a key measure to manage risks for spread of MRSP in accordance with internationally agreed guidance. Special considerations should be given to routine perioperative use in companion animals when implementing these guidelines.
- Development of non-antimicrobial MRSP treatments should be encouraged. Measures like promoting scientific advice should be considered.
- No specific recommendations for the Summary of Product Characteristics (SPC) of antimicrobials can be made.
- In cases where no veterinary medicinal product for animals is authorised for the specific MRSP condition, animals might be treated with other medicinal products¹. These may contain antimicrobial agents that are regarded as critically important in human medicine for use against MRSA. Treatment of dogs and cats with such antimicrobial agents could result in development of additional resistances with subsequent spread to humans.
- Use of antimicrobials for decolonisation seems to be of limited value and should be avoided.
- If antimicrobial treatment of a severe infection is necessary, the risk of emergence of further resistance in the strain of MRSP infecting the animals should be managed to avoid subsequent spread of resistance to animals and humans.
- Use of antimicrobials listed by the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR, 2009) as sole therapy or one of few alternatives to treat MRSA in humans (glycopeptides, streptogramins, glycolcyclines, lipopeptides and oxazolidinones) should be avoided to the extent possible. Treatment of MRSP with products containing any of these substances should be evidence based and restricted to very specific, carefully selected cases where the disease is life

¹ Article 10 and 11 of Directive 2001/82/EC (as amended)

threatening and alternative treatments (including non-antimicrobial) have failed. MRSA carriers and animals in contact with people with confirmed MRSA infection or people at high risk for MRSA infections should not be treated.

- 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 receives applications for authorisation of products containing molecules used as last resort medicines for MRSA treatment in humans, the CVMP will pay special attention in the assessment to the need to ensure the continued efficacy of such molecules in human medicine.

Surveillance of consumption of antimicrobial agents in dogs and cats (including use of products approved for use in humans) is required to evaluate the effect of different interventions and for further risk analysis.

MRSP should not be considered as separate to the general issue of antimicrobial resistance and a global approach to the problem is needed. Therefore, the CVMP, in addition to the recommendations above, strongly supports the following more general suggestions regarded as important to reduce MRSP. It is recognised that those suggestions are outside the remit of the CVMP.

Suggested action	Responsible body
Appropriate hygiene is the corner stone in minimising the spread of MRSP between animals.	Animal owners and keepers, veterinarians and related professionals including people responsible for kennels and other premises where dogs are kept.
Detailed guidelines for the appropriate use of antimicrobials in companion animal medicine are needed.	Veterinary associations and other organisations dealing with this issue.
More information is needed on the efficacy of various therapeutic strategies in animals infected with MRSP. Research should focus on non-antimicrobial strategies to treat the most common conditions associated with MRSP.	Universities, research institutions, veterinarians, pharmaceutical industry.
Vaccines and other non antimicrobial options for the prevention of MRSP and linked diseases (e.g. canine pyoderma) should be developed to reduce the need for antimicrobials.	Pharmaceutical industry, research institutions.
There is a need to establish harmonised surveillance of MRSP, including additional resistances in the isolates. Possibly this could also include notification of confirmed cases to a central register.	European Commission, European Food Safety Authority (EFSA), National competent authorities.
Better diagnostic tools should be developed for the identification of <i>S. (pseud)intermedius</i> , and to avoid misidentification with <i>S. aureus</i> and <i>S. intermedius</i> .	Community Reference Laboratory Antimicrobial Resistance (CRL AMR) and other laboratories, universities, research institutions.
Better knowledge on the virulence factors	CRL AMR, universities, research institutions.

Suggested action	Responsible body
associated with MRSP infections is required.	
Veterinary education on the recent taxonomical and resistance evolutions with regard to MRSP is needed.	CRL AMR, universities, research institutions.
Diagnostic Laboratories are recommended to state on their diagnostic reports in any case of a confirmed case of MRSP: Due to the specific resistance pattern of the most common variant it is recommended to handle and treat animals carefully and explain to the owner that MRSP might be difficult to treat and constitute a risk for colonisation/infection of other dogs and cats.	Diagnostic laboratories.

The Committee recommends these recommendations to 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.

Table of contents

CVMP recommendations for action	2
1. Mandate	7
2. Objective	7
3. Background	7
3.1. Evolution of the taxonomy of <i>S. pseudintermedius</i>	7
3.2. <i>Staphylococcus pseudintermedius</i> : commensal and pathogen	7
3.3. Virulence factors of <i>S. pseudintermedius</i>	8
3.4. Definition of methicillin-resistant <i>S. pseudintermedius</i> (MRSP).....	8
4. Problem statement	9
5. Identification of <i>S. pseudintermedius</i> and methicillin- resistant <i>S. pseudintermedius</i>.....	9
5.1. Methods used for identification of <i>S. pseudintermedius</i>	9
5.1.1 Phenotypic methods.....	9
5.1.2 Molecular methods	10
5.2. Methods used for detection of methicillin-resistance in <i>S. pseudintermedius</i>	10
5.2.1 Phenotypic methods.....	10
5.2.2 Molecular methods	11
6. Epidemiology and ecology	11
6.1. Definition of colonisation, occurrence and characteristics	11
6.2. Additional resistances	12
6.3. Risk factors for colonisation and infection	13
6.4. Human contact hazard	14
6.4.1. Colonisation/contamination with methicillin-susceptible <i>S. pseudintermedius</i> (MSSP):	14
6.4.2. Infection with MSSP:	14
6.4.3. Colonisation/contamination with MRSP:	14
6.4.4. Infection with MRSP:.....	15
7. Control options	15
7.1. Control options for colonised or infected animals.....	15
7.1.1. Control options for colonised animals	15
7.1.1.1 Non-antimicrobial therapy options.....	15
7.1.1.2 Antimicrobial therapy options	15
7.1.2. Control options for infected animals	16
7.1.2.1 Non-antimicrobial treatment.....	16
7.1.2.2 Antimicrobial treatment	16
8. Prevention of transmission.....	17
8.1 Prevention of transmission of MRSP between animals	17
8.2 Prevention of transmission to persons in close contact with animals	17
9. Concluding Remarks – Summary assessment.....	18
Identification, epidemiology and ecology	18
Risk factors and control options	18

10. References 20
Abbreviations 27

1. 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 methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) in animals.

2. Objective

The CVMP requested that the advice should address the definitions of MRSP and the methods used for typing, the occurrence of MRSP in animals and the risk factors involved, the prevention of spread of MRSP between companion animals, therapeutic options, control options for colonised or infected animals and the zoonotic potential of MRSP and prevention of spread to humans.

3. Background

3.1. Evolution of the taxonomy of *S. pseudintermedius*

Staphylococcus intermedius (*S. intermedius*) was first described in 1976 (Hajek, 1976), but during the past few years, there has been confusion about its classification. In 2005, a novel staphylococcal species, *S. pseudintermedius*, was described (Devriese et al., 2005). Isolates formerly identified as *S. intermedius* by phenotypic characteristics were then reclassified based on molecular techniques, following which isolates belonging to the *S. intermedius* group were divided into three clusters: *S. intermedius*, *S. pseudintermedius* and *S. delphini* (Sasaki et al., 2007b). This has clarified that *S. pseudintermedius* and not *S. intermedius* is the species of the *S. intermedius* group (SIG) which colonises and causes infections in dogs and cats (Perreten et al., 2010).

It is difficult to differentiate *S. intermedius* from *S. pseudintermedius* during routine diagnostic procedures, but the vast majority of canine isolates are *S. pseudintermedius*. Therefore, it has been proposed to report all strains belonging to the SIG from dogs as *S. pseudintermedius*, unless genomic investigations prove that the strain belongs to another related species (Devriese et al., 2009). It must be noted that, when reviewing the literature, older reports on *S. intermedius* can in fact be reports on *S. pseudintermedius*. In this Reflection Paper we use the term *S. (pseud)intermedius* when the isolates previously identified as *S. intermedius* are probably *S. pseudintermedius*.

3.2. *Staphylococcus pseudintermedius*: commensal and pathogen

Staphylococcus (pseud)intermedius is a normal inhabitant of the skin and mucosa and can be isolated from the nares, mouth, forehead, groin and anus of healthy dogs and cats (Cox et al., 1985, Cox et al., 1988, Lilenbaum et al., 1999, Talan et al., 1989a). The anal region and the nose are colonised more frequently than other areas in healthy dogs, the anal mucosa being colonised most heavily (Devriese and De Pelsmaecker, 1987). *S. (pseud)intermedius* is an opportunistic pathogen and a leading cause of skin and ear infections, infections of other body tissues and cavities and post-operative wound infections in dogs and cats (Abraham et al., 2007, Griffeth et al., 2008, Weese and van Duijkeren, 2010)

One of the most common diseases caused by *S. pseudintermedius* is canine recurrent pyoderma. Some dog breeds are predisposed for pyoderma. Pyoderma can be primary/idiopathic or secondary. Primary pyoderma occurs in otherwise healthy animals, without an identifiable predisposing cause, and is usually due to infections with *S. pseudintermedius*. This form is rare. The most common form,

however, is secondary pyoderma, which is triggered by an underlying cause like ectoparasites (e.g. fleas), hypersensitivity (e.g. atopy, food allergy, flea allergy) or endocrinal diseases (e.g. hypothyroidism, hyperadrenocorticism). In these cases diagnosing and treating the underlying cause is essential, because antimicrobial therapy alone is insufficient. Other infections caused by *S. pseudintermedius*, e.g. otitis externa, are usually also triggered by underlying causes and the same principles as with secondary pyoderma also apply to the treatment of these conditions.

3.3. Virulence factors of *S. pseudintermedius*

The pathogenesis of *S. pseudintermedius* has recently been reviewed (Fitzgerald, 2009). In general, the knowledge of the pathogenesis of *S. pseudintermedius* is limited (Fitzgerald, 2009). In *S. aureus* enzymes and toxins are thought to be involved in the conversion of host tissues into nutrients for bacterial growth in addition to having numerous modulatory effects on the host immune response.

S. pseudintermedius has various virulence factors, including some which are closely related to virulence factors of *S. aureus* (Fitzgerald, 2009, Futagawa-Saito et al., 2004b). These virulence factors are involved in almost all processes from colonisation of the host to bacterial nutrition and dissemination. *S. pseudintermedius* produces enzymes such as coagulase, protease, thermonuclease and toxins, including haemolysins, exfoliative toxins and enterotoxins (Fitzgerald, 2009). Exfoliative toxin is a virulence factor involved in canine pyoderma, because the exfoliative toxin gene could mainly be found among *S. (pseud)intermedius* isolated from skin infections (Lautz et al., 2006, Iyori et al., 2010). Dogs injected with purified exfoliative toxin develop clinical signs like erythema, exfoliation and crusting which are signs of canine pyoderma (Terauchi et al., 2003). *S. (pseud)intermedius* also produces a leukotoxin known as Luk-I, which is very similar to Panton-Valentine Leukocidin (PVL) from *S. aureus* (Futagawa-Saito et al., 2004a, Futagawa-Saito et al., 2009). Luk-I shows a strong leukotoxicity on various polymorphonuclear cells (Futagawa-Saito et al., 2004a). *S. pseudintermedius* expresses surface proteins that resemble those from *S. aureus*. *S. pseudintermedius* has the capacity to bind to fibrinogen, fibronectin and cytokeratin, which could explain how *S. pseudintermedius* adheres to canine corneocytes (Geoghegan et al., 2009). *S. pseudintermedius* produces an immunoglobulin-binding protein called staphylococcal protein A (*spa*) similar to that of *S. aureus* (Moodley et al., 2009). Like most staphylococci, *S. (pseud)intermedius* has the capacity to form biofilms (Futagawa-Saito et al., 2006). Accessory gene regulator (*agr*) homologues were found in *S. (pseud)intermedius* (Dufour et al., 2002). The *agr* quorum-sensing and signal transduction system was first described in *S. aureus* and plays a key role in the regulation of virulence during infection (Dufour et al., 2002).

3.4. Definition of meticillin-resistant *S. pseudintermedius* (MRSP)

MRSP stands for meticillin-resistant *Staphylococcus pseudintermedius* (*S. pseudintermedius*). MRSP are resistant to all beta-lactam antibiotics including meticillin, other isoxazolylpenicillins and cephalosporins. As in meticillin-resistant *Staphylococcus aureus* (MRSA), the meticillin resistance of *S. pseudintermedius* is mediated by the *mecA* gene which encodes production of a modified penicillin binding protein (PBP). Normally, beta-lactam antibiotics bind to PBP of *S. pseudintermedius* to prevent cell wall construction by the bacterium. The modified PBP of MRSP has a low affinity for beta-lactams and therefore cell wall construction is not prevented by these antimicrobials. The *mecA* gene is located on the chromosome of the bacterium on a mobile element called staphylococcal chromosomal cassette (*SCCmec*) (Weese and van Duijkeren, 2010). The *SCCmec* element can be transferred between different staphylococcal species (Wielders et al., 2001).

4. Problem statement

In the past, *S. (pseud)intermedius* isolates were generally susceptible to penicillinase-stable beta-lactam antibiotics (Medleau et al., 1986, Pellerin et al., 1998, Werckenthin et al., 2001, van Duijkeren et al., 2004), but since 2006, methicillin-resistant *S. pseudintermedius* (MRSP) has emerged as a significant animal health problem in veterinary medicine (Weese and van Duijkeren, 2010). As with susceptible *S. pseudintermedius*, infections with MRSP are (surgical) wound infections, infections of the skin, urinary tract and ear, respiratory tract and other body sites (Weese and van Duijkeren, 2010). Infections with MRSP are more common in dogs than in cats (Morris et al., 2006). MRSP isolates are often not only resistant to beta-lactam antibiotics but also to many other classes of antimicrobial drugs. The treatment of infections with MRSP is a new challenge in veterinary medicine because of the very limited therapeutic options (Wettstein et al., 2008). Several reports on isolates not susceptible to any antimicrobials authorised for use in veterinary medicine have been published (Weese and van Duijkeren, 2010, Loeffler et al., 2007, Wettstein et al., 2008, Couto et al., 2009, Perreten et al., 2010, Pomba et al., 2010). This has resulted in a potential pressure for veterinarians to use antimicrobials authorised for human medicine (Weese and van Duijkeren, 2010). The limited therapeutic options may lead to suffering of the infected animal. MRSP colonisation or infection has so far been rarely reported in humans. Therefore, and in contrast to MRSA, MRSP is at present a problem mainly related to veterinary medicine.

5. Identification of *S. pseudintermedius* and methicillin-resistant *S. pseudintermedius*

In the first section (5.1) the current knowledge on the differentiation between the members of the SIG group will be reviewed briefly, because proper identification of *S. pseudintermedius* is a prerequisite to detect MRSP. The interpretative criteria to determine methicillin-resistance in staphylococci differ according to species and the species identification within the SIG is difficult (Sasaki et al., 2010). In the second section (5.2) the methods used for confirming *S. pseudintermedius* as MRSP are summarised.

5.1. Methods used for identification of *S. pseudintermedius*

5.1.1 Phenotypic methods

Differentiation between the members of the SIG by phenotypic tests is very difficult. *S. intermedius* can be differentiated from *S. pseudintermedius* by a combination of biochemical tests (arginine dihydrolase test, β -gentiobiose test and D-mannitol test). In contrast, there are no differences in the biochemical reactions between *S. pseudintermedius* and *S. delphini* (Sasaki et al., 2007b). Commercial identification systems for the fast and correct identification of *S. pseudintermedius* are not available to date. *S. pseudintermedius* is a relatively new species and remains to be included in the databases of most systems.

In many cases isolates will be erroneously identified as *S. intermedius* or *S. aureus* (Van Hoovels et al., 2006, Schwarz et al., 2008). The occurrence of *S. (pseud)intermedius* in human infections is probably underestimated, because in many laboratories all coagulase-positive staphylococci are grouped together as *S. aureus* (Pottumarthy et al., 2004). Talan et al. (1989a) reported 14 isolates from human dog-bite wounds that were originally identified as *S. aureus* and of these three were found to be *S. (pseud)intermedius*. In a case study reporting a postoperative sinusitis, a methicillin-resistant *S. (pseud)intermedius* was initially misidentified as MRSA because the identification as *S. aureus* was only based on a positive tube coagulase test (Kempker et al., 2009). The isolate was re-identified as *S.*

intermedius but this isolate was most likely *S. pseudintermedius* because the source of the isolate was a dog. A Listeria-CAMP test strain originally designated as *Staphylococcus aureus* ATCC 49444 was recently reclassified as *S. pseudintermedius* (Ramsey et al., 2010). Rapid, easy-to-use tests could enhance the correct differentiation between coagulase-positive staphylococci in veterinary and human laboratories.

5.1.2 Molecular methods

Correct differentiation between all members of the SIG is only possible by using molecular methods.

Phylogenetic analysis based on partial *sodA* gene sequences and *hsp60* gene sequences was the first molecular method described which was sufficiently discriminative for *S. intermedius* and *S. pseudintermedius* (Sasaki et al., 2007b). Various DNA-based techniques have been developed for typing and epidemiological surveillance of *S. (pseud)intermedius*, including ribotyping (Hesselbarth and Schwarz, 1995) pulsed-field gel electrophoresis (PFGE) (Black et al., 2009, Shimizu et al., 1996, Bes et al., 2002). More recently, techniques such as restriction fragment length polymorphism (PCR-RFLP) (Bannoehr et al., 2009, Blaiotta et al., 2010), *spa*-typing (Moodley et al., 2009) and Multilocus Sequence Typing (MLST) (Bannoehr et al., 2009) have been adapted for this purpose.

PFGE is time-consuming, often difficult to standardise for inter-laboratory comparison and therefore not suitable for long-term epidemiological surveillance. It cannot be used for discrimination between the members of the SIG group. This method has, however, been used successfully to analyse and compare isolates from outbreaks (van Duijkeren et al., 2008, Latronico et al., 2009).

A species-specific *spa* typing method in combination with *mecA* typing can be used for rapid typing of MSSP and MRSP (Moodley et al., 2009). This single locus sequence-based approach is less time-consuming than PFGE, and results of *spa*-typing can be compared between laboratories. Sasaki et al. (2010) developed a multiplex-PCR method for species identification of coagulase-positive staphylococci targeting the *nuc* gene locus.

MLST is time consuming and expensive, but inter-laboratory comparability of the results is good.

PCR-RFLP also seems an effective approach to *S. pseudintermedius* identification, allowing discrimination from the other SIG species and *S. aureus* (Bannoehr et al., 2009, Blaiotta et al., 2010). The first results of identification of the SIG by the very fast Matrix Assisted Laser Desorption Ionization- Time of Flight mass spectrometry (MALDI-TOF) identification system are promising (Fasola, 2009).

5.2. Methods used for detection of meticillin-resistance in *S. pseudintermedius*

5.2.1 Phenotypic methods

Most veterinary diagnostic laboratories use phenotypic methods for the detection of meticillin resistance in staphylococci. Commonly oxacillin or cefoxitin is used as a surrogate for meticillin because it is sensitive and more stable. Broth microdilution and disk diffusion tests are most commonly used.

As screening test for meticillin resistance of *S. pseudintermedius* cefoxitin disk diffusion testing using the interpretative criteria for *S. aureus* leads to an unacceptable high percentage of false negative results and has been reported to be inappropriate (Schissler et al., 2009, Bemis et al., 2009, Weese et al., 2009b).

In 2008, the Clinical and Laboratory Standards Institute (CLSI) published a document M31-A3 with new interpretive criteria for the determination of *in vitro* antimicrobial susceptibility of MRSP for isolates from animals to replace those from 2004. These guidelines advise that oxacillin susceptibility of *S. pseudintermedius* should be determined using clinical breakpoints equivalent to those recommended for human and veterinary isolates of *S. aureus* (i.e., more than or equal to 4 mg/l for agar and broth dilution and less than or equal to 10 mm for disk diffusion). It must be noted that these interpretive criteria fail to detect meticillin resistance in some *mecA*-positive isolates of *S. pseudintermedius* (Schissler et al., 2009).

Oxacillin minimum inhibitory concentrations (MIC) of ≥ 0.5 mg/l (agar and broth dilution) and a zone diameter of ≤ 17 mm around a 1 μ g oxacillin disc (disk diffusion) used for coagulase negative staphylococci (CNS) are highly correlated with the detection of *mecA* in *S. pseudintermedius* (Bemis et al., 2009). Therefore, the 2004 CLSI criteria for oxacillin disk diffusion and oxacillin broth microdilution tests can assist in the interpretation of meticillin resistance in *S. pseudintermedius* isolates (Bemis et al., 2009, Schissler et al., 2009).

5.2.2 Molecular methods

The most reliable test for the detection of meticillin resistance is *mecA* PCR. However, few laboratories perform PCR for *mecA* in routine diagnostics (Schissler et al., 2009). PBP2a latex agglutination testing developed for MRSA can result in false-positive reactions when applied to *S. pseudintermedius* isolates (Pottumarthy et al., 2004). As in MRSA, SCC*mec* typing can also be used in MRSP (Black et al., 2009, Shimizu et al., 1996, Perreten et al., 2010, Ruscher et al., 2010).

6. Epidemiology and ecology

6.1. Definition of colonisation, occurrence and characteristics

Contamination, colonisation and infection: animals and humans can be contaminated, colonised or infected with MRSP. Colonisation is the presence, growth, and multiplication of MRSP in one or more body sites without observable clinical signs or immune reaction. The term carrier in animals or humans refers to an individual colonised with MRSP. The most common site of MRSP colonisation in dogs is the nose and the anus. Infection is a condition whereby MRSP has invaded a body site, is multiplying in tissue, and is causing clinical manifestations of disease. Contamination of the coat, skin and nose can occur. When an individual is only contaminated, the bacteria can be washed off easily and often only one culture is MRSP-positive while subsequent cultures are negative. As most studies on MRSP are one point prevalence studies and only one sample per individual is investigated, it is often unclear whether individuals are colonised or merely contaminated with MRSP. Longitudinal studies involving repeated cultures of the same individuals could help to clarify if animals or humans are colonised or contaminated by MRSP.

Occurrence: MRSP colonisation and infection has been described in dogs, cats, horses, birds and humans (Weese and van Duijkeren, 2010, Ruscher et al., 2010). Colonisation with MRSP is more common in dogs than in cats (Couto et al., 2009). Dogs can carry the same or similar MRSP strains for months without active infection (Frank et al., 2009a). In dogs with pyoderma, indistinguishable strains as the one isolated from the lesions can be found at other sites, most frequently the anus. These sites can thus be reservoirs for MRSP infections (Boost et al., 2009). The prevalence of MRSP colonisation or contamination has been studied in various dog populations in different countries, with rates of 0–4.5% in dogs in the community and upon admission to veterinary hospitals (Murphy et al., 2009, Hanselman et al., 2009, Griffeth et al., 2008, Hanselman et al., 2008, Vengust et al., 2006), and 0–7% in dogs with skin disease (Griffeth et al., 2008, Kania et al., 2004, Medleau et al., 1986). An unexpectedly high

prevalence of 30% was found in dogs at a veterinary clinic in Japan (Sasaki et al., 2007a). Another Japanese study reported that 66 % of the *S. pseudintermedius* isolates cultured from dogs with pyoderma visiting two referral hospitals were meticillin resistant based on the detection of *mecA* (Kawakami et al., 2010). The prevalence of MRSP in cats was 4% in healthy cats whereas no MRSP was found in cats with inflammatory skin disease (Abraham et al., 2007). In Canada, the prevalence of MRSP colonisation in healthy cats was 1.2 % (Hanselman et al., 2009). No MRSP was found among 300 horses in different farms in Slovenia (Vengust et al., 2006).

In Germany, the prevalence of MRSP in 16,103 clinical specimens of small animal and equine origin was 0.8% in dogs (61 out of 7490), 0.1% in cats (6 out of 3903) and 0.1% in horses and donkeys (5 out of 4710). MRSP prevalence in dogs was significantly higher than in cats and equines (Ruscher et al., 2009). The skin and the ears are the most common MRSP infection sites (Ruscher et al., 2009).

Clonal distribution: Black et al. (2009) compared MRSP and meticillin-susceptible *S. pseudintermedius* (MSSP) isolates from Tennessee by PFGE and MLST and found that MSSP were more genetically diverse than MRSP. MRSP were predominantly MLST ST 68 and fell within the same PFGE-cluster. These findings are in agreement with those of Bannoehr (2007) who investigated 89 MRSP and MSSP isolates from different animal species originating from different countries in Europe and the USA. They found 61 different sequence types (ST's) among the isolates revealing considerable clonal diversity, but the 16 MRSP isolates belonged to only 5 distinct ST's. Together these data show that although MSSP are genetically diverse, a limited number of MRSP clones are disseminated worldwide, with a distinct geographical distribution. One major clonal lineage seems to dominate in Europe (MLST ST71-spa t02-SCC*mec* II-III), whereas in North America another clonal lineage is predominant (MLST ST68-spa t06-SCC*mec* V) (Ruscher et al., 2010, Perreten et al., 2010). MRSP isolates of ST71 carrying SCC*mec* II-III have also been found in dogs with pyoderma in Hong Kong (Boost et al., 2009) and in dogs in Canada and the USA (Perreten et al., 2010) suggesting worldwide dissemination of certain clones. The reason why certain MRSP clones are so successful remains unclear. The situation resembles that of MRSA in which the worldwide dissemination is also mainly due to a few successful clones with a rather specific geographical pattern (Enright et al., 2002).

Outbreaks and nosocomial transmission: a fatal outbreak of MRSP in a litter of puppies and the isolation of the same clone from the vagina of the bitch and the puppies indicates that vertical perinatal transmission can occur (Latronico et al., 2009). Zubeir et al. (2007) investigated 10 MRSP isolated in 8 dogs and a cat at one veterinary clinic during a period of 6 month and found the same PFGE pattern for all isolates indicating cross-infection at the clinic or the distribution of a single clone in the pet population. Meticillin-resistant *S. (pseud)intermedius* isolates that were indistinguishable by PFGE were cultured from several dogs and a cat, the environment and personnel at a veterinary practice in The Netherlands. This indicates that veterinary hospitals and practices play a role in the dissemination of MRSP (van Duijkeren et al., 2008).

6.2. Additional resistances

Besides *mecA*, MRSP also contains a wide range of different antibiotic resistance genes which can render them resistant to almost all classes of commonly used antimicrobial agents (Perreten et al., 2010). The multidrug resistance profile of MRSP in Europe and North America includes resistance to all oral antimicrobials routinely used for treatment of infections in pets and the drugs to which they remain susceptible are not authorised for animals (Perreten et al., 2010). In addition to beta-lactam resistance, resistance was observed to eleven other antimicrobials in a study on 103 epidemiologically unrelated MRSP isolates from dogs from Canada, the USA, Denmark, Germany, France, Italy, Sweden, Switzerland and the Netherlands (see Table 1) (Perreten et al., 2010). Isolates originating from North America were often susceptible to chloramphenicol, whereas isolates from

Europe were often resistant. Eighty percent of all isolates were resistant to 7 or more antimicrobials and only 3% were susceptible to all antimicrobials except for beta-lactams.

Table 1: Resistance to antimicrobial agents for 103 MRSP isolates from Europe and North America (Perreten et al., 2010)

	Resistance breakpoint (mg/l)	Percent of resistant isolates (%)	Resistance genes involved
Erythromycin	≥8	89	<i>erm</i> (B)
Clindamycin	≥4	89	<i>erm</i> (B); <i>Inu</i> (A)
Trimethoprim	≥16	90	<i>drf</i> (G)
Ciprofloxacin	≥4	87	ND
Gentamicin	≥16	70	<i>aac</i> (6')-Ie- <i>aph</i> (2')-Ia
Streptomycin	≥32	90	<i>ant</i> (6')-Ia
Kanamycin	≥64	93	<i>aph</i> (3')-III
Tetracycline	≥16	70	<i>tet</i> (M); <i>tet</i> (K)
Chloramphenicol	≥32	57	<i>cat</i> _{PC221}

Similar resistances have been found by Ruscher et al. (2010). The presence of different SCC*mec* elements among members of different genetic lineages suggests that the *mecA* gene has been acquired by different *S. pseudintermedius* strains on multiple occasions (Kadlec et al., 2009). To date, several types of SCC*mec* elements (SCC*mec* II-III, SCC*mec*III, SCC*mec*IV, SCC*mec* V, SCC*mec* VII and non-typeable cassettes) have been characterised in MRSP (Descloux et al., 2008, Black et al., 2009, Perreten et al., 2010). SCC*mec* VII and SCC*mec* II-III, which consists of a combination of SCC*mec* II from *S. epidermidis* and of SCC*mec* III from *S. aureus*, are new elements whereas SCC*mec* V is largely homologous to SCC*mec* type VT from *S. aureus*. The latter finding suggests recent transfer of the SCC*mec* element from *S. aureus* to *S. pseudintermedius* (Kania et al., 2009).

6.3. Risk factors for colonisation and infection

Studies on the risk factors for MRSP colonisation or infection are scarce. Dogs with MRSP infections had more likely been treated with antimicrobials within the 30 days prior to the onset of the infection compared to dogs with MSSP infections (Weese et al., 2009a). This indicates that antimicrobial use is a risk factor for MRSP infections. Dogs with MRSP infections were more likely to require further hospitalisation than dogs with MSSP infections, but the difference was not significant (Weese et al., 2009a). No differences in survival rates were found between dogs with MRSP and MSSP infections in a small case-control study (Weese et al., 2009a). Further studies are needed to confirm these findings. Because post-operative wound infections are often caused by MRSP, potential additional risk factors could be surgical interventions.

6.4. Human contact hazard

The zoonotic potential of MRSA and MRSP has recently been reviewed by (Weese and van Duijkeren, 2010). As the information on zoonotic transmission of MRSP is very limited, all information available on *S. (pseud)intermedius* will be discussed.

6.4.1. Colonisation/contamination with meticillin-susceptible *S. pseudintermedius* (MSSP)

S. (pseud)intermedius colonisation is uncommon in humans, even among people with frequent contact with animals (Talan et al., 1989b). *S. (pseud)intermedius* isolates are also rare among coagulase positive staphylococcal isolates from hospitalised humans (Mahoudeau et al., 1997). The importance of *S. (pseud)intermedius* as a zoonotic pathogen is therefore much smaller than that of MRSA. However, several cases of zoonotic transmission of meticillin-susceptible *S. (pseud)intermedius* between companion animals and humans have been reported. In some cases humans were only colonised or contaminated, but in other cases transmission resulted in human infections.

Owners of dogs with deep pyoderma were more often culture positive for *S. (pseud)intermedius* than individuals without daily contact with dogs and they often carried the same *S. (pseud)intermedius* strain as their dogs. However, persons were sampled for a second time at the time the dogs had no longer purulent lesions and were found to be no longer culture positive, thus long term colonisation seems uncommon in humans (Guardabassi et al., 2004). Daily direct contact with lesions may be a risk factor for the transmission of the organism to humans. One recent study reported an unexpected high prevalence (4.1%) of *S. pseudintermedius* among humans living in a household with a cat or dog. However, the veterinary profession was over-represented accounting for 42.5 % of the participants (Hanselman et al., 2009). The finding of indistinguishable strains of *S. pseudintermedius* in 44% of the households where both a dog and person were culture positive together with the low prevalence of the organism in humans, may indicate a canine to human route of transmission (Hanselman et al., 2009).

6.4.2. Infection with MSSP

S. (pseud)intermedius is a common and potential invasive pathogen of dog-bite wounds in humans (Lee, 1994). In addition *S. (pseud)intermedius* has been associated with bacteraemia (Vandenesch et al., 1995), a brain abscess (Atalay et al., 2005), pneumonia (Gerstadt et al., 1999), ear infections (Kikuchi et al., 2004, Tanner et al., 2000), varicose leg ulcers (Lee, 1994), an infected suture line (Lee, 1994), and an infected implantable defibrillator (Van Hoovels et al., 2006, Riegel et al., 2010). However, in most cases the origin of the organism remained unknown and zoonotic transmission was not proven. Recently a case report on a catheter-related bacteraemia caused by *S. pseudintermedius* in a child with dog exposure was published, but no effort was made to isolate the organism from the dog (Chuang et al., 2010).

6.4.3. Colonisation/contamination with MRSP

Colonisation of humans with MRSP seems to be uncommon and transient. MRSP was identified in 1 of 242 (0.4%) humans living together with a dog or cat (Hanselman et al., 2009). In a veterinary clinic in Japan, MRSP was cultured from one of 20 staff members and this isolates showed susceptibility patterns and PFGE patterns similar to dog-derived isolates from the same hospital indicating zoonotic transmission (Sasaki et al., 2007a). Transmission of meticillin-resistant *S. (pseud)intermedius* between humans and animals in a veterinary practice has also been reported in The Netherlands (van Duijkeren et al., 2008). In Hong Kong, veterinary personnel (n=150) were sampled for nasal colonisation/contamination with MRSP and only one person was found positive (Boost et al., 2011). A

similar study in Japan found 3/92 (3.3%) personnel at a veterinary academic hospital MRSP-positive (3.3%) in 2007 and 10/127 (7.9%) in 2008 (Ishihara et al., 2010). Transmission of MRSP between an infected cat and two owners within the same household has been reported (van Duijkeren, unpublished data). MRSP was isolated from 2 of 25 owners of dogs with pyoderma, 15 of which were MRSP positive. MRSP was not longer isolated from the owners after treating the dogs for one month (Frank et al., 2009b). A study investigating the prevalence of MRSP in veterinary dermatology practice staff (n=171) revealed that nine persons (5.3%) were MRSP-positive (Morris et al., 2010). Owners of infected pets and veterinarians in contact with infected animals seem to have a higher risk of being MRSP positive although this risk seems to be smaller than with MRSA. All humans involved were asymptomatic.

6.4.4. Infection with MRSP

Reports on infections of humans with meticillin-resistant *S. (pseud)intermedius* are rare. One report describes isolation of meticillin-resistant *S. (pseud)intermedius* from a patient with gastric adenocarcinoma and developing bacteraemia (Campanile et al., 2007). Another case involved a patient with pneumonia (Gerstadt et al., 1999). In the first case no information on animals contact was available and in the second case the patient had no exposure to dogs. Recently, a human case of post-operative sinus infection caused by meticillin-resistant *S. (pseud)intermedius* was described. The patient's pet dog carried a meticillin-resistant *S. (pseud)intermedius* strain with a PFGE pattern indistinguishable from the patient's strain, strongly suggesting zoonotic transmission. The dog had recent bouts of pyoderma which had been treated with antimicrobials (Kempker et al., 2009). A similar case of sinusitis caused by meticillin-resistant *S. pseudintermedius* of MLST ST71, the predominant clone disseminating in dogs and cats throughout Europe, was reported from a patient in Switzerland. The patient owned a dog that had been treated with antimicrobials, but no samples were taken from the dog (Stegmann et al., 2010).

7. Control options

7.1. Control options for colonised or infected animals

7.1.1. Control options for colonised animals

7.1.1.1 Non-antimicrobial therapy options

As now, evidence of the effectiveness of routine application of measures such as disinfecting shampoos to decolonize animals is lacking. Expected effectiveness is particularly dubious for animals that have mucosa colonised with MRSP. Non-antimicrobial management may include washing the animal with e.g. chlorhexidine containing products which may help to decontaminate the coat. There are no studies on long-term colonisation of animals with MRSP, thus it is unknown if MRSP carriage is transient or persistent. Cleaning and disinfection of the house will probably help to prevent re-colonisation through the contaminated household environment.

7.1.1.2 Antimicrobial therapy options

At present, there is no evidence of the effectiveness of antimicrobials to decolonise animals. Use of antimicrobials for this purpose is likely to increase the risk for selection of additional resistances. Decolonisation with antimicrobial drugs might be considered in individual animals in certain cases. However, no antimicrobials have been studied or approved for local or systemic application to decolonize MRSP carrier animals. In some countries veterinary use of last resort antimicrobials,

including mupirocin is limited to exceptional conditions or prohibited by law (Regulation 847/2008 Ministry of Agriculture and Forestry, on prohibiting or limiting the use of certain medicinal substances for animal treatment, 12 December 2008, Finland).

7.1.2. Control options for infected animals

Infections with MRSP may lead to suffering of the animal and therefore animal welfare aspects should be considered when deciding on the best control options.

7.1.2.1 Non-antimicrobial treatment

Many MRSP infections are (post-operative) wound infections and the improvement of wound management without the use of antimicrobial drugs is likely to be adequate and the preferred option for treatment. This would include proper wound toilet and debridement. Topical antiseptics currently used for wound management include e.g. chlorhexidine and products containing iodine (e.g. povidone iodine).

A commercial ear antiseptic containing chlorhexidine and Tris-EDTA showed good *in vitro* bactericidal activity against MRSP (Guardabassi et al., 2010). Disinfectants might thus be used in the therapy of MRSP infections, but controlled studies are necessary to evaluate their clinical efficacy and side effects. To date, no such studies have been published.

Novel approaches for the prevention of canine pyoderma, like vaccines, could help to improve the control options (Fitzgerald, 2009). Curtis et al. (2006) demonstrated that an autogenous bacterin of MRSP could be used successfully for the control of idiopathic pyoderma.

Alternative therapeutic strategies of MRSP infections could include the use of bacteriophages with lytic activity towards MRSP. There is a recent interest in phage therapy in human and veterinary medicine because of the emergence of multi-drug resistant bacteria. In addition to using phages themselves, their products, e.g. phage lysins, could potentially be used in the treatment or prophylaxis of MRSP. To date, there are no data on the efficacy of bacteriophages or lysins in the prevention or therapy of MRSP infections. At present, no authorised products containing phages or lysins are available for MRSP infections.

7.1.2.2 Antimicrobial treatment

As the clinical manifestations of MRSP infections are variable, no single treatment protocol is suitable for all infections and therefore the treatment must be tailored to the individual patient.

When choosing a treatment plan, the risk for development of further resistance in the infecting strain needs to be considered. In addition, the susceptibility profile of the MRSP isolated from the animal, the severity and site of the infection, presence of systemic disease, presence of an underlying disease or any co-morbidity should be taken into account. Local antimicrobial therapy may be an option in certain cases e.g. wound and ear infections, whilst in other patients systemic antimicrobial therapy will be required. Close monitoring of progress of the localised disease or development of systemic disease is required.

Many infections with MRSP are (surgical) wound infections. The European Wound Management Association has written a position document on the management of human wound infections (EWMA, 2006). The principles underpinning this guidance are to provide an optimal environment to promote rapid healing, to restrict the use of antimicrobial agents to occasions when they are specifically indicated, and to use antimicrobial agents appropriately to reduce the selection of resistant strains.

Information on the efficacy of antimicrobial treatment of animals infected with MRSP is scarce.

The only available information on the outcome of patients with MRSP infections is based on case studies with only few patients included (Wettstein et al., 2008, Loeffler et al., 2007). From these preliminary data it may be concluded that clinical and microbiological cure of patients with MRSP infections is possible with or without antimicrobials, but larger controlled studies with more patients are needed to define the best therapeutic strategies.

The potential use in pets of antimicrobials that are critical for MRSA treatment in humans is controversial, due to the risk for development of resistance against those agents (Weese and van Duijkeren, 2010). In some European countries there are already legal restrictions for the use of certain antimicrobial drugs e.g. mupirocin in animals. Recently rifampicin-resistant MRSP isolates have been found in clinical infections of ten dogs. Nine out of ten dogs had been treated with rifampicin. From nine dogs rifampicin-susceptible MRSP had been isolated prior to the use of the antimicrobial drug (van Duijkeren et al., 2010).

8. Prevention of transmission

8.1 Prevention of transmission of MRSP between animals

Guidelines on the management of MRSA in veterinary practices have been developed by the British Small Animal Veterinary Association (BSAVA, 2007) and are generally also applicable to MRSP. Proper hand hygiene is essential.

In line with standard infection control principles, patients diagnosed with or suspected of MRSP infections can be isolated in order to minimise the risk of nosocomial transmission. In veterinary clinics, this includes using barrier nursing precautions and limiting staff contact. Other methods are using contact precautions such as protective aprons, overshoes, gloves and masks. MRSP-infected wounds should be covered with clean bandages if possible. Intra-household transmission from MRSP infected or colonised animals to healthy contact animals has been described (Wagenaar et al., 2008) . Widespread contamination of the environments of households and veterinary hospitals has been reported indicating that direct contact with a patient or colonised animal is not necessary, but indirect transmission through the environment could also occur. It is difficult or even impossible to clear the organism from this environment as long as the MRSP-infected animal still has clinical signs of MRSP infection and lives in this environment, especially when the infection site is the skin of ears, because shedding of the organism will continue (Wagenaar et al., 2008). Proper cleaning and disinfection of the contaminated environment will reduce the number of organisms. Other possible interventions in households with MRSP positive animals are removing the pet from the household (temporarily) in order to avoid transmission to other pets and washing the pet to reduce the contamination of the coat.

8.2 Prevention of transmission to persons in close contact with animals

Although the risk of zoonotic transmission of MRSP is small and colonisation of humans seems to be transient, persons in close contact with infected animals seem to have a higher risk to be MRSP positive. Clearly, for all people having contact with companion animals, appropriate hygiene as described above is the corner stone in minimising the spread of MRSP between animals to humans. One study indicates that routine hand hygiene may be effective at reducing transmission of *S. pseudintermedius* between humans and pets in the household (Hanselman et al., 2009).

9. Concluding remarks – Summary assessment

Identification, epidemiology and ecology

1. There is a sudden emergence and clonal spread of MRSP of unknown reason.
2. Two major clones of MRSP predominate, one in Europe and the other in North-America.
3. Better diagnostic tools are needed for the identification of *S. (pseud)intermedius*, and to avoid misidentification with *S. aureus* and *S. intermedius*.
 - a. Rapid, easy-to-use tests would enhance the correct differentiation between coagulase-positive staphylococci in veterinary and human laboratories. Molecular methods are needed for the correct differentiation of *S. pseudintermedius*.
 - b. The incidence of *S. (pseud)intermedius* in human infections is probably underestimated, because this bacterium is relatively unknown in human medicine.
4. MRSP can colonise or infect animals, especially dogs and to a lesser extent cats.
5. Most common MRSP infections are (surgical) wound infections and infections of the skin and ears.
6. Knowledge on the virulence factors associated with MRSP infections is limited.
7. Detection of meticillin resistance in *S. pseudintermedius* differs from other staphylococci.
 - a. Oxacillin minimum inhibitory concentrations (MIC) of ≥ 0.5 mg/l (broth and agar dilution) and the breakpoint of ≤ 17 mm (disk diffusion) are highly correlated with the detection of *mecA* in *S. pseudintermedius*.
 - b. Cefoxitin disk diffusion testing using the interpretative criteria for *S. aureus* leads to an unacceptable high percentage of false negative results and is therefore inappropriate as screening test for meticillin resistance of *S. pseudintermedius*.
 - c. PBP2a latex agglutination testing can result in false-positive reactions when applied to *S. pseudintermedius* isolates and is therefore not recommended as the sole test for confirmation of meticillin resistance in *S. pseudintermedius*.
 - d. *mecA* PCR is a reliable method for the detection of methicillin resistance in MRSP
8. MRSP is resistant to virtually all β -lactam agents. In addition, resistance to most other classes of antimicrobials licensed for companion animals is common. In human medicine there is evidence that the use of a variety of antimicrobials is a major risk factor for colonisation and infection with MRSA. As most patients infected with MRSP have been treated with antimicrobials, this might also be true for MRSP colonisation and infection in animals.
9. Veterinary education on the recent taxonomical and resistance evolutions with regard to MRSP is needed.

Risk factors and control options

10. Risk factors for MRSP colonisation and infection have to be determined.
11. The transfer of *SCCmec* elements between different staphylococcal species is a concern. Although MRSP isolates are rare in humans, the potential transfer of new *SCCmec* elements from MRSP to other staphylococcal species like *S. aureus* and the subsequent clonal spread of such a new MRSA clone might be a threat for human health in the future.

12. The zoonotic potential of MRSP is much smaller for MRSP than for MRSA. However, humans in close contact with infected animals seem to have a higher risk of being MRSP-positive. Nosocomial transmission of MRSP at veterinary clinics has been documented and therefore decolonisation of personnel that test MRSP-positive repeatedly should be considered.
13. Well controlled hygiene and quarantine measures are needed to clear and avoid hospital epidemics. Strategies that effectively reduce the risk of hospital acquired infections need to be applied. One component of such strategies would be to limit the prophylactic use of antimicrobials related to surgery.
14. Studies have to document whether the long-term colonisation of MRSP exists and to find efficient ways to decolonise animals.
15. Most dogs diagnosed with MRSP infection or colonisation have been treated with antimicrobials and the selective pressure might have contributed to the positive culture.
16. While MRSA strains infecting companion animals are evolutionarily related to different typical human-associated MRSA clones and are thought to be of human origin, this is not the case for the clonally-spread MRSP isolates. MRSP originate from an animal reservoir.
17. Hygiene measures such as hand disinfection and adequate wound management are essential to minimise the spread of MRSP.
18. Detailed guidelines for the appropriate use of antimicrobials in companion animal medicine are needed.
19. More information is needed on the efficacy of various therapeutic strategies in animals infected with MRSP. Research should focus on non-antimicrobial strategies to treat (surgical) wounds, skin diseases like pyoderma and otitis externa, the most common conditions associated with MRSP.
20. Novel approaches for the prevention of canine pyoderma, like vaccines, could help to improve the control options.
21. Limitation of veterinary use of last resort antimicrobial agents for MRSA and other serious infections in humans needs to be considered due to the risk for development of resistance against these agents and subsequent spread of resistant bacteria to humans.
22. Surveillance of consumption of antimicrobial agents in companion animals would be needed to evaluate the effect of different interventions and for further risk analysis.
23. There is a need to establish harmonised surveillance of MRSP, including additional resistances.

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Abbreviations

MRSP: Meticillin-resistant *Staphylococcus pseudintermedius*

MSSP: Meticillin-susceptible *Staphylococcus pseudintermedius*

SCC*mec*: Staphylococcal chromosomal cassette

SIG: *S. intermedius* group

PVL: Panton-Valentine Leukocidin

Agr: Accessory gene regulator

MRSA: Meticillin-resistant *Staphylococcus aureus*

PBP: Penicillin binding protein

PFGE: pulsed-field gel electrophoresis

PCR-RFLP: restriction fragment length polymorphism

MLST: Multilocus Sequence Typing

MALDI-TOF: Matrix Assisted Laser Desorption Ionization- Time of Flight mass spectrometry

MIC: Minimal inhibitory concentration

CLSI: Clinical and Laboratory Standards Institute

PCR: Polymerase Chain Reaction