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# Recommendations for approaches to meticillin-resistant staphylococcal infections of small animals: diagnosis, therapeutic considerations and preventative measures.

## Clinical Consensus Guidelines of the World Association for Veterinary Dermatology

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**Background –** Multiple drug resistance (MDR) in staphylococci, including resistance to the semi-synthetic penicillinase-resistant penicillins such as meticillin, is a problem of global proportions that presents serious challenges to the successful treatment of staphylococcal infections of companion animals.

**Objectives –** The objective of this document is to provide harmonized recommendations for the diagnosis, prevention and treatment of meticillin-resistant staphylococcal infections in dogs and cats.

**Methods –** The authors served as a Guideline Panel (GP) and reviewed the literature available prior to September 2016. The GP prepared a detailed literature review and made recommendations on selected topics. The World Association of Veterinary Dermatology (WAVD) provided guidance and oversight for this process. A draft of the document was presented at the 8th World Congress of Veterinary Dermatology (May 2016) and was then made available via the World Wide Web to the member organizations of the WAVD for a period of three months. Comments were solicited and posted to the GP electronically. Responses were incorporated by the GP into the final document.

**Conclusions –** Adherence to guidelines for the diagnosis, laboratory reporting, judicious therapy (including restriction of use policies for certain antimicrobial drugs), personal hygiene, and environmental cleaning and disinfection may help to mitigate the progressive development and dissemination of MDR staphylococci.

## Clinical Consensus Guidelines

Clinical Consensus Guidelines (CCGs) provide the veterinary community with current information on the pathophysiology, diagnosis and treatment of commonly encountered dermatological conditions. The World Association for Veterinary Dermatology (WAVD) oversees selection of relevant topics, identification of panel members possessing the expertise to draft the Clinical Consensus Guidelines, and any other aspects required to assure the integrity of the process. The statements are derived from evidence-based medicine whenever possible, however when such evidence does not exist then expert opinions would be utilized by the members of the panel. A draft is prepared by the panel, followed by a presentation of the guidelines at major national and/or international veterinary meetings. Access to the guidelines will be available on the WAVD web site. Solicitation for input from WAVD member organizations and affiliate and provisional member groups will result in the incorporation of this feedback into the guidelines. The final CCG manuscript will be submitted to the *Veterinary Dermatology* journal, where it is reviewed and edited before publication. The authors are solely responsible for the content of the statements.

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## Summary of the Clinical Consensus Guidelines

### Recommendations for approaches to meticillin-resistant staphylococcal (MRS) infections of small animals: diagnosis, therapeutic considerations and preventative measures

| | |
|---|---|
| 1 | *Staphylococcus pseudintermedius*, *S. schleiferi* (including the coagulase-negative variant) and *S. aureus* are the primary pathogens encountered in small animal dermatology practice. Clinical isolates of all three species commonly express meticillin resistance and multidrug resistance. |
| 2 | In addition, several other species of coagulase-negative *Staphylococcus* (CoNS) have been reported to cause skin and soft tissue infections, and the pathogenic role of a CoNS must be deduced by the clinician on a case-by-case basis. |
| 3 | The pathogenic potential of any CoNS isolate obtained from a secondary skin lesion or a contaminated body site should be interpreted in light of the clinical disease process (urgency, co-morbidities, risk for adverse reactions to specific antibacterial drugs) and with respect to any other pathogenic species of bacteria that may be co-isolated with it. |
| 4 | Minimum reporting by microbiology laboratories should include complete speciation of staphylococci—regardless of tube coagulase status—and an antibiogram for all cultured isolates. |
| 5 | Topical therapy, using antibacterial agents and biocides with proven anti-staphylococcal efficacy, is the recommended treatment modality for any surface or superficial pyoderma involving MRS; particularly those with localized lesions, and for otitis and superficial wound infections. |
| 6 | Topical therapy should be used as the sole on-animal antibacterial treatment for surface and superficial infections whenever the pet and owner can be expected to be compliant. |
| 7 | Geographical differences exist in the availability and licensure of antimicrobial drugs for use in animals. Judicious use decisions need to take into account regional prescribing recommendations in veterinary and human medicine. |
| 8 | Empirical drug selection for systemic therapy is always contraindicated when a MRS infection is suspected based on historical factors, due to the high prevalence of multidrug resistance within these strains. |
| 9 | A restriction-of-use policy should apply to glycopeptides (vancomycin, teicoplanin, telavancin), linezolid (oxazolidinon), anti-MRSA cephalosporins and potentially new compounds that may be approved in the future for treatment of multidrug resistant pathogens of people. |
| 10 | There is little evidence for a difference in outcome between MRS and meticillin susceptible *Staphylococcus* infections in animals, and the prognosis for MRS skin infections in pets is good, depending on the underlying cause and co-morbidities. |
| 11 | There is currently not enough evidence to recommend routine decolonization of MRS carrier animals. |
| 12 | Molecular strain typing methods are research tools used to investigate the epidemiology and ecology or certain outbreak situations of MRS. However, the clinical value of strain typing largely depends on the organism's population structure, the typing method(s) used and the goals of the investigation. Strain typing rarely has impact on patient- or clinic-level management. |
| 13 | Hand hygiene (proper washing/drying and use of alcohol-based hand sanitizers) is the mainstay of personal responsibility for infection control. No data exist regarding optimal personal protective equipment practices for handling animals infected with MRS. However, the use of some degree of enhanced precautions to reduce contamination of clothing and skin is reasonable. Typically, this would consist of a gown or dedicated laboratory coat and disposable gloves. |
| 14 | In contemporary veterinary practices, routine cleaning and disinfection protocols are the cornerstone of hospital infection control. MRS are susceptible to commonly used disinfectants. Protocols should be designed to reduce or eliminate pathogenic burdens in the environment and on equipment. These protocols must be communicated clearly (and often) to the hospital team and practiced correctly and consistently. |
| 15 | Transmission of MRS by infected pets to other individuals in the home or community is known to occur, but data to guide recommendations are incomplete. In lieu of such data, it is reasonable to restrict animals from contact situations until treatment has started and a clinical response is evident. In the home, this could include social distancing from 'at risk' individuals and enhanced hygienic measures for the occupants and the environment. |
| 16 | Screening of clinically normal animals for carriage of MRS—regardless of the setting—rarely leads to clear and justifiable actions. Screening of humans leads to issues of confidentiality, and testing of clinic personnel (especially if not clearly voluntary and anonymous) could lead to a host of legal problems for clinic management. Testing of healthy individuals, particularly humans, should be a rare event that is based on a specific need and with a clear plan to act on the results. |

## 1 Introduction

Since the inception of antimicrobial drug use in the practice of modern medicine, staphylococci have evolved in response to the presence of antimicrobial drugs in biological systems. This evolution has included the *de novo* development or acquisition of antimicrobial drug resistance mechanisms, and the amplification and proliferation of epidemiologically successful strains of pathogenic staphylococci across human and animal populations. Currently, some degree of antimicrobial resistance has been documented within all *Staphylococcus* species that infect humans and domestic animals.[1,2] Pan-susceptible strains within any given species still exist, but have become uncommon in clinical practice.[3,4] Even staphylococci of low pathogenic potential (e.g. most coagulase-negative staphylococci) may harbour resistance determinants and serve as reservoirs for their transmission to species of greater pathogenic potential.[5] Collectively, the genus *Staphylococcus* is known to harbour resistance mechanisms to all antimicrobials that are available in clinical practice.[6–9]

In human medicine, meticillin resistance in *Staphylococcus aureus* has contributed to the medical and economic burdens associated with skin and soft tissue infections since the early 1960s.[10] In veterinary medicine, meticillin resistance has been recognized as a serious and widespread problem within the past decade, during which time its prevalence within populations of the *Staphylococcus* species of greatest clinical importance to dogs and cats, namely *S. pseudintermedius, S. aureus* and *S. schleiferi,* has escalated rapidly.[3,4,11,12]

The term "skin and soft tissue infection" (SSTI) is used commonly in human medicine to describe an inflammatory response to microbial invasion of the epidermis, dermis or subcutaneous tissues.[13] Although staphylococci are the most common cause of human SSTI, the term is not limited to staphylococcal infections. In dogs and cats, the terms superficial and deep pyoderma are used more commonly, and infection by a *Staphylococcus* species is implied unless otherwise stated. Guidelines for the approach to treatment of SSTI of people were published in 2005[14] and updated in 2014.[15] The Infectious Diseases Society of America has also published guidelines for the treatment of human meticillin-resistant *S. aureus* (MRSA) infections, including SSTI, bacteraemia and endocarditis, and infections of bone, joints and the central nervous system.[16] Although instructive to veterinarians, these guidelines do not address many of the nuances relevant to small animal veterinary practice. Guidelines for the treatment of canine pyoderma, in general,[17] and for canine superficial bacterial folliculitis, in particular,[18] have been published, but there are no comprehensive guidelines available regarding management of canine or feline SSTI caused by meticillin-resistant staphylococci (MRS).

This review provides an instructive overview of MRS for the veterinary clinician, then presents consensus statements regarding the laboratory diagnosis, transmission dynamics and environmental mitigation of MRS (Appendix). Finally, the document offers management recommendations for cases of SSTI shown to be caused by MRS.

## 2 Meticillin resistance and multidrug resistance

Meticillin is a semi-synthetic, penicillinase-resistant penicillin that was developed to circumvent penicillin resistance mediated by staphylococcal penicillinases. Penicillinases are bacterial enzymes that deactivate both natural penicillins (penicillin G and V) and aminopenicillins (e.g. ampicillin and amoxicillin) by breaking the core structure of these β-lactam antibiotics. Shortly after the introduction of meticillin in human medicine, *S. aureus* developed resistance to it by acquisition of *mecA*, a gene encoding a specific penicillin-binding protein (PBP2a) with low affinity to all β-lactams, including cephalosporins.[20] Even though meticillin is no longer used in clinical practice, the term "meticillin-resistant" has persisted and has been used since the discovery of cephalosporins in the 1970s to indicate strains that are resistant to all beta-lactams except the newest generation of cephalosporins which were specifically developed for treatment of MRSA infections (e.g. ceftaroline). MRS may express co-resistance to any combination of other drug classes, including aminoglycosides, fluoroquinolones, lincosamides, macrolides, tetracyclines, potentiated sulfonamides, chloramphenicol and rifampicin.[7] When a MRS strain expresses co-resistance to at least two additional antimicrobial classes, it may be referred to as multidrug resistant (MDR) and the term extensively drug resistant (XDR) may be used if the strain is nonsusceptible to all but two or fewer antimicrobial classes.[21] Both MDR and XDR strains have emerged worldwide amongst clinical MRS isolates from dogs and cats.[22]

## 3 Staphylococcal colonization

Bacteria of the genus *Staphylococcus* are Gram-positive, facultatively anaerobic cocci that exist as part of the normal cutaneous and mucosal microbiota of mammals and birds. Most animals will be colonized by one or more *Staphylococcus* species, with particular body sites being predisposed to colonization by certain staphylococcal species.[23,24] The origins of colonizing strains likely vary over a lifetime, but the first opportunity for acquisition occurs at the time of birth. It is known that puppies are colonized by maternal staphylococcal flora during the neonatal period,[25] and often maintain the strain transferred from the dam for many months after they are separated.[26] As adults, it may not be uncommon for dogs to harbour two or more genetically unrelated strains of *S. pseudintermedius* simultaneously but at different body sites.[27] The mouth appears to be the most consistent site for staphylococcal carriage in dogs and cats, followed by the perineum.[23] Co-carriage with multiple species of staphylococci at the same time, including pathogenic species, also is possible.[23,28,29] Furthermore, a study of the complete microbiome present at putative staphylococcal carriage sites has suggested that feline nasal carriage of staphylococci is consistent with that carried by the humans in their households.[30]

Colonization implies that a bacterial population is self-sustaining for an extended period of time in the absence of disease. The term "carriage" is commonly used in a generic sense, when colonization has not been confirmed by longitudinal sampling of the animal. It may also be used to imply that a bacterial population is not biologically self-sustaining, but could be mechanically transmitted by its temporary host or from an environmental reservoir.[31,32] Human nasal carriage of *S. aureus* may be classified as "persistent" or intermittent" as defined by the nasal "culture rule," where persistence is reliably predicted by two positive nasal swabs collected at a 1 week interval, from which a minimum number of colony forming units (cfu) is derived.[33] Such a rule has not been established for dogs or cats, but the mouth is the most sensitive sampling site to identify carriage in dogs and cats at a single time point,[23] and the mouth and perineum are nearly equal in sensitivity for identifying longitudinal colonization in dogs.[27]

In some cases, colonization by a particular staphylococcal species or strain may be short-lived, if a more dominant strain proliferates, outcompetes and displaces the original strain from its niche.[34] One example would be obliteration of a colonizing staphylococcal population by an antimicrobial drug and re-colonization by a strain that is resistant to that drug. It is widely believed that this is the mechanism by which MRS spread laterally across human and animal populations, and epidemiological evidence supports this assumption.[35,36]

## 4 Staphylococcal pathogenicity and virulence

Several *Staphylococcus* species serve dual roles as commensals and opportunistic pathogens, and are capable of causing serious infections of the skin and many other tissues.[37–39] When cutaneous or systemic disease disrupts the skin's surface defence mechanisms, skin infection (bacterial pyoderma) or otitis externa may result. In the case of canine superficial bacterial folliculitis, infection is typically caused by the same strain of *Staphylococcus* that is present at carriage sites.[40] Invasive staphylococcal infections of deeper soft tissue planes, the genitourinary tract, respiratory tract, central nervous system, joints, bone and body cavities may also result either from ascension along epithelial tracts, introduction via penetrating wounds or through haematogenous spread.

The potential for pathogenicity is determined primarily by the arsenal of virulence factors expressed by any given *Staphylococcus* strain. An excellent review of staphylococcal virulence is available.[5] Virulence factors may include expression of adhesins by which the bacterium binds to cells and extracellular matrix, formation of biofilm which protects the bacterium from the immune response, production of toxins (which may include cytolytic, exfoliative, enterotoxigenic and superantigenic toxins) and expression of factors which assist in evasion of the host's immune response.[5,41] Of the latter, it is the ability to coagulate plasma *in vitro*—mediated by either a coagulase protein (produced by the *coa* gene) or a von Willebrand factor-binding protein—which is best known to clinicians as an indicator of pathogenic potential. Production of a coagulase factor promotes formation of a fibrin clot scaffold for tissue invasion, is associated with abscess formation and protects staphylococcal micro-colonies (*in vitro*) against neutrophils.[42,43] It should be noted that genetic expression of antimicrobial resistance is not a true virulence factor; thus, a resistant strain is not necessarily more invasive or pro-inflammatory than a susceptible one. However, acquisition of certain antimicrobial resistance genes may come at a fitness cost to the bacterium. For example, meticillin resistance in some strains of MRSA is associated with reduced production of biofilm and cytolytic toxins.[44]

## 5 *Staphylococcus* species of relevance to veterinary medicine

### 5.1 Coagulase-positive staphylococci (CoPS)

In veterinary medicine, it is the CoPS that cause the great majority of SSTIs. Historically, *S. intermedius* was the first CoPS recognized to be distinct from *S. aureus* in the mid-1970s. It was isolated from pigeons, dogs, mink and horses, and the species name derived from the investigator's observation that the biochemical characteristics of this new species were "intermediate" between those of *S. aureus* and *S. epidermidis*.[45] *Staphylococcus intermedius* was subsequently identified as the major CoPS commensal and pathogen of dogs,[46] and many other domestic animal species. More recently, however, the phylogenetic structure and nomenclature of *S. intermedius* has changed due to advances in molecular characterization.[47,48] The *S. intermedius* group (SIG) now comprises three genetically demonstrable species: *S. intermedius*, *S. pseudintermedius* and *S. delphini*, each of which occupy distinct ecological niches.[46] Of this group, the primary canine and feline pathogen is now known to be *S. pseudintermedius*.[49,50] This consensus document therefore uses the current nomenclature while recognizing that the older scientific literature (prior to 2007) references the primary canine and feline pathogen as *S. intermedius*.

The CoPS which may colonize the skin of the domestic dogs and cats have been well characterized, and include *S. pseudintermedius* and *S. aureus*.[23,27–29,51–53] *Staphylococcus pseudintermedius* clearly dominates on dogs, whereas in cats studies differ on whether *S. pseudintermedius* or *S. aureus* is carried most frequently.[28,54–57] It appears that the prevalence of *S. aureus* on canine and feline carriage sites is more common when these pets live with a person who has been recently diagnosed with MRSA infection.[23] *Staphylococcus schleiferi, a* coagulase-variable species, has rarely been isolated from the healthy skin of either dogs or cats in cross-sectional studies of skin and mucous membrane carriage,[23,28,29] yet it is commonly isolated from skin and ear canal infections of dogs with histories of prior antimicrobial exposures.[38,58,59]

These three staphylococcal species cause the overwhelming majority of SSTI in dogs and cats,[3,4] and isolation of any one of them from a clinical sample should warrant careful consideration of the animal's

need for antimicrobial therapy based on history and clinical signs. Anecdotally, another coagulase-variable species, *S. hyicus*, has occasionally been isolated from healthy cats[28] although it is primarily known to veterinarians as the most common aetiological agent associated with porcine exudative epidermitis[1] ("greasy pig disease").

Consensus statement 1: *Staphylococcus pseudintermedius*, *S. schleiferi* (including the coagulase-negative variant) and *S. aureus* are the primary pathogens encountered in small animal dermatology practice. Clinical isolates of all three species commonly express MR and MDR (see below).

### 5.2 Coagulase-negative staphylococci (CoNS)

It is critical to note that *S. schleiferi* is a coagulase-variable species, currently classified as comprising two sub-species: *S. schleiferi* subsp. *coagulans* (coagulase-positive) and *S. schleiferi* subsp. *schleiferi* (coagulase-negative). However, recent genotypic and epidemiological studies have shown that these two biotypes are not genotypically distinct enough to be considered true sub-species,[59,60] nor do they differ in their pathogenic effects.[38] This fact has led to a paradigm shift in the way veterinary microbiology laboratories must report culture and susceptibility results for CoNS (see below). The CoNS species *S. lugdunensis, S. haemolyticus and S. epidermidis* have also been isolated from pyogenic infections of small animals, albeit rarely.[62,63]

Consensus statement 2: Several species of coagulase-negative *Staphylococcus* (CoNS) have been reported to cause skin and soft tissue infections, and the pathogenic role of a CoNS must be deduced by the clinician on a case-by-case basis.

Although CoNS have traditionally been considered to be nonpathogenic resident or transient commensals in animals, this viewpoint is likely to be oversimplified and in human medicine CoNS are known to be pathogenic in many settings.[64–68] This is in part due to the increasing prevalence of immunosuppression within the human population and use of invasive medical instruments, which have allowed greater susceptibility and exposure to less pathogenic organisms on a population-wide basis.[67] To compound the problem, CoNS commonly express MR and often even MDR,[69,70] and colonization with MR-CoNS is not uncommon in both healthy and diseased individuals. However, with the exception of *S. saprophyticus* as a cause of urinary tract infections that arise outside of the healthcare setting, human infection by CoNS remains largely a hospital-associated problem in compromised hosts.[67]

In veterinary medicine, where most CoNS are still thought to be minimally pathogenic,[63] a common question posed by clinicians is what should be done when a laboratory reports that a CoNS has been isolated from a clinical sample. The consensus of this working group is that this interpretation should depend largely on how confident the clinician is that the "true" aetiological agent has been isolated. Coagulase-negative *S. schleiferi* should generally be considered pathogenic when isolated from inflamed tissue or a pyogenic fluid.[38,57,58] In the case of other CoNS species, the solution is much less clear. In general, if good aseptic technique has been used to obtain a culture sample from a site generally not expected to harbour bacteria (e.g. joint fluid, blood, cerebrospinal fluid, closed body cavity, cystocentesis), or the sample has been collected from an intact primary skin lesion (pustule, bulla, nondraining abscess) and another more pathogenic bacterium was not also identified, the authors recommend that treatment may be considered and antimicrobial therapy chosen (if needed) based upon susceptibility results. The microbiology laboratory may also be helpful to the clinician in making this assessment, based upon the number of cfu isolated from the sample. If the specimen was obtained from a contaminated site (such as the skin or ear canal surface, an open wound, the upper respiratory tract or oral cavity) the result should be interpreted with caution. In these cases, the clinician should consider repeating the culture, especially if extensive MDR presents a therapeutic dilemma and if the patient's health will not be compromised by waiting for additional test results. When a CoNS is isolated from a clinical sample as part of a mixed population of bacteria, consideration must be given to the composite antibiogram of these organisms and deference paid to any organisms known to have greater pathogenic potential. When conflicts of drug choice arise, antimicrobial therapy should be targeted toward the organism of greatest pathogenic potential.

Consensus statement 3: The pathogenic potential of any CoNS isolate obtained from a secondary skin lesion or a contaminated body site should be interpreted in light of the clinical disease process (urgency, co-morbidities, risk for adverse reactions to specific antibacterial drugs) and with respect to any other pathogenic species of bacteria that may be co-isolated with it.

### 5.3 Meticillin-resistant *Staphylococcus aureus* (MRSA)

Since the early 1960s, the prevalence of MR in *S. aureus* has escalated in many countries and MRSA is a common cause of hospital-associated infections of people throughout the world.[71] During the mid-1990s, MRSA strains which cause SSTI in people with no known nosocomial risk factors arose *de novo* within the community.[71,72] These strains originally exhibited more favourable antimicrobial susceptibility profiles than hospital-associated strains, but expressed more virulence factors, such as the Panton–Valentine leucocidin toxin gene.[73,74] However, a progressive trend toward MDR has now been documented.[6] Risk factors associated with transmission of MRSA within the community include crowded living

conditions, shared bathing facilities and participation in contact sports.[32] Over the past decade, niche drift has occurred, with the archetypal hospital strains "escaping" into community circulation, whereas community-onset strains have become resident in some hospitals where they have caused nosocomial infections.[71,75]

Overall, isolation of MRSA from small animal infections remains rare compared to MRSP and MRSS, with some geographical differences. In North America and Europe, the dominant strain types of MRSA that are carried by (and infect) dogs and cats appear to reflect the prevalence of lineages successful within the human population in the particular region or country.[41,76–78] Unfortunately, these often are the strains that express the most extensive MDR. The true prevalence of MRSA infections in domestic pets within the community is difficult to estimate, as reports have been hospital-based and national population-based surveillance is not performed in pets. An excellent review of the genomic structure and epidemiology of veterinary-sourced MRSA strains is available.[78]

### 5.4 Meticillin-resistant *S. pseudintermedius* (MRSP)

Over the past decade, MRSP has emerged as a clinically important pathogen which causes treatment-resistant infections of dogs and cats.[3,4,36,79] Like hospital MRSA strains, most MRSP isolates co-express resistance to several other classes of antimicrobials, such as the fluoroquinolones, macrolides, tetracyclines and aminoglycosides.[3,4] Currently, it is common to isolate MRSP that is susceptible to very few antimicrobials; susceptibility only to amikacin, rifampicin, vancomycin and linezolid is a widely encountered pattern. This type of antibiogram presents a true therapeutic dilemma, due both to potential for drug toxicities (amikacin and rifampicin) and ethical use considerations (vancomycin and linezolid).

Because MRSA evolved with a clonal population structure and global dissemination of specific clones occurred through the years, it was hypothesized that MRSP isolates would also be highly clonal. Studies of the population genetic structure of *S. pseudintermedius* infection isolates obtained from animals in North America, Europe and Japan have indeed proven this hypothesis.[46] Two major clonal lineages have disseminated throughout Europe [Sequence Type (ST) 71], North America (ST 68) and Japan (ST 71) and other less common clonal lineages may be emerging.[49,80] Sequencing of the *mec*A gene from *S. pseudintermedius* has revealed a high degree of homology (95–100%) with the *mec*A gene of *S. aureus*, suggesting horizontal transfer of the gene or acquisition from a common source (e.g. CoNS).[46] The structure of the MRSP phylogenetic tree suggests that the *mec*A gene has been received by this staphylococcal species on multiple occasions and on several different continents.[46]

### 5.5 Meticillin-resistant *S. schleiferi* (MRSS)

In humans, *S. schleiferi* infections appear to be rare. The coagulase-negative variant of *S. schleiferi* is most commonly associated with disease, causing primarily post-surgical skin and soft-tissue infections, whereas reports of infection by the coagulase-positive subspecies remains very rare.[81] In dogs, both subspecies are commonly associated with skin and ear canal infections, and statistically associated with prior antimicrobial use or recurrent pyoderma.[38,57] Isolation of *S. schleiferi* from pyogenic infections of cats remains exceedingly rare.[3,28] Although both subspecies have been isolated from the healthy skin and ear canals of dogs, this remains a rare finding, and the true natural reservoir for *S. schleiferi* remains in question (although it is likely to be the dog).[23,28,29] The prevalence of MR in *S. schleiferi* clinical isolates is high and was reported to exceed 50% within two veterinary teaching hospitals in the USA.[38,82]

Not unlike MRSA and MRSP, MRSS is evolving within a clonal population structure. A limited number of strain types, as defined by pulsed field gel electrophoresis, were identified in a collection of 161 clinical isolates that were submitted to a clinical microbiology laboratory in the USA between 2003 and 2007.[38] In a follow-up report from the same laboratory, it was noted that the population had undergone further periodic selection (reduction of dominant strain types) to three major clonal groups, during the period 2008 to 2013.[83] A global survey and comparison of *S. schleiferi* strain types has not been reported.

### 5.6 Conclusion

For more detailed information on these three MRS pathogens, the reader is referred to several excellent reviews on the topic.[7,39,78,82] Table 1 provides a summary of studies evaluating the prevalence of MRS and meticillin susceptible staphylococci among dogs and/or cats in hospital and community settings. These data suggest potential regional, temporal, and host species and contextual differences in animal carriage rates that may underpin or explain differences in clinical experience.

## 6 Laboratory identification of MRS

*Staphylococcus pseudintermedius* has traditionally been distinguished from *S. aureus* based on colony appearance on blood agar and phenotypic tests.[39] Phenotypic identification of *S. pseudintermedius* has been complicated by the recent taxonomic changes, because this species cannot be easily distinguished from the other members of the SIG—*S. intermedius* and *S. delphini*—on the basis of simple and readily available phenotypic tests.[39] Molecular diagnostic methods based on PCR are recommended for accurate species identification of CoPS, including *S. schleiferi* subsp. *coagulans*.[84] Proteomic mass spectrometry (MALDI-TOF or matrix-assisted laser desorption/ionization time-of-flight) is a valuable cost-effective, rapid and highly accurate alternative to PCR, provided that the database has been refined by strict quality control protocols.[85,86] The great limitation of this technology is the very high cost of purchasing a MALDI-TOF instrument, which implies a high-throughput workload to recoup investment costs. MALDI-TOF mass spectrometry can be used to identify any bacterial species, including CoNS, provided that

  

**Table 1.** Epidemiological studies evaluating prevalence of carriage of *Staphylococcus aureus, S. pseudintermedius* and *S. schleiferi* in dogs and cats

| Sample Population | Study Design | Number of pets | *S. aureus* | | *S. pseudintermedius* | | *S. schleiferi* | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | MSSA | MRSA | MSSP | MRSP | MSSS | MRSS | |
| *Veterinary clinical populations* | | | | | | | | | |
| University vet hospital (USA) | Case-control | 48 \| 50 cats* | 27% \| 16% | 2% \| 4% | 23% \| 23% | 0% \| 4% | 0% \| 2% | 2% \| 0% | Abraham[28] |
| University vet hospital (USA) | Case-control | 59 \| 50 dogs* | 7% \| 12% | 2% \| 0% | 81% \| 64% | 7% \| 2% | 17% \| 2% | 3% \| 2% | Griffeth[29] |
| University vet hospital (Canada) | Cross-sectional | 193 dogs | – | 0.5% | – | 2% | – | 0.5% | Hanselman[223] |
| University vet hospital (Canada) | Case-control | 173 \| 41 dogs* | – | 6.4% \| 0% | – | 34% \| 0% | – | 4% \| 0% | Beck[36] |
| Veterinary practices (Poland) | Cross-sectional | 172 dogs | 5.8% | 0% | 41% | 0% | 0% | 0% | Garbacz[224] |
| Veterinary practice (Germany) | Cross-sectional | 1 dog \| 9 cats | – | 0% \| 22% | – | 0% | – | 0% | Weib[225] |
| University vet hospital (Thailand) | Cross-sectional | 100 dogs | 3% | 1% | 55% | 45% | 12% | 17% | Chan-chaithong[226] |
| Veterinary practices (USA) | Cross-sectional | 276 dogs or cats | 4% | 0% | 1% | 0% | 0% | 0% | Davis[227] |
| Veterinary practices (Korea) | Cross-sectional | 30 dogs[e] | 67% | 0% | – | 0% | – | – | Jang[228] |
| Veterinary practices (UK) | Cross-sectional | 724 dogs | 6.5% | 1% | 11% | 0% | – | – | Wedley[229] |
| Veterinary practices (Lithuania) | Cross-sectional | 345 dogs[e] \| 40 cats | – | 0% \| 0% | – | 1.4% \| 7.5% | – | 0% \| 0% | Ruzauskas[230] |
| *Human exposed pet populations* | | | | | | | | | |
| Pet owning households (Canada) | Cross-sectional | 132 dogs \| 161 cats[†] | 14% \| 4.3% | 1.5% \| 0% | 42% \| 6% | 5% \| 1% | 0.8% \| 0% | 0% \| 0% | Hanselman[176] |
| Therapy pets visiting long-term care (Canada) | Longitudinal | 96 \| 98 dogs* | – | 7% \| 2% | – | 0% \| 1% | – | 0% \| 0% | Lefebvre[142] |
| Pets belonging to veterinarians in dermatology specialty clinics (USA & Canada) | Cross-sectional | 258 dogs \| 160 cats[†] | – | 0.8% \| 3.8% | – | 6.2% \| 3.1% | – | 0.8% \| 0% | Morris[178] |
| Dog show (Germany) | Cross-sectional | 108 dogs | 1.8% | 0% | 14% | 0% | 0.9% | 0% | Walther[231] |
| Healthy pets (Spain) | Cross-sectional | 54 dogs \| 12 cats[†] | 9.3% \| 25% | 0% \| 0% | 23.2% \| 8.3% | 3.7% \| 0% | – | – | Gomez-Sanz[232] |
| Shelter dogs (Spain) | Cross-sectional | 98 dogs | 24% | 0% | 16% | 8% | 1% | 0% | Gomez-Sanz[233] |
| Pets and shelter dogs (USA) | Cross-sectional | 123 dogs | – | 0% | – | 1.6% | – | 0% | Mouney 2013[234] |
| Pets of MRSA-infected owners (USA) | Longitudinal | 71 dogs \| 63 cats[†] | 43% \| 14%[‡] | 6% \| 5% | 79% \| 14%[‡] | 1% \| 0% | 1% \| 0%[‡,§] | 0% \| 0%[§] | Iverson[23] |

MSSA meticillin susceptible *Staphylococcus aureus*, MRSA meticillin-resistant *S. aureus*, MSSP meticillin susceptible *S. pseudintermedius*, MRSP meticillin-resistant *S. pseudintermedius*, MSSS meticillin susceptible *S. schleiferi* MRSS meticillin-resistant *S. schleiferi*. These papers are limited to those studies testing for multiple staphylococcal species and do not include studies targeting just *S. aureus, S. pseudintermedius* or *S. schleiferi*.

*Given as Case *n* or % | Control *n* or %;

[†]Given as Dog *n* or % | Cat *n* or %;

[‡]MSSA & MSSP prevalence rates estimated from a subset of 28 animals; some of these data have not previously been published;

[§]*S. schleiferi* subspecies coagulans only; [e]Shelter or kennel dogs also tested, results not summarized here.

the database has been validated for the species of interest. This condition may explain the discrepancies between those studies that have assessed the suitability of this technology for species differentiation within the SIG.[85,86] Indeed, a significant improvement of the SIG identification score values was achieved in one of the studies by refining the original database provided by the manufacturer of one of the two MALDI-TOF instruments available in the market.[87] On rare occasions in clinical practice, further strain identification may be useful; these methods are described in detail later.

The PCR amplification of the MR gene *mecA* or commercial agglutination tests designed to detect its gene product (penicillin-binding protein 2a, PBP 2a or PBP 2′) are presently regarded as the gold standards for the identification of MR.[88] One of these two methods should be used to confirm presumed MRSA, MRSP or MRSS detected by oxacillin or cefoxitin susceptibility testing.[89] The cefoxitin minimum inhibitory concentration (MIC) is a poorer predictor of MR than the disk diffusion test for staphylococci other than *S. aureus*.[90] Although for *S. aureus* the cefoxitin disk test is equivalent to the oxacillin MIC test, the use of cefoxitin as a surrogate for MRSP detection by disk diffusion is controversial[91–93] and not recommended currently by the Clinical Laboratory Standards Institute (CLSI). This controversy may be explained by differences in media used in the different studies and should be investigated further. Strains that are oxacillin/cefoxitin-resistant and *mecA*-positive or PBP 2a-producing should be reported as being resistant to all penicillins, cephalosporins (except anti-MRSA cephalosporins), carbapenems and cephems regardless of the *in vitro* susceptibility test results obtained with these agents.[89] This so called "expert rule" was originally established for MRSA to minimize very major errors of antimicrobial susceptibility testing (i.e. resistant strains reported as susceptible) because MRSA infections generally respond poorly to β-lactam therapy, even though MRSA strains may display *in vitro* susceptibility and could erroneously be reported as susceptible to β-lactam agents. The latter phenomenon is due to poor *in vitro* expression of *mecA* in the presence of β-lactams other than oxacillin and cefoxitin, which are used as surrogate drugs for this reason. It should be noted that this expert rule has never been validated for MRSP and MRS, other than *S. aureus* and *S. lugdunensis*, which display significantly lower oxacillin MICs compared to the two latter species. This difference is reflected in the oxacillin resistance breakpoints for *S. aureus/S. lugdunensis* (>2 μg/mL) versus all other *Staphylococcus* species (>0.25 μg/mL).[90]

Consensus statement 4: Minimum reporting by microbiology laboratories should include complete speciation of staphylococci—regardless of tube coagulase status—and an antibiogram for all cultured isolates.

## 7 Therapeutic considerations for MRS infections

### 7.1 Topical therapy

Consensus statement 5: Topical therapy, using antibacterial agents with proven anti-staphylococcal efficacy, is the recommended treatment modality for any surface and superficial pyoderma involving MRS, particularly those with localized lesions, and for otitis and superficial wound infection.

The skin is easily accessible by topical treatment and antimicrobial formulations for use in small animals are available in most countries. A systematic review of topical therapy for canine skin infections concluded that evidence from randomized controlled trials was sparse on topical treatments, but that good evidence supported the use of shampoos containing 2–3% chlorhexidine and to a lesser extent of benzoyl peroxide in bacterial skin infections.[94] This review had included studies on canine pyoderma irrespective of MR amongst staphylococcal pathogens and an extrapolation of results is therefore limited. However, MICs reported for MRS isolates from pets in North America, Europe and Asia have so far remained low, likely to be exceeded by drug concentrations achievable with topical application. Amongst the almost 200 MRSP isolates included in recent *in vitro* studies, low MICs were found for chlorhexidine (≤16 μg/mL), miconazole (≤2 μg/mL), fusidic acid (≤2 μg/mL), mupirocin (≤0.5 μg/mL) and polymyxin B (≤4 μg/mL); only one isolate in a collection of 49 showed a MIC of 16 μg/mL to fusidic acid.[95–99] In the three studies that included MRSA isolates from pets, MICs were at least one dilution higher than for MRSP, with individual outliers of MICs exceeding 256 μg/mL fusidic acid (6 of 102 isolates).[95–97]

Consensus statement 6: Topical therapy should be used as the sole on-animal antibacterial treatment for surface and superficial infections whenever a pet and owner can be expected to be compliant.

Although dermatology texts still recommend systemic antimicrobial therapy for superficial pyoderma with or without added topical medication, this recommendation can be challenged during times of increasing antimicrobial resistance. Newer studies have provided evidence that topical therapy as the sole antibacterial treatment can be effective in superficial pyoderma, providing opportunity to reduce the need for systemic therapy in some cases. Chlorhexidine and benzoyl peroxide shampoos resolved or substantially improved clinical signs within 3 weeks in the majority of dogs with meticillin susceptible Staphylococci (MSS) superficial pyoderma.[100,101] Likewise, good response to topical therapy alone and no adverse effects were reported in 19 of 28 dogs with MRSP pyoderma and in all 14 dogs with MRSP pyoderma treated topically in other case series.[79,100,101] Furthermore, the efficacy of a twice-weekly chlorhexidine shampoo combined with daily chlorhexidine spray was shown to be comparable to oral amoxicillin-clavulanate in a four week comparative study in 51 dogs.[102]

Although the argument in favour of topical antibacterial therapy is convincing, the choice of drug, particularly in creams, gels and ointments, is more complicated. Geographical differences in availability and authorization for different species exist. In view of the potential for transmission of staphylococci between humans and animals, antimicrobial choices for treatment of animals need to take into account regional prescribing recommendations in veterinary and human medicine. Concern over resistance to fusidic acid, mupirocin and chlorhexidine exists; resistance genes and increasing MICs in staphylococcal isolates have been described in isolates from humans and animals.[97,103–106] However, the clinical relevance of currently known resistance markers and of higher MICs remains unclear for topical drug application and clinical treatment failure of topical anti-staphylococcal therapy has not been conclusively reported, to the knowledge of the authors.

Fusidic acid is included in different topical formulations (gels, ophthalmic and otic preparations) and approved for use in dogs in several European countries and in Canada but not, for example, in the US. It is also available as an anti-staphylococcal ointment for use in humans in Europe, Canada, Australia and countries in Asia, but also not in the US, and is available for systemic use in humans on both continents. In contrast, mupirocin is approved as an antibacterial ointment formulation in the US for use in dogs, but in most European countries, mupirocin is used only in humans as treatment of bacterial skin infections and as the most frequently prescribed antibiotic for MRSA decolonization.[107] In the UK, the British National Formulary recommends that mupirocin should be reserved for the eradication of nasal MRSA carriage in hospital patients and staff.[108] Mupirocin is not used systemically so that *in vitro* resistances may be less relevant as high drug concentrations are likely to be achieved at the site of infection or at carriage sites. In fact, previous treatment failures could so far be linked to environmental contamination or vector transmission, although caution should be used.[103] For fusidic acid, though, topical therapy has been associated with the emergence of strains showing high fusidic acid MICs and which may therefore fail to respond to systemic treatment in humans.[109] These differences in use and licensing between countries is unfortunate at a time when intercontinental travel of people, pets and their staphylococci continues to increase. However, although discussion should be encouraged in this area, only products approved for the respective species in each

country should be used in the interest of patient safety.

Consensus statement 7: Geographical differences exist in the availability and licensure of antimicrobial drugs for use in animals. Judicious use decisions need to take into account regional prescribing recommendations in veterinary and human medicine.

Despite the absence of reports on clinical treatment failure of topical anti-staphylococcal treatment so far, monitoring of MICs, clinical efficacy and further evaluation of topical treatment alternatives[110,111] such as hypochlorite (bleach), manuka honey and of synergistic combinations is warranted.[112,113] For MRS infections involving biofilm-producing strains (for example, around lip folds or implants), additional measures to improve efficacy of topical antibacterial agents may be needed. In addition, constant vigilance of owner compliance is indicated.

### 7.2 Systemic therapy

For deep pyoderma and for widespread or severe superficial infections and in animals that are not amenable to topical therapy, systemic treatment is indicated. Basic principles of responsible use of antibacterial drugs apply to MRS as for any other bacterial infections. For comprehensive information on treatment of canine staphylococcal skin infections, irrespective of MR, readers are referred to two published guideline documents, both available online with open access. Although MRS infections are mentioned, they are not discussed specifically. One document addresses diagnosis and treatment of canine bacterial skin infections and classifies drugs into first and second line antibiotics.[17,114] The other guideline, which represents a consensus by members of the Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Disease (ISCAID), focuses on management specifically of superficial bacterial folliculitis and groups antimicrobial drugs into first and second tier categories.[18] Both sets of guidelines include discussion of empirical and culture-based drug choices, adverse effects and dosage recommendations for antimicrobial drugs.

The efficacy of systemic antibacterial therapy for MRS infections depends predominantly on susceptibility of the organism but will also be determined by correct drug administration including accurate dosing, owner compliance and clinical variables such as severity of disease and causative and concurrent diseases. Due to the extensive MDR associated with all MRS, treatment choices for systemic therapy are substantially limited. Information from a published systematic review of evidence for systemic antimicrobial treatments in superficial and deep pyoderma are not applicable as no known MRS were included in the reviewed studies.[115]

Consensus statement 8: Empirical drug selection for systemic therapy is always contraindicated when a MRS infection is suspected based on historical factors, due to the high prevalence of multidrug resistance within these strains.

Susceptibility test results should always be available to make treatment decisions once MRS have been identified. However, if MRS is only suspected, for example following previous infections or based on cytological evidence of infection after antimicrobial therapy, a careful, susceptibility test-based approach is indicated to ensure best use of the remaining effective agents. This applies even though trends of susceptibilities may be known in some regions, at least for the most successfully spreading lineages. For example, for treatment of the currently dominant human healthcare associated MRSA CC22, which is also the MRSA lineage most frequently isolated from pets in the US and the UK, tetracyclines and trimethoprim-potentiated sulfonamides remain good treatment choices based on *in vitro* data and clinical case reports.[116] Amongst MRSS, susceptibility to tetracyclines and trimethoprim-potentiated sulfonamides had remained in over 80% of isolates as shown in large retrospective studies.[3,38] For MRSP, though, individual susceptibilities are infrequent and unpredictable.[3,80,117] In fact, molecular studies have shown that the presence of individual resistance genes can vary even on a single mobile genetic element and within the same lineages.[78,118]

Amongst antimicrobials for which *in vitro* testing has shown susceptibility of a particular isolate, the choice will be based on clinical characteristics. No single drug has been shown to be better than another in a Cochrane review on antibiotic treatment of MRSA wounds in humans.[119] If the initial laboratory report includes susceptibilities to drugs that are available and licensed for the species, these should be considered first. Additionally, preference should be given to agents with a narrow anti-staphylococcal spectrum and to considerations of safety and patient characteristics such as previous adverse drug reactions, concurrent disease, practicalities in dosing and cost as for other drugs. Specific points to consider for licensed drugs in the context of MRS are:

1. Beta-lactam antibiotics should not be used for MRS infections, irrespective of the susceptibility report.[89] Although third-generation cephalosporins have a broader spectrum of efficacy than first-generation cephalosporins, they do not have efficacy against MRS, as shown for cefovecin[120] and cefpodoxime.[121]
2. Care is needed when interpreting clindamycin susceptibility because inducible resistance has been reported in MRSA and MRSP associated with certain sequence types.[122] Erythromycin-clindamycin-D-zone testing is recommended prior to treatment to avoid treatment failure, particularly with MRSA.[123]
3. Resistance to the tetracyclines is mediated by four different genes and the genes most commonly expressed by *S. pseudintermedius* are *tet*(M) and *tet*(K). Strains which possess only *tet*(K) maintain susceptibility to minocycline but not to other tetracyclines. The newly approved canine breakpoints for doxycycline[124] are a reasonable surrogate for

**Table 2.** Second tier antimicrobial drugs not widely approved in many countries that may be considered for systemic treatment of meticillin-resistant staphylococci pyoderma in dogs after susceptibility testing

| Antibacterial agent | Chloramphenicol | Doxycycline | Minocycline | Tetracycline | Amikacin | Gentamicin | Tobramycin | Netilmicin | Rifampicin |
|---|---|---|---|---|---|---|---|---|---|
| WHO classification | HI | HI | HI | HI | CIA | CIA | CIA | CIA | CIA |

HI highly important antimicrobial for human medicine, CIA critically important antimicrobial for human medicine.[129]

minocycline susceptibility.[125] Tetracycline may be used as a surrogate for testing susceptibility to doxycycline, but canine-specific MIC or disc-diffusion breakpoints should always be used.[124]

4 Where possible, empirical choice of fluoroquinolones should be avoided, particularly when an MRS is suspected. For the first-generation fluoroquinolones in particular, the disparity in resistance rates between MRSP and meticillin susceptible *S. pseudintermedius* (MSSP) is striking;[3] and fluoroquinolone use has been associated with increased rates of MRSA in human hospitals.[126] However, where susceptibility to fluoroquinolones is confirmed *in vitro* for an MRS isolate, this risk needs to be balanced with the safety profiles of the other drugs available according to the antibiogram.

When no susceptibilities to clinically relevant, routinely used and licensed antimicrobials are reported, extended resistance testing needs to be requested from the laboratory. A list of agents then to be considered and for which some information on treatment of canine MRS infections has been published.[127,128]

It is important to remember, though, that the majority of antimicrobial drugs mentioned here are listed as critically important antimicrobials (CIA) for human medicine in the most recent, third revision of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR).[129] This does not just apply for drugs which are not widely approved for veterinary use. Even those approved in many countries for use in pets, such as amoxicillin, the fluoroquinolones and the third-generation cephalosporins (cefovecin, cefpodoxime), are classified as CIA (Table 2). Of the antimicrobial agents frequently used in small animal practice, only first-generation cephalosporins (e.g. cefalexin, cefadroxil), clindamycin and lincomycin, fusidic acid, the tetracyclines and sulfonamides are included in the second category of highly important for human medicine.

For the glycopeptides (vancomycin, teicoplanin, telavancin), linezolid (oxazolidinone) and potentially new compounds in the future, this group of authors recommends implementation of a restriction-of-use protocol as already in place at one of the author's institution.[130] Briefly, prescriptions would be considered appropriate after discussion with a specialist experienced in treatment of infectious diseases, after it could be shown that the patient's infection requires systemic therapy, is life-threatening but with a reasonable chance for survival following treatment, and when *in vitro* susceptibility has been shown for the relevant pathogen without other treatment options available based on susceptibility testing and patient's medical circumstances. Glycopeptides and linezolid are drugs needed in human medicine for the treatment of serious infections due to Gram-positive bacteria (e.g. peritonitis in peritoneal dialysis patients, endocarditis) or for surgical prophylaxis if there is a high risk of MRSA. Vancomycin and teicoplanin given orally (poor enteric absorption) are further used in the treatment of *Clostridium difficile* infection. Recently, increasing vancomycin resistance amongst enterococci (VRE) has become a major concern in human and veterinary medicine, and individual isolates of vancomycin-resistant MRSA also have been reported.[131–133]

Consensus statement 9: A restriction-of-use policy should apply to glycopeptides (vancomycin, teicoplanin, telavancin), linezolid (oxazolidinon), anti-MRSA cephalosporins and potentially new compounds that may be approved in the future for treatment of MDR pathogens of people.

Some general recommendations on duration, dosage and combination with topical therapy apply for MRS infections in the same way as for meticillin susceptible staphylococcal (MSS) infections. An excellent review is provided in the ISCAID document on the treatment of superficial bacterial folliculitis.[18] Clinical trials of antimicrobial efficacy for the treatment of pyoderma have not been designed to determine a true and universal cut-off point for duration of therapy. However, as noted by a consensus statement on therapeutic antimicrobial use in animals, durations of treatment are typically shorter in humans than in animals, with little apparent justification for this difference.[134] In summary, good evidence for recommendations on treatment duration is sparse and specific dose assessment for treatment of MRS has not been published. In the absence of such data, current published advice on the duration of treatment (3 weeks for superficial pyoderma or 1 week beyond clinical resolution and 4–6 weeks for deep pyoderma or 2 weeks beyond clinical resolution) remain the standard.[17,18] The authors concur with the ISCAID guidelines which suggest that if treatment regimens are prescribed for <3 weeks duration, the attending veterinarian should be confident that the patient will be presented for re-evaluation prior to discontinuation of therapy.[17]

The combination of systemic therapy with topical antibacterial treatment is recommended whenever possible to reduce environmental contamination and the risk of transmission to other hosts, and potentially to abbreviate the duration of systemic drug exposure.

## 8 Treatment outcomes for staphylococcal infections

Veterinary case-control studies have shown that MRS infections do not necessarily have less favourable outcomes than MSS infections in dogs and cats, as long as a safe antimicrobial alternative is available for

treatment.[37,38,79,135] Treatment outcome of MRS infections in small animals appears to depend on restoring the skin barrier function and removal of implants combined with antibacterial therapy, either by topical, systemic or intralesional route. However, when inserted into a highly virulent strain, extensive antimicrobial resistance may greatly complicate therapeutic interventions and could ultimately worsen outcome if resistance is not promptly identified and proper therapy instituted.

Outcomes of MRSA infection in comparison with MSSA infection are frequently studied in human hospitals due to concern about increased mortality from drug resistance and also to assess the impact on healthcare cost. Although some of the more recent reports appear to document an increased risk of mortality in certain patient groups with MRSA,[136] conflicting results remain, likely due to the heterogeneity of MRSA infections (blood stream infections versus skin and soft tissue infections) and healthcare provision and bias from patient characteristics (age, co-morbidities). In a case series of 11 dogs with MRSA surgical site or skin infection, systemic antibacterial therapy based on susceptibility testing improved or resolved the infection in nine of 11 dogs; one dog had been euthanized with radiographic evidence of osteomyelitis, the other lost to follow-up.[116] In a multi-institutional retrospective case-control study of 40 dogs with MRSA infection and 80 dogs with MSSA infection, no significant differences in duration of hospitalization or euthanasia rates were found. Most infections were limited to the skin, with no difference in body tissue/organ distribution between the groups.[37] In a small retrospective case-control study of 11 cats with MRSA and 29 cats with MSSA, no statistically significant differences between groups were detected in signalment or mortality, nor subjective differences in clinical signs/morbidity and response to therapy based on culture-directed antimicrobial therapy.[135]

For *S. pseudintermedius*, a retrospective comparison of medical records of 123 dogs with MSSP pyoderma and 93 dogs with MRSP infections showed no difference in outcome between groups, although individual MRSP infections took longer to resolve.[79] Likewise, of 12 pets with MRSP infection, clinical signs resolved or markedly improved in 11 patients; one dog was euthanized with signs of osteomyelitis after chronic otitis media.[117]

It may be concluded, therefore, based upon these limited clinical data, that MRS are generally no more virulent than MSS and not associated with a worse outcome. The findings of clinical reports are compatible with the lack of genetic markers for invasive behaviour so far identified in staphylococci. A large microarray study previously compared invasive clinical *S. aureus* isolates with nasally carried strains from humans and concluded that the outcome of the patient–staphylococcal relationship was strongly dependent on host factors.[137] Likewise, known *S. pseudintermedius* toxin genes such as *siet* and *luk I* have been described in MSS and MRS with no known association with specific disease or prognosis.[138–140]

In summary, with the potential for selection, referral and many other study design biases in mind, it has to be concluded that there is little evidence for a difference in outcome between MRS and MSS infections in animals and that the prognosis for MRS skin infections in pets is good, depending on underlying causes and co-morbidities. This of course assumes that an effective drug has been selected for treatment, either empirically or based upon culture and susceptibility testing.

Consensus statement 10: There is little evidence for a difference in outcome between MRS and MSS *Staphylococcus* infections in animals, and the prognosis for MRS skin infections in pets is good, depending on the underlying cause and co-morbidities.

## 9 Follow-up after infection has resolved

Once MRS infection has clinically resolved, humans and animals can continue to carry MRS at skin and mucosal sites. For MRSP, it was shown that carriage can persist on dogs for more than 1 year after clinically apparent infection had resolved.[141] Such MRS carrier animals or contaminated pets can pose a risk to susceptible in-contact people and animals as staphylococci typically reside on surface sites ideally suited to transmission by direct contact, such as licking.[142] Furthermore, staphylococci adhere to corneocytes[143] and can be transmitted via indirect routes through desquamation and shedding into the environment, enhanced by their ability to survive on surfaces for many months.[144,145] For MRSA, there is ample, although still indirect, evidence for transmission from pets to people and vice versa[103,145–147] via either or both direct and indirect routes; transmission of MRSP between hosts has been reported less frequently. However, environmental MRSP contamination was associated with the presence of infected or colonized index dogs in two studies where MRSP-infected dogs, in-contact animals and people and environmental sites were sampled over time.[148,149] The results of both studies indicated that MRSP could be easily transmitted to dogs but not to people. This finding is further supported by *in vitro* adhesion tape corneocyte assays which showed that *S. pseudintermedius* adhered better to canine corneocytes, whereas *S. aureus* showed preference to human squames.[143]

The need for identification of carrier animals after resolution of infection remains controversial. Recommendations on carrier swabbing and management of healthy carrier animals vary within the Guideline Panel (GP). In countries where the prevalence of MRS is low, such as in the UK where MRSP has accounted for <1% of clinical *S. pseudintermedius* submissions between 2006 and 2012,[150] identification of carrier animals and continuation of infection control measures, including topical antibacterial therapy, until carriage swabs are negative can have a positive effect on limiting the spread of MRSP. In high-prevalence countries, this 'stumping out' approach is less likely to result in meaningful action (see below under 'screening').

## 10 MRSA decolonization in human medicine

In a medical context, the term "decolonization" is most commonly used to describe a reduction of MRSA from skin

and mucosal carriage sites through antimicrobial treatment. Eradication of MRSA from all carriage sites with practical and safe antibacterial therapy is unlikely. Alternatively, decolonization may occur naturally if a patient loses MRSA carrier status without medical intervention over time.[151] The efficacy of a combination of decolonization treatment with MRSA surveillance sampling, mostly prior to hospital admission, in the prevention of healthcare-acquired infections is supported by good evidence from a systematic review of 83 European studies published between 2000 and 2012.[152] However, decolonization remains a controversial topic in human medicine as efficacy is often short term, best protocols are not established, ethical concerns remain about the use of antimicrobial agents in essentially otherwise healthy carriers, and adverse events and development of resistance during therapy has been reported.[153] Systematic assessment of decolonization regimes include variation in outcomes assessed (e.g. negative culture at different time points, effect on bacteraemia rates or surgical site infections), the competing effects of additional environmental hygiene interventions, differences in transmission pathways between settings and, importantly, the effect of MRSA prevalence on screening, isolation and decolonization.

A justification for decolonization is supported by the finding that 80% of *S. aureus* bacteraemia cases in humans were shown to involve genetically identical isolates as those carried by the patient nasally on admission, suggesting that carried strains are well adapted to their host and thus, with an advantage for proliferating to infection should the opportunity arise.[154] Even though data on the impact of pre-operative nasal MRSA carriage on post-operative MRSA infection are conflicting,[155,156] the concept is plausible that eradication of MRSA carriage can reduce the risk of MRSA infection from endogenous MRSA. However, decolonization of a single host would not be expected to impact the re-acquisition of MRSA through transmission from in-contact people or from environmental contamination.

## 11 Decolonization in dogs

In dogs, no studies have assessed the need or best protocols for decolonization of MRS carriers. However, a small number of longitudinal studies of MRSP carrier dogs are reported and similarities between human *S. aureus* carriage and canine *S. pseudintermedius* carriage exist that may allow comparison and possibly support or refute a case for screening and decolonization or at least conclusions on hygiene recommendations.

Mucosal *S. pseudintermedius* carriage appears to play a similar role in canine skin infection to that described for *S. aureus* blood stream infection in humans.[154] In dogs, 80% of *S. pseudintermedius* carriage isolates from mucosae were genetically identical to isolates from pustules of the same dog.[157] For MRSP in particular, a prospective multicentre study of 549 dogs showed that MRSP carriage on admission predisposed to post-TPLO surgical site infection with an odds ratio of 6.72.[158] MRSP carriage appears to be a common sequel to infection as shown through longitudinal sampling after resolution of infection. In 42 dogs sampled after clinical resolution of their MRSP infection, MRSP carriage was detected in 61.9% between 3 and 15 weeks after initial presentation,[36] and persistence of carriage could be shown to last for up to 11 months following clinical cure of infection.[141]

## 12 Natural decolonization

Natural decolonization—the loss of MRS from carriage sites without on-animal treatment— is likely to occur due to competition within the bacterial microflora. Multidrug resistance in a bacterial isolate improves the probability of survival at times of drug treatment. However, this advantage fades when treatment stops and carriage or expression of resistance genes becomes a metabolic burden for the MDR strain competing for its niche. Such fitness cost in exchange for drug resistance has been well documented for *S. aureus* and the emergence of different successful MRSA lineages over time.[159–162]

Evidence for natural decolonization is difficult to find, in part because environmental contamination is closely interlinked but more difficult to assess. Carriage swabs, taken at a single occasion and processed by selective culture for the MRS target organism, will identify colonizing bacteria but also transient contamination of carriage sites, either from the environment or contact with infected sites. Such transient carriage was illustrated in an older study where human hospital nurses were sampled for MRSA carriage immediately following a duty shift and of 13 carriers, 12 were found to be negative the following morning before duty.[163]

Natural decolonization was also demonstrated in healthy MRSA carrier dogs kept in regularly cleaned environments. Ten of a total of 129 dogs at a rescue facility were found positive for MRSA at mucosal and skin carriage sites, whereas all 16 companions sharing a kennel with one of the carriers were negative. All carriers sampled negative within 2 weeks. Kennels were cleaned twice and disinfected once daily.[164] In a cross-sectional study of dogs and cats that resided with human MRSA patients, the odds of MRSA isolation from "carriage" sites decreased by 14% for each day that pet sampling was delayed after the person started antimicrobial therapy.[31] These studies suggest that dogs do not support MRSA carriage for long periods, at least in clean environments. MRSP carriage on the other hand, was shown to persist for over 12 months after infection had resolved albeit in household settings without special cleaning interventions.[36,141,148]

## 13 Would decolonization with antimicrobial agents work?

Resolution of MRS infection is a pre-requisite of decolonization as carriage sites will otherwise be contaminated by pathogens. MRSP decolonization with systemic therapy, even using agents to which the MRSP shows *in vitro* susceptibility, is unlikely to be effective based on the persistence of MRSP carriage after successful treatment and resolution of pyoderma shown in two studies.[36,141] Decolonization using topical antimicrobial agents can be effective at least for short periods. Significant reductions

in cfu of *S. pseudintermedius* from treated mucosal carriage sites and untreated cutaneous sites have been seen following twice daily application of fusidic acid in a 1% viscous eye drop formulation.[165] Mucosal treatment reduced bacterial counts typically from multiples of $10^3$ to less than 10 colony-forming units per swab at 2 days after treatment and reduced *S. pseudintermedius* counts were still seen 3 weeks after cessation of fusidic acid therapy. Provided that there is good compliance, the same effect may be expected against MRS carriage in dogs as MICs of antibacterial agents available for use in pets tended to be low.

### 13.1 Conclusions on decolonization

Consensus statement 11: There is currently not enough evidence to recommend routine decolonization of MRS carrier animals.

However, MRS carrier dogs pose a risk to susceptible in-contact humans and animals through direct contact and contribute to MRS contamination of their environments. Natural decolonization should be supported through rigorous hygiene measures, where possible combined with temporary isolation to ease cleaning and disinfection.

## 14 Methods for establishing strain concordance in a proposed "outbreak"

Molecular characterization of staphylococcal strains is a widely used research tool that can provide information about genetic relatedness, evolutionary history, virulence factors, mechanisms of antimicrobial resistance and other properties. It can be used as part of molecular epidemiological investigation for various reasons, such as determination of whether a group of infections are potentially linked or to determine whether infections are caused by a recognized or new strain. A range of methods is available and selection of methods for a particular investigation is based on a combination of factors, such as availability, cost, throughput and discriminatory power.[1–5,166–170] Common methods are outlined in Table 3. As a general trend, access to inexpensive Next Generation Sequencing (NGS) has determined a gradual shift from DNA band-based methods such as PFGE to sequence based methods such as MLST and *spa* typing.

Although typing methods are widely available, molecular characterization typically provides limited clinically relevant information and typing of isolates is usually reserved for rare situations such as outbreaks. Typing is an important component of outbreak investigation, but even within outbreaks, the usefulness of typing may be limited, depending on the organism, epidemiology, typing method(s) and investigation goals. In the context of investigation of a potential outbreak, identification of different strains can provide assurance that a single point source is not present. Finding indistinguishable isolates according to one or even two typing mechanisms *suggests* that they *might* be linked, but this depends to a large degree on the discriminatory power of the typing method. Typing alone may not be definitive,[171] although advances in typing methods, particularly whole genome sequencing, increase the potential yield of molecular investigations. Whole genome sequencing currently is used almost exclusively in the research setting as real-time analysis, necessary for clinical application, is difficult and resource intensive. As ease and speed of sequencing and data analysis improve, this will likely become more clinically applicable in the near future.

Some pathogens are relatively clonal, with a small number of discernible strains present in a circulating area. MRSP exemplifies this situation, with a small number of clones, predominating internationally and locally.[80,166,167] Thus, identification of the same strain in a group of cases from a clinic could represent a true outbreak or simply the 'background' molecular makeup of MRSP in the region. Typing can provide useful data, but those data must be evaluated with an understanding of the typing method (e.g. What it is assessing? What is the discriminatory power?) and with corresponding epidemiological data.[172] From a clinical standpoint, the potential actions that would result from obtaining typing data must also be considered. Although it is possible that identification of a clonal outbreak of a

**Table 3.** Comparison of common molecular typing methods for discrimination of meticillin-resistant staphylococci (MRS)

| Method | Inter-laboratory comparison | Throughput | Discriminatory power | Comment |
|---|---|---|---|---|
| Pulsed field gel electrophoresis (PFGE) | Moderate/low? | Moderate | Excellent | Common method but limited by inter-laboratory variation. Good for within-lab comparison of isolates or when reference stains are available. |
| Spa typing | Excellent | High | Variable (species dependent) | Widely used tool for routine typing of *Staphylococcus aureus*. Less useful for *S. pseudintermedius*. |
| Multi-locus sequence typing (MLST) | Excellent | Moderate | Moderate | Good for evolutionary studies and broad comparisons. Not available for MRSS. |
| Dru typing | Excellent | High | Good | Can only be performed on MRS. |
| *SCC*mec typing | Moderate | Moderate | Low | Limited discriminative power. Good for broad characterization of types and evolutionary studies. Not useful for outbreak investigation. Can only be performed on MRS. |
| Whole genome sequencing | Excellent | Low | Excellent | Ultimate method that will become the standard as costs and analytical challenges decrease. It can be used to perform any other sequence-based method listed in this table. |

MRSS meticillin-resistant *Staphylococcus schleiferi*.

*Staphylococcus* would lead to a specific infection control intervention, this would be uncommon. Most often, typing provides interesting data about the epidemiology and ecology of the organism, but does not have any impact on patient- or even clinic-level management. Molecular characterization is therefore typically reserved for research studies. If an ongoing, large or unusual cluster of staphylococcal infections is occurring within a clinic, there might be a benefit to characterization of isolates; however, that should only be considered as part of a broader infection control investigation, typically with the involvement of infectious disease specialists.

Questions often arise about characterization of isolates from animals when there may be a corresponding human infection, typically involving MRSA. Characterization of human and animal isolates in those situations is interesting but provides little practical information. From a logistical standpoint, there can be challenges in securing both human and animal isolates and having them transferred to the same laboratory. This may not be required for all methods, because some (e.g. spa typing) are amenable to accurate inter-laboratory comparison. However, more subjective methods such as PFGE should be performed side-by-side in the same laboratory. Even if isolates are obtained and able to be tested, the relevance of the results is usually unclear. For example, finding the same strain of MRSA in a person and pet is interesting, and supports interspecies transmission. Yet, it is difficult to elucidate direction of transmission, or even if there was transmission between those individuals.[31] It is possible that both human and pet could be exposed by another unknown individual (human or animal) or via a shared environment. Whole genome sequencing can provide important insight into some outbreaks, where subtle changes in the pathogen over time can be used to elucidate potential sources and directions of transmission. This is most applicable to outbreaks or high endemic infection rates that occur over time.

Consensus statement 12: Molecular strain typing methods are research tools used to investigate the epidemiology and ecology or certain outbreak situations of MRS. However, the clinical value of strain typing largely depends on the organism's population structure, the typing method(s) used and the goals of the investigation. Strain typing rarely has impact on patient- or clinic-level management.

## 15 Veterinary hospital infection control

There is an ever-present risk of MRS exposure for patients and humans in a veterinary hospital. *Staphylococcus aureus*[5,10] and *S. schleiferi*[173,174] are well-documented human pathogens, so potential for cross-species transmission exists. Although not considered to be a human pathogen, *S. pseudintermedius* can be detected by culture of nasal swabs from dog owners[149,175–177] and veterinarians.[149,178] However, human nasal carriage appears to be fleeting.[177] As opportunistic pathogens that are not uncommonly found as part of the commensal microbiota, every human or animal poses some risk of introducing an MR *Staphylococcus* into the facility. Routine infection control practices are the cornerstone to control of MR staphylococci. This involves a collection of procedures and practices designed to reduce the risk of exposure to various pathogens. "Good routine practices done consistently and well" should be the emphasis. Design and implementation of an infection control programme is beyond the scope of this document, but some good general resources are available.[179–181] Selected areas are briefly outlined below.

### 15.1 Personal protective equipment

Personal protective equipment (PPE) is designed to protect the wearer, preventing contamination of underlying skin and clothing, as well as protect patients from exposure to contaminated body surfaces and clothing.[182] Routine personal protective equipment is ideally a laboratory coat over street clothes or scrubs, as the laboratory coat provides full torso and arm coverage and can be changed easily. Scrubs are often worn by veterinary personnel but should not be the outer PPE layer because they do not provide arm cover and are not as easy to change. When possible, coats and scrubs should be laundered routinely in hospital rather than at home to reduce microbial contamination and take-home exposures.[183] Ties, scarves, lanyards and other accessories that may become contaminated should be covered by outer PPE or not worn.[184]

In some situations, enhanced PPE may be required. This would include one or more of the use of a gown or outerwear layer that is only used for one patient, gloves, mask, eye protection or face protection.[185] No data exist regarding optimal PPE practices for handling animals infected with MR staphylococci. However, the use of some degree of enhanced precautions to reduce contamination of clothing and skin is reasonable. Typically, this would consist of a gown or dedicated laboratory coat and gloves. Disposable gloves can be effective additional barriers but are often misused.[185] Common errors with glove use are continuing to wear the gloves after the patient contact and contaminating various surfaces, as well as failure to perform hand hygiene after glove removal. Masks are occasionally used in human healthcare when managing MRSA-infected patients, mainly to reduce hand to nose contact (and the associated risk of becoming colonized). The same could be considered in veterinary hospitals, particularly with personnel who frequently touch their face inadvertently during patient care. However, masks are rarely used or indicated.

When to use routine versus enhanced practices has not been well defined in the context of veterinary dermatology. The combination of a high prevalence of MR staphylococcal infection or colonization in the caseload and frequent contact with animals at increased risk of staphylococcal infection (e.g. diseases that affect the normal skin barrier) presumably creates abundant risk of MRS transmission in many dermatology practices. In areas where the prevalence of MR staphylococci is high, consideration should be given to enhancing routine PPE, such as changing laboratory coats between patients and

wearing gloves for any contact with potentially infected or compromised skin.

### 15.2 Hand hygiene

Hand hygiene is perhaps the simplest and least expensive infection control practice, but it also tends to be poorly used.[186] The role of hands in transmission of MR staphylococci between patients or as a source of infection of personnel is unknown, but probably substantial. Proper hand washing and drying,[187] or use of an alcohol-based hand sanitizer,[188] can effectively reduce staphylococcal skin contamination and therefore presumably reduce the risk of MR staphylococcal transmission. The actual efficacy of hand hygiene is unclear, even in human medicine, because it is exceptionally difficult to differentiate the role of hands versus other sources, but hand hygiene compliance is a major component of virtually any infection control programme.

Ensuring adequate numbers, accessibility and stocking (soap, paper towels) of sinks can facilitate hand-washing compliance; however, hand washing can be limited by access to sinks, and adding or repositioning sinks is often cost-prohibitive. Alcohol-based hand sanitizers can be provided to personnel and easily placed or mounted throughout a facility, facilitating access to hand hygiene in all patient care areas. Hand washing should be performed when there is abundant gross contamination (e.g. pus) of the hands, but, otherwise, hand washing and hand sanitizers are essentially interchangeable. Hand sanitizers may be less damaging to the user's skin with frequent use.

Consensus statement 13: Hand hygiene (proper washing/drying and use of alcohol-based hand sanitizers) is the mainstay of personal responsibility for infection control. No data exist regarding optimal PPE practices for handling animals infected with MRS. However, the use of some degree of enhanced precautions to reduce contamination of clothing and skin is reasonable. Typically, this would consist of a gown or dedicated laboratory coat and disposable gloves.

### 15.3 MRS case or carrier? Isolation practices

Isolation is designed to limit direct and indirect contact between an individual and other individuals, as well as the general environment. It is an effective tool for reducing transmission of various pathogens, including those such as staphylococci that are spread primarily by direct and indirect contact. In human medicine, contact precautions are typically used with MRSA-infected individuals. This usually involves housing the patient in a private room, limiting visitation and using enhanced protective equipment for any patient contact. In veterinary hospitals, isolation may involve housing a patient in a dedicated isolation ward or using enhanced precautions in a general ward. Although direct and indirect transmission should be able to be effectively controlled in a general ward with isolation practices, physical and procedural separation (isolation unit) is presumed to be more reliable than procedural separation alone. The size of the isolation unit, ability to perform patient care activities in isolation, number of animals with MRS infections and nature of the rest of the hospital caseload (e.g. presence of a large population of high risk surgical cases) impact decisions on whether to house animals with MRS infection or colonization in isolation or wards. Regardless of the location, clear management policies (e.g. cleaning and disinfection, animal movement, PPE) must be available.

### 15.4 Cleaning and disinfection

Cleaning and disinfection are designed to reduce or eliminate pathogenic burdens in the environment and on equipment.[189,190] Routine cleaning and disinfection practices are the most important part of a comprehensive programme. Staphylococci are readily inactivated by routine disinfectants, including those that predominate in veterinary facilities (e.g. quaternary ammonium disinfectants, accelerated hydrogen peroxide). However, cleaning and disinfection are two separate steps, and cleaning is required for effective disinfection. Failure to properly clean a surface can result in ineffective disinfection through inhibitory effects of organic debris (e.g. dirt, hair, pus) and biofilm. Good cleaning will remove the majority of contaminants and prepare the surface for effective disinfection. In addition to a proper surface, adequate disinfection requires an appropriate concentration (dilution) of the disinfectant and the proper contact time, which varies between products. Of note, recontamination following cleaning is typical, which emphasizes the importance for such practices to be conducted on a frequent schedule.

Enhanced practices are sometimes used in response to specific contamination events or cases. Because MRS are susceptible to commonly used disinfectants, identification of an infected patient does not necessarily mean that a change in cleaning and disinfection is needed. Periodically, MRS-harbouring genes (e.g. *nor*A, *qac*A/B) that confer resistance to certain disinfectants may be identified, and such situations may warrant closer examination of disinfection protocols.[191]

If routine cleaning and disinfection are performed properly, no additional work should be needed. This emphasizes the need for a properly designed cleaning and disinfection programme, with documentation of disinfectant practices (product, dilution, contact time), when cleaning and disinfection must be performed, and related basic information. In some situations, changes to the timing of cleaning and disinfection may be indicated, such as performing this immediately after an infected patient leaves the room rather than at the end of the day. Disinfection of items that are not routinely disinfected might also be considered, such as clippers after use on an infected patient. However, because only a potentially small percentage of animals harbouring MRS are known at the time of examination, focusing cleaning and disinfection (and other infection control practices) on the known cases risks missing a large number of other infectious individuals. This emphasizes the importance of routine, consistent general practices rather than MRS-targeted practices.

Consensus statement 14: In contemporary veterinary practices, routine cleaning and disinfection protocols are the cornerstone of hospital infection control. MRS are susceptible to commonly used disinfectants. Protocols should be designed to reduce or eliminate pathogenic burdens in the environment and on equipment. These protocols must be communicated clearly (and often) to the hospital team and practiced correctly and consistently.

### 15.5 Identification of infected animals

Identification of MRS infections is important for case management and infection control purposes and this can only be achieved through diagnostic testing. Early identification of MRS infections is important, so diagnostic testing prior to empirical treatment is preferred, although the realities of clinical practice can limit testing. Testing should be considered to be particularly important with serious infections and infections that have not responded to empirical therapy. It also should be strongly recommended in situations where a resistant pathogen is more likely, such as in animals with previous MRS infection, recent antimicrobial exposure, recent hospitalization or those that live with a person or animal with a history of MRS infection. Testing of potentially hospital-associated infections is also beneficial to provide important information about endemic rates and to identify clusters of infections as early as possible.

### 15.6 Surveillance

Related to identification of infected animals is recording of data pertaining to infections. Understanding endemic rates of disease is critical for accurate and prompt identification of 'abnormal' rates, whether it is a gradual change in rate or a sudden high-incidence outbreak.[192]

The most common and practical form of surveillance in veterinary hospitals is passive surveillance. This involves recording (or being able to retrieve) basic data about disease incidence or characteristics (e.g. antimicrobial susceptibility profiles). Understanding the typical incidence of MRS infections can be facilitated by central recording of MRS diagnoses from routine clinical activities. This can be used to generate information about the baseline/endemic rate, which can be monitored over time. Changes in rates can then be investigated. Antimicrobial susceptibility data also can be monitored to provide guidance for empirical therapy and to detect changes that might suggest a change in the epidemiology of the pathogen in the clinic or region. Use of electronic health records and laboratory software programs for tracking data can enable or enhance these passive surveillance activities. This can be of use for practice-specific decision making, as well as provide data that can be used for broader evidence-based guideline development.

Active surveillance is a more expensive and time-consuming method that involves *de novo* collection of data for infection control purposes, such as MRSA or MRSP screening at the time of admission. Active surveillance is rarely used in veterinary hospitals because of the cost, time commitment, relatively low burden of hospital-associated MRS infections and limited evidence of usefulness. Active surveillance might be useful as a periodic surveillance tool to understand the epidemiology of MRS in a clinic, or in response to an increased incidence of disease or an outbreak, but such situations would be uncommon. Any active surveillance should be designed with the input of a specialist to ensure that useful data are obtained and that resources are effectively used.

### 15.7 Community spaces

Control of MRS at the community level is exceptionally complicated, in part due to the overlapping human and animal epidemics and shifting epidemiology on both sides. On one hand, limiting further dissemination of important pathogens such as MRSA and MRSP is a laudable goal. On the other, if these are carried by even a small percentage (e.g. <1–3%; see Table 1) of healthy individuals, it becomes clear that animals with known infections constitute only a fraction of the pool of potentially infectious individuals. They might pose a somewhat higher risk because of higher staphylococcal burdens at infected sites; however, virtually nothing is known about the relative risk of transmission from healthy versus clinically infected versus recently infected individuals.

It would be logical to consider a few different groups in terms of risk of infectivity. Individual animals at highest risk are those with active MRS SSTIs that may be shedding the organism from both the site of infection and colonization sites. The next risk group would be animals with recent infections. Duration of shedding has not been well defined, and appears to differ among staphylococcal species and hosts. In general, it is thought that MRSA shedding is relatively short term (days to weeks) after resolution of clinical infection,[142,164,193] whereas MRSP shedding may be prolonged in some individuals, especially dogs.[141,148,149] The potential for long-term (months to years) shedding of MRSP post-infection complicates control measures because no defined period of risk can be given in the absence of testing. Another group would be individuals with known risk factors for MRS carriage, such as recent antibiotic exposure, visitation of human hospitals or hospitalization in a veterinary clinic.[142,194–197] Animals in this group could be highly variable, and this variability could mean that the potential risk conferred is best assessed on an individual basis. Beyond these would be the 'lowest' risk population, healthy animals with no hospitalization or antibiotic exposure. However, even in this population, MRS carriage is possible. Therefore, although some animals likely pose greater risk than others, any community-level contact with an animal is presumably associated with some (albeit low) risk of MRS exposure. Further, although the risk posed by any individual animal–animal or human–animal contact is presumably low, there is an accumulating risk of MRS carriage with more contacts. More contacts, and more contact with higher-risk individuals, presumably increase the risk of community-based transmission. This applies for virtually every other infectious disease and should not itself be taken as an indication of the need for social distancing or contact isolation.

Determination of how to manage community risk is difficult because of a lack of clear data and the

  

subjective (and variable) determination of costs versus benefits. Social aspects of animal–animal and animal–human interaction are difficult to quantify but should not be ignored. Other benefits such as exercise and practical aspects of boarding (day care or longer term) also bear consideration. Further, it is possible that animals harbour microbes or participate in microbial sharing that increases beneficial bacterial diversity for in-contact animals and humans.[30,198] Case-by-case consideration of the costs and benefits to the individual animal, the animal's family, and broader human and animal populations should be performed, as difficult as this may be.

In terms of restriction of individuals conferring risk, the greatest attention should be paid to individuals with active infections, because they likely constitute the greatest risk. Restricting these individuals from contact situations (e.g. dog parks, play groups, competitions, and kennels) is logical. How long to do so is unclear, as risk is presumably highest prior to the onset of treatment, with a relatively rapid decline thereafter. Considering the potential duration of treatment of staphylococcal skin infections, restrictions throughout the entire treatment period can become problematic. In lieu of data to guide recommendations, it is reasonable to restrict animals from contact situations until treatment has started and a clinical response is evident. Thereafter, some degree of elevated risk is still presumably present, perhaps more from carriage sites than the infected site. Although recently infected animals or those with risk factors for carriage (e.g. recent hospitalization) likely pose additional risk, the costs of restriction may outweigh the benefits, and the presence of an unknown but not insubstantial pool of other MRS carriers limits the benefits of restricting this small but known population. Human guidelines for management of community-associated MRSA, even in high risk environments such as childcare or sports teams, do not recommend exclusion of colonized or high-risk individuals.[198,199] Instead, they focus on covering infected sites (something that is rarely possible with skin infections in animals) and general personal and environmental hygiene practices.

Correspondingly, management of particularly susceptible individuals that are at increased risk of acquisition of MRS or increased risk of progression to clinical infection given MRS exposure is worthy of consideration. In some situations, a period of increased risk is short and defined, such as after undergoing surgery, having a wound, or being treated with an antimicrobial or short-term immunosuppressive therapy. It is easier to justify short-term restriction such as keeping dogs away from off-leash parks, playgroups or kennels during a defined and short-term period of risk, because the costs may be limited and manageable. When individuals have persistently elevated risk (e.g. uncontrolled inflammatory skin disease, chronic immunosuppressive therapy), the issue becomes more complicated. Overall, the risk of mixing in community settings is presumably low, even in high-risk individuals. Basic practices such as limiting overall dog–dog contact, trying to keep dog–dog contact to defined groups (as opposed to random encounters with a more variable population), avoiding contact with animals that may be at increased risk (something that is difficult to identify but possible in some situations) and avoiding contacts during periods of heightened risk (e.g. an atopic flare) are logical but unproven.

Consensus statement 15: Transmission of MRS by infected pets to other individuals in the home or community is known to occur, but data to guide recommendations are incomplete. In lieu of such data, it is reasonable to restrict animals from contact situations until treatment has started and a clinical response is evident. In the home, this could include social distancing from 'at risk' individuals and enhanced hygienic measures for the occupants and the environment.

## 16 In-home mitigation

Within the community, households have shown the greatest potential, not just as a point of transmission of relevance in a clinical context for both people and pets, but also as a potential intervention point.[32] Exchange of staphylococci between humans and pets, both in the context of recurrent disease and colonization, may be common. Humans, other companion animal household members, and home environments (including pet bedding) have been implicated in or associated with staphylococcal carriage or infection in dogs and cats.[171,176,178] The potential for transmission of staphylococci among all human and animal members of the household, to home surfaces, and from home surfaces is accepted, although consensus has not yet been achieved regarding how frequently this occurs in the context of causation and the predominant direction(s) of transmission. Although household interventions have been minimally assessed in the literature, certain precautions deserve attention, especially if the household includes immunosuppressed patients.

## 17 Hygiene and contact precautions

Transmission of staphylococci—particularly *S. aureus*—may occur in both directions between owners and their pets; pets typically carry *S. aureus* strains genetically similar to locally dominant human clones.[176,178,200–202] Similar relatedness has been identified in pets and owners that are co-colonized with *S. pseudintermedius*.[176,178] Because of this potential, contact isolation strategies (e.g. crating and exclusion from the bedroom) have been recommended to segregate infected or positive pets from other pets and humans.[32] Not only may pets become carriers or colonized with staphylococci once in contact with infected or colonized people or other pets, but their fur (i.e. "petting zone") also may become contaminated, presumably through the hand contact of owners.[142] This suggests an important potential role for good hand hygiene (e.g. hand washing or use of a hand sanitizer) before and after owner–pet contact, although the effectiveness of such strategies has not been formally tested.

## 18 Environmental measures

Despite a growing consensus in the literature that home environments may serve as reservoirs for staphylococci in the context of both human and animal disease, the efficacy of environmental control strategies is largely unexplored in the literature. Laundering, including on normal low-temperature settings, has been demonstrated to reduce *S. aureus* contamination of clothing in the context of hospital settings;[203] laundering of bedding materials in household settings may be beneficial. Household disinfectants (e.g. chlorine and quaternary ammonium-based cleaners) appear to be effective in reducing *S. aureus* contamination from surfaces.[32] However, data from hospital settings also suggest that environmental surfaces and clothing may rapidly become re-contaminated following successful treatment.[204,205] Hence, when animals are being treated, concurrent home cleaning may be helpful to prevent re-exposure and recurrence. In some cases of recurrence, addressing human and animal household members also may be necessary, although the human literature demonstrates that adopting a similar approach of household-wide decolonization to reduce recurrence of SSTIs in people has shown weaker benefit than anticipated.[206,207]

## 19 Screening of healthy pets and people

Screening of healthy pets and people for carriage of selected staphylococci (e.g. MRSA or MRSP) can provide interesting information about the epidemiology of staphylococci, as well as interspecies transmission. It is also an area that can be fraught with potential problems, particularly when clear plans for how to access and use the results have not been determined and communicated prior to testing. Testing of clinically normal animals rarely leads to clear and justifiable action. Testing of humans leads to issues of confidentiality, and testing of clinic personnel (especially if not clearly voluntary and anonymous) could lead to a host of legal problems for clinic management. Testing of healthy individuals, particularly humans, should be a rare event that is based on a specific need and associated with a clear plan to act on the results.

### 19.1 Testing to identify increased risk in a veterinary patient

Using screening to inform risk-profiling among patients has the greatest potential, among all potential scenarios, for widespread adoption. In humans, MRSA screening is used judiciously in certain risk groups to target specific interventions; for example, patients admitted to the intensive care unit may be screened and MRSA-positive individuals subjected to barrier precautions. Likewise, patients scheduled for orthopaedic surgeries may be prescribed decolonization treatment, although evidence of this risk and efficacy of decolonization are variable.[156,208–210] There is limited corresponding information in veterinary medicine. MRSP carriage has been associated with increased risk of MRSP infection following tibial plateau levelling osteotomy (TPLO) in dogs,[158] suggesting that screening could be considered in this population and susceptibility results used to guide perioperative antimicrobial drug administration for MRSP carriers. However, the potential clinical impact of screening has not been investigated and there is limited evidence to identify other high-risk situations that would be accompanied by a potential intervention. As more evidence about risk groups, rapid screening methods and studies of interventions become available, there may be broader use of targeted screening for select, high-risk patients. Currently, the evidence for potential benefit from screening programmes is strongest for surgical patients and most limited for dermatology patients.

### 19.2 Testing to identify potential personnel sources of an outbreak

Screening of personnel has been performed in veterinary clinic or farm MRSA outbreaks.[211,212] However, these investigations were more focused on understanding the epidemiology of MRSA as it emerged in animals rather than constituting a tool to identify and mitigate an infectious focus. Veterinary personnel are known to be at elevated risk of MRSA and MRSP carriage in the absence of outbreaks,[213–218] and screening results are difficult to interpret in the midst of an outbreak. Finding MRSA or MRSP in personnel could indicate that they were a source of infection, but it could equally indicate they were infected by a patient or coworker, were exposed to a contaminated environment, or were exposed to an unrelated strain outside the hospital setting. Removal of colonized veterinary personnel from patient care duties is not recommended, and attempts to do so could lead to management or even legal challenges for the clinic. Given the importance of good personal hygiene and routine infection control practices at all times (not just during outbreak settings), knowing an individual's status is unlikely to change a hospital-level approach to infectious disease management. The exception might be in a situation where there is clear evidence of a hospital focus and enhanced control measures have failed to contain the problem. Even then, the confidentiality issues associated with testing and management of a colonized individual complicate testing decisions.

### 19.3 Testing of humans after contact with an infected animal

Owners periodically raise concerns about their personal exposures to MRS and request testing for themselves or their families. Any testing would have to be done within the human healthcare system, and discussions of this would be between the individual and their physician. Although the veterinarian could—and arguably should, if indicated—be an integral part of a "one health approach" to household-wide interventions, the owner would need to actively involve the veterinarian given privacy laws protecting human health information in many countries. Regardless, consideration of how the results would be handled is important. Without highly discriminatory methods such as whole genome sequencing, combined with repeated sample collection from all individuals over time,

standard microbial culture cannot be used to determine if the pet has infected people. If a pet had an MRSA infection and the owner was subsequently identified as colonized, a positive culture would not differentiate pet-to-human transmission from the more likely human-to-pet scenario. Indeed, genetic testing of animal isolates has implicated the human MRSA epidemic of spilling over into the pet population.[200] Testing of a person would only be of relevance in a situation where knowing their MRSA status would impact their medical care, such as before the owner would undergo elective surgery or if the owner was particularly susceptible due to a medical condition. Routine decolonization of healthy individuals in the community is rarely indicated, being restricted mainly to situations where there are recurrent infections in an individual or ongoing transmission in a household that is not responsive to other control measures.[176] With that approach, there would typically be no relevant impact of testing owners of MRSA-infected pets.

### 19.4 Testing of pets of owners who have been diagnosed with MRSA and other MRS infections

Requests to test pets of infected owners—particularly when an owner has a MRSA infection—is not uncommon, and must be approached with the question "Why?". MRSA carriage can be identified in pets of infected owners,[31,219] but that provides limited useful information for management of MRSA in a household. The vast majority of human MRSA infections are human-associated, with exceptions for certain regions, communities, or occupations where livestock- or equine-associated MRSA may be a consideration in people. Thus, finding MRSA in the pet could represent pet–human transmission, but more likely represents human–pet transmission. Because MRSA carriage tends to be short-term in pets[31,142,164,193] and there is no evidence that active decolonization is useful or effective in pets, finding an MRSA-positive pet in such a household would typically lead to a recommendation to focus on personal hygiene and temporary contact isolation to reduce the risk of transmission of MRSA in both directions. Further, no screening test is 100% effective; screening the most sensitive site, the mouth, was shown to miss up to a third of animals with CoPS and almost 10% of cats with *S. aureus*.[23] If the animal was MRSA-negative, the recommendations would be the same, with a focus on hygiene to reduce the risk of human–pet transmission.

Pet screening could be considered in the context of a broader household approach to recurrent MRSA infections in people, alongside testing or treatment of all human household members,[194] but only if there is a specific plan for the pet's results (e.g. short-term removal from the household to allow the positive pet to naturally eliminate MRSA while the humans are being treated and, in extreme situations, with re-testing prior to re-entry into the home after people and environmental reservoirs also have been shown to be negative). It is possible that, if owners are diagnosed instead with MRSP, MRSS or another MRS known to be linked to companion animals, that pet screening may be indicated in these rare situations.

### 19.5 Testing of animals that partake in human hospital visitation programmes

Although dogs that visit human hospitals are known to have an elevated risk of MRSA carriage,[142] current guidelines for these programmes do not recommend MRSA screening.[220,221] Screening for other MRS also is not recommended. Good hygiene practices during visitation visits, including but not limited to hand washing by participants *before* and *after* the assistance animal visit, is essential.

### 19.6 Screening of animals in households with high-risk humans

A relatively large percentage of pets reside in households with individuals who are at increased risk of disease because of age (very young or old), immunosuppressive disorders or treatments, or pregnancy.[222] As awareness of zoonotic infections increases, owners or physicians occasionally inquire about MRSA (or less commonly MRSP) screening of pets in households such as these. However, screening in situations like this is difficult to justify for many reasons. One is that MRS are not the only relevant (or potentially even the most relevant) zoonotic pathogens that might be shed by a healthy animal. Screening for MRS while ignoring other opportunistic pathogens is illogical. Furthermore, screening only provides point-in-time information, and an animal that is negative could become exposed any time after testing. Testing also is not likely 100% sensitive. As is discussed above, given the absence of evidence that decolonization therapy would be indicated or effective, the main recommendations for an animal colonized with MRS would be an emphasis on hygiene practices, such as avoiding contact with typical colonization sites and paying close attention to hygiene practices (especially hand hygiene). In a household with high-risk individuals, those same recommendations would be made for animals that were not colonized because of concerns about exposure to a wide range of other pathogens. Therefore, because the outcome of a positive or negative result would essentially be the same, screening provides little to no benefits.

## 20 Conclusions

There are many areas of concern identified within this document for which insufficient evidence is available to draw definitive conclusions about the management and prevention of MRS infection, colonization and transmission. Therefore, the recommendations made herein are by consensus of the authors, following careful consideration of the current literature. It is the hope of the authors that this review has helped to reveal the gaps in the veterinary profession's collective knowledge base regarding MRS. In doing so, it has been our intention to stimulate collaborative dialogue and encourage investigators to pursue the types of studies that will inform more definitive guidelines and recommendations in the future.

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**Résumé**

**Contexte –** Les multirésistances (MDR) de staphylocoques, comprenant la résistance aux pénicillines semi-synthétiques résistantes aux pénicillinases telles que la méticilline, est un problème de proportion globale qui représente un défi sérieux à la réussite des traitements des infections à staphylocoque des animaux de compagnie.

**Objectifs –** L'objectif de cet article est de fournir des recommandations harmonisées pour le diagnostic, la prévention et le traitement des infections à staphylocoques résistants à al méticilline du chien et du chat.

**Méthodes –** Les auteurs ont formé un groupe d'expert (GP) et ont revu la littérature disponible avant septembre 2016. Le GP a préparé une revue de la littérature détaillée et ont fait des recommandations des sujets sélectionnés. La WAVD (World Association of Veterinary Dermatology) a fourni une orientation et a supervisé le processus. Un projet de document a ensuite été présenté au 8ieme congrès mondial de dermatologie vétérinaire (Mai 2016) et a été rendu disponible aux membres de l'organisation de la WAVD par le World Wide Web pour une période de 3 mois. Les commentaires ont été sollicités et postés au GP par voie électronique. Les réponses ont été incorporées par le GP dans le document final.

**Conclusions –** Le respect des recommandations pour le diagnostic, les tests de laboratoires, les traitements adaptés (y compris les politiques de restriction d'utilisation de certains antimicrobiens), l'hygiène personnelle et le nettoyage et la désinfection de l'environnement peut aider à atténuer le développement progressif et la diffusion des staphylocoques MDR.

**Resumen**

**Introduccion –** La resistencia múltiple a fármacos en los estafilococos (MDR), incluida la resistencia a las penicilinas semisintéticas resistentes a la penicilinasa, como la meticillina, es un problema de proporciones mundiales que plantea serios retos para el éxito del tratamiento de las infecciones estafilocócicas de los animales de compañía.

**Objetivos –** El objetivo de este documento es proporcionar recomendaciones armonizadas para el diagnóstico, la prevención y el tratamiento de las infecciones estafilocócicas resistentes a meticilina en perros y gatos.

**Métodos –** Los autores actuaron como Panel de Orientación (GP) y revisaron la literatura disponible antes de septiembre de 2016. El GP preparó una revisión bibliográfica detallada y formuló recomendaciones sobre algunos temas seleccionados. La Asociación Mundial de Dermatología Veterinaria (WAVD) proporcionó orientación y supervisión para este proceso. El borrador del documento fue presentado en el VIII Congreso Mundial de Dermatología Veterinaria (mayo de 2016) y fue puesto a disposición de las organizaciones miembros de la WAVD a través de la World Wide Web por un período de 3 meses. Se solicitaron comentarios que fueron enviados al GP electrónicamente. Las respuestas fueron incorporadas por el GP en el documento final.

**Conclusiones –** la aplicación de las directrices recomendadas para el diagnóstico, informes de laboratorio, la terapia juiciosa (incluida la restricción mediante normas en el uso de ciertos antimicrobianos), la higiene personal y la limpieza y desinfección del medio ambiente cercano pueden ayudar a mitigar el desarrollo progresivo y la diseminación de estafilococos MDR.

**Zusammenfassung**

**Hintergrund –** Die Multiresistenz (MDR) von Staphylokokken, die auch eine Resistenz gegenüber semi-synthetischen Penicillinase-resistenten Penicillinen wie etwa Methicillin bedeutet, ist ein Problem von globalem Ausmaß, welches ernsthafte Herausforderungen für eine erfolgreiche Behandlung von Staphylokokkeninfektionen der Haustiere darstellt.

**Ziele –** Das Ziel dieses Dokuments ist es übereinstimmende Empfehlungen für eine Diagnose, die Prävention und die Behandlung von Methicillin-resistenten Staphylokokkeninfektionen bei Hunden und Katzen zu erstellen.

**Methoden –** Die Autoren fungierten als Kommission für Richtlinien (GP) und durchforsteten die Literatur, die vor September 2016 zur Verfügung stand. Die GP bereitete eine detaillierte Literaturrückschau vor und sprach Empfehlungen in Bezug auf einzelne ausgewählte Inhalte aus. Die World Association of Veterinary Dermatology (WAVD) unterstützte diesen Prozess durch Anleitungen und Supervision. Es wurde beim 8. Weltkongress für Veterinärdermatologie ein Entwurf des Dokuments präsentiert (Mai 2016) und im

Anschluss daran über das World Wide Web den Mitgliedsorganisationen des WAVD für eine Zeitspanne von 3 Monaten zugänglich gemacht. Es wurden Kommentare erbeten, die elektronisch an die GP weitergeleitet wurden. Die Antworten wurden durch die GP im Abschlussdokument eingebaut.
**Schlussfolgerungen –** Das Einhalten der Richtlinien in Bezug auf die Diagnose, den Laborbericht, eine vernünftige Behandlung (inklusive der Einsatzbeschränkungen für gewisse Antibiotika), persönliche Hygiene, und eine Umweltbehandlung und Desinfektion könnte dabei helfen, die fortschreitende Entwicklung und Verbreitung der MDR der Staphylokokken zu mäßigen.

**要約**
**背景 –** メチシリンなどの半合成ペニシリナーゼ耐性ペニシリンに対する耐性を含むブドウ球菌における多剤耐性(MDR)は、コンパニオンアニマルのブドウ球菌感染の治療成功を困難にさせる世界規模な問題である.
**目的 –** 本文書の目的は、犬および猫におけるメチシリン耐性ブドウ球菌感染の診断、予防および治療のための一致した提言を提供することである.
**方法 –** 我々はガイドラインパネル(GP)として、2016年9月以前に入手可能な文献を再検討した。GPは文献の詳細な再検討を行い、選択されたトピックについての提言を作成した。この過程の指針および監視は世界獣医学学会(WAVD)によって行われた。文書の草案は第8回世界獣医学会(2016年5月)で発表され、3か月間ワールドワイドウェブを介してWAVDの構成組織に提供された。コメントが要請され、電子的にGPに掲示された。回答はGPによって最終文書に組み込まれた.
**結論 –** 診断、検査報告、慎重な治療(特定の抗菌薬の使用制限など)、個人の衛生、環境の清掃と消毒のガイドラインを順守することは、MDRブドウ球菌の進行と蔓延を軽減するのに役立つ.

**摘要**
**背景 —** 葡萄球菌的多重耐药性(MDR),包括对半合成青霉素酶的青霉素(如甲氧西林)耐药,是一个全球性问题。这对成功治疗伴侣动物葡萄球菌感染也是一个严重挑战.
**目的 —** 本文旨在为犬猫耐甲氧西林葡萄球菌感染的诊断、预防和治疗,提供协调性建议.
**方法 —** 作者们成立指导小组(GP),查阅了2016年9月之前所有可获得的文献资料,撰写出一份详尽的文献综述,同时就选定的主题提出相应建议。世界兽医皮肤病学会(WAVD)给予全程指导与监督。本文的草案在第八届世界兽医皮肤病大会(2016年5月)上正式发布,随后,通过万维网向WAVD的成员组织提供为期3个月的免费查阅,广泛征求意见,并以电子方式反馈给指导小组,指导小组将所有答复整合纳入最终文献.
**结论 —** 遵守指南中的诊断、实验室报告、合理治疗(包括某些抗菌药物的使用政策限制)、个人卫生和环境清洁与消毒,将有助于缓解葡萄球菌多重耐药性的进一步发展与传播.

**Resumo**
**Contexto –** A multirresistência a drogas antimicrobianas (MDR) em estafilococos, incluindo a resistência a penicilinas semissintéticas resistentes a penicilinase como a meticilina, é um problema com proporções globais que apresenta sérios desafios para o sucesso no tratamento de infecções estafilcocicas de animais de companhia.
**Objetivos –** O objetivo desde trabalho é fornecer recomendações harmonizadas para o diagnóstico, prevenção e tratamento de infecções por *Staphylococcus* spp resistente à meticilina em cães e gatos.
**Métodos –** Os autores compuseram o Comitê de Diretrizes (CD) e revisaram toda a literatura disponível até setembro de 2016. O CD preparou uma revisão de literatura detalhada e fez recomendações em tópicos selecionados. A *World Association of Veterinary Dermatology* (WAVD) forneceu orientação e supervisão durante todo o processo. Um resumo do documento foi apresentado no *8th World Congress of Veterinary Dermatology* (Maio/2016) e depois foi disponibilizado no portal *World Wide Web* para as organizações que são filiadas à WAVD por um período de três meses. Comentários foram solicitados e postados ao CD eletronicamente e as respostas foram incorporadas pelo CD no documento final.
**Conclusões –** A adesão às diretrizes para diagnóstico, relatórios laboratoriais, tratamento consciente (incluindo as políticas de restrição ao uso de determinadas drogas), higiene pessoal, e higiene ambiental e desinfecção podem auxiliar na atenuação do desenvolvimento progressivo e disseminação de estafilococos MDR.