International Journal of Medical Microbiology 301 (2011) 635–641

Contents lists available at SciVerse ScienceDirect

International Journal of Medical Microbiology

journal homepage: www.elsevier.de/ijmm

Mini Review

Methicillin-resistant staphylococci (MRS) and extended-spectrum beta-lactamases (ESBL)-producing *Enterobacteriacea*e in companion animals: Nosocomial infections as one reason for the rising prevalence of these potential zoonotic pathogens in clinical samples

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ARTICLE INFO

Keywords:
MRSA
MRSP
ESBL
Veterinary medicine
Companion animals
Nosocomial infections

ABSTRACT

The ongoing change in the relationship between humans and companion animals is hallmarked by the increasing intensive care provided to companion animals in veterinary medicine, resulting in growing numbers of high-risk animal patients. The emergence of nosocomial infections in small animal clinics is one of the major drawbacks of this development, especially in terms of multidrug-resistance and potentially zoonotic pathogens. This mini-review therefore addresses recent findings regarding the increasing prevalence of multi-resistant bacterial pathogens like methicillin-resistant staphylococci (MRS), including *Staphylococcus aureus* (MRSA) and *Staphylococcus pseudintermedius* (MRSP) as well as extended-spectrum beta-lactamases (ESBL)-producing *Enterobacteriacea*e in companion animals.

Along with the steady increase of nosocomial infection rates in veterinary clinics, particular attention has recently been drawn to the genetic background of multi-resistant strains, resulting in the identification of certain genetic lineages which frequently appear in both, human and animal samples. These sequence types (ST), included ST254, ST8 and ST22 in terms of MRSA and ST131, ST405 and ST648 for ESBL-producing *E. coli*. The interspecies distribution of these STs resulted in the assumption that certain extended-host spectrum genotypes (EHSG) might exist both for MRS and ESBL-producing *E. coli*. These initial findings underline the necessity to investigate the major molecular or functional driving forces facilitating interspecies transferability of such EHSG strains.

Due to the zoonotic potential of these multi-resistant bacteria, another aspect of the changing social role of companion animals needs to be addressed: the close contact of pets with their owners, resulting in presumptive new transmission and infection routes. We therefore envision retaliatory actions like initial surveillance and monitoring programs not only in livestock, but also particularly in companion animals. Interdisciplinary approaches including human and veterinary experts should be implemented to develop reliable investigation procedures with respect to the current reality of animal owners and their pets. Additionally, consequent basic hygienic measures, prudent use of antimicrobials in companion animals and efforts regarding implementation of antibiotic stewardships should be fostered.

Introduction

In our society, the relationship between companion animals (i.e. dogs, cats, horses) and their owners has changed dramatically during the last decades. Animals now live in much closer contact with the human population than decades ago, and they have increasingly gained the status of a family member in urban households (Blouin, 2008). Pets, in particular dogs and cats, are provided with certain privileges like spending time on furniture at home or close face-to-fur contact. Principal changes in social relationships also influence the human–companion animal relationships regarding substitution of social (human) contacts with these animals. In addition, due to increasing intensive care provided to the animals, the population of animal risk patients (old, chronically ill, immune compromised) is also on the rise.

Faced with this reality, it is tempting to take a closer look at the possible infection risks for both sides, that is humans (namely animal owners and veterinarians), as well as companion animals. Keeping in mind that more than 60% of all human pathogens are zoonotic, and that the percentage of multiple host pathogens is particularly high among emerging and re-emerging pathogens (Cleaveland et al., 2001; Woolhouse and Gowtage-Sequeria, 2005), this mini-review summarizes the current knowledge about infections caused by multi-resistant bacterial pathogens, that

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doi:10.1016/j.ijmm.2011.09.009

are increasingly isolated from clinical samples of companion animals.

In fact, multidrug-resistant (MDR) strains of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, coagulase-positive staphylococci (CPS) as well as different *Enterobacteriaceae* species have been regularly isolated from the skin of companion animals (Walther et al., 2008; Murphy et al., 2009; Umber and Bender, 2009). However, the growing number of such reports seems to reflect an increasing problem, which urgently needs to be properly analysed in the future to develop strategies for risk management. This increase of antimicrobial resistance in pathogens is accompanied by a similar development observed with opportunistic and commensal bacterial species, which are usually associated with skin/mucosal infections of humans and animals, exacerbating the current situation dramatically (Alekshun and Levy, 2006; Weese, 2008).

An exemplary case highlighting this new development has been described by Manian (2003), who identified asymptomatic nasal carriage of mupirocin-resistant, methicillin-resistant *Staphylococcus aureus* (MRSA) in a pet dog as the likely source of concurrent re-colonization and re-infection of an amputated diabetic patient with stump infection and his wife. On the other hand, humans may also serve as a source of infecting animals, especially in clinical veterinary environments (Loeffler et al., 2005; Weese et al., 2006a,b; Walther et al., 2009a) or even in the household (Vincze et al., 2010).

In analogy with the development in medical hospitals, the accumulation of immune-deficient, geriatric or patients with joint implanted in clinical environments abets health-care associated (ha-) infections in veterinary medicine (Boerlin et al., 2001). Several outbreaks due to classical nosocomial pathogens like methicillin-resistant staphylococci (MRS) (Boerlin et al., 2001; Weese et al., 2006a,b; Ishihara et al., 2010), *Acinetobacter baumannii* (Francey et al., 2000) and *Salmonella enterica* ssp. (Wright et al., 2005; Dallap Schaer et al., 2010; Zordan et al., 2011) have already been reported for small animal and horse clinics. In conclusion, nosocomial infections, in particular surgical site infections (SSI), are of growing concern in veterinary medicine (Eugster et al., 2004), and the shutting down of veterinary clinics or sections due to nosocomial outbreaks also has a substantial financial impact (Dallap Schaer et al., 2010).

Different substances of the penicillin family, first- to fourth-generation cephalosporins and beta-lactamase inhibitors are recommended for the treatment of companion animals, according to the animal species involved and the underlying infectious disease (Guardabassi et al., 2008; Smet et al., 2010). Thus, as beta-lactams constitute one of the most important groups of antimicrobial agents used in veterinary medicine, we particularly summarize clinical and epidemiological issues arising from the current emergence of MRS and ESBL-producing *Enterobacteriaceae* in companion animals. The complex nature and scarce knowledge about this critical new emerging development urgently requires action.

This mini-review addresses recent findings regarding the increase of multi-resistant bacterial pathogens in companion animals, emphasizing their zoonotic potential. In terms of infections, one may ask if the risk of transmission of zoonotic or multi-resistant pathogens between companion animals and their owners is increasing due to the growing number of animals at risk and the frequent, daily and prolonged contacts between companion animals and humans, as well as increasing intensive care.

Methicillin-resistant staphylococci

Staphylococcus (S.) aureus

Apart from being a commensal colonizer of skin and mucosa, *S. aureus* is one of the leading causes of suppurative infections in humans and animals (Umber and Bender, 2009), including skin and invasive infections such as bacteremia, pneumonia, osteomyelitis, and endocarditis (Archer, 1998). Due to the significant amount of MRSA-associated infections, therapeutic options are often limited, inpatient therapy costs are enhanced and mortality rates are increased in affected patients (Engemann et al., 2003).

Methicillin-resistance in staphylococci is conferred by an additional penicillin-binding protein (PBP2a) encoded by the gene *mec*A, which is located on a mobile element, named staphylococcal chromosomal cassette (SCC) (Pinho et al., 2001). The initial origin of *mec*A seems to be associated with coagulase-negative staphylococcal species (Enright et al., 2002). A recent report from Tsubakishita and co-workers suggests that an intrinsic *mec*A region of *S. fleuretti*, a commensal bacterial species, was possibly adopted by an SCC element, resulting in SCC*mec* (Tsubakishita et al., 2010). Beyond *mec*A-encoded methicillin resistance, which confers resistance against all beta-lactam antibiotics (Clinical and Laboratory Standards Institute, 2005), MRS often display clinically relevant resistance against further classes of antimicrobials, tending to result in either limited or no therapeutic option at all (Ruscher et al., 2010).

Carriage of *S. aureus,* e.g. in the anterior nostril, is a matter of concern in human medicine since nearly fifty years (Williams, 1963) and the global emergence of MRSA has worsened the situation (Kluytmans et al., 1997). Likewise, MRSA-colonized veterinary personnel or other people with animal contact can be involved in interspecies transmission of MRSA (Willey et al., 2003; Loeffler et al., 2005; Weese et al., 2006a,b; Walther et al., 2009b). While the particular importance of MRSA-colonized or -infected domestic animals as a source of human infection in the community is sparsely investigated, the general transferability of MRSA between humans and animals and vice versa is well documented nowadays, even though the original source of the pathogen mostly remains unclear (Cohn and Middleton, 2010).

Basic molecular epidemiology aspects of animal-associated MRSA strains published so far revealed that the sequence types (STs), assigned by multilocus sequence typing (MLST) of the majority of those strains from companion animals correspond to well-known human ST lineages, including widely distributed human epidemic strains (Table 1).

This observation indicates that some genetic lineages possess the capacity to adapt to different hosts. For example, MRSA isolates belonging to ST22, ST254, ST8, and ST239 have been isolated from humans as well as from animals (Table 1) and are therefore considered to represent extended host spectrum genotypes (EHSG) (Walther et al., 2009a,b). By definition, EHSGs are not only able to colonize but also to infect a broad range of different human and animal hosts.

These principal findings, which are mainly based on molecular epidemiology, represent a sound basis for further detailed comparative studies with defined EHSG isolates, unraveling those factors (e.g. gene content, virulence or metabolic determinants, mobile genetic elements), that basically provide *S. aureus* with the ability to adapt to certain hosts. For instance, host adaptation of a known human *S. aureus* strain (ST5) to chicken was found to be associated with the loss of genes involved in human pathogenesis as well as with the acquisition of presumptive avian-specific mobile genetic elements (Lowder et al., 2009). Moreover, highly mobile pathogenicity islands (SaPIs) carrying presumptive animal-specific alleles of the von Willebrand factor-binding protein (vWbp) gene, have been associated with the host adaptation of *S. aureus* (e.g. ST133, ST97, and ST398) only recently. These vWbps affect the *S. aureus* coagulation activity in ruminant and equine hosts (Viana et al., 2010).

Whether similar or other molecular mechanisms are involved in the process of host adaptation of EHSG *S. aureus*, particularly

Table 1
Sequence types (STs) commonly associated with MRSA strains of human and household animal origin.

Animal species	Sequence type (ST)	Reference (ST)
Dog	**22, 239, 254**, 398, **5**	Baptiste et al., 2005 (**ST22**); Loeffler et al., 2005 (**ST22**); Strommenger et al., 2006 (**ST22**); Walther et al., 2008 (**ST22**); Malik et al., 2006 (**ST239**); Walther, 2007 (**ST254**); Witte et al., 2007 (ST398); Kwon et al., 2006 (**ST5**); Lin et al., 2011 (**ST5**)
Cat	**22**, 225, **8**	Moodley et al., 2006 (**ST22**); Walther et al., 2008, 2009a,b (**ST22**, ST225); Lin et al., 2011 (**ST8**)
Horse	**1, 8, 254,** 398	Cuny et al., 2006 (**ST254**); Walther et al., 2009a,b (**ST8, ST254, ST22**, ST398); Van Den Eede et al., 2009 (ST398); Cuny et al., 2008 (**ST1, ST254**, and ST398); Lin et al., 2011 (**ST8**)
Rabbit	**22**	Walther et al., 2008 (**ST22**)
Turtle	**22**	Walther et al., 2008 (**ST22**)
Parrot	**22**	Walther et al., 2008 (**ST22**)

Selected sequence types (STs: based on multilocus sequence analysis) often associated with MRSA strains of companion animal (dog, cat, horse and parrot) and pocket animal (chinchilla and turtle) origin. Each displayed ST was found to be associated with *S. aureus* isolates of human origin (according to www.mlst.net), and STs corresponding to pandemic lineages of well known human epidemic MRSA strains are shown in bold letters (according to (Crossley, 2009, xii', 623 p.)). This list is not complete, but numerous other studies on MRSA of companion animal origin do not include distinct data concerning STs.

in those MRSA STs frequently associated with transmission events between companion animals and humans, is yet to be clarified. At present, mechanisms of host adaptation processes and their genetic backgrounds are generally poorly understood (Cuny et al., 2010).

Staphylococcus pseudintermedius

In veterinary medicine, another important opportunistic staphylococcal species associated with companion animals, mostly dogs and horses, is *S. pseudintermedius* (Ruscher et al., 2009). *S. pseudintermedius* causes purulent and opportunistic infections, dominated by dermatitis, otitis and wound infection (Futagawa-Saito et al., 2009; Fazakerley et al., 2010; Yoon et al., 2010).

Methicillin-resistant *S. pseudintermedius* (MRSP) have been reported with increasing frequency (Weese and Van Duijkeren, 2010), and are meanwhile recognized as a serious animal health problem (De Lucia et al., 2010; van Duijkeren et al., 2011), in particular with regard to nosocomial infections (Perreten et al., 2010), challenging hygiene prevention measures and therapy concepts in veterinary clinical facilities. Like other typical nosocomial pathogens, MRSP are frequently associated with multidrug resistance (Ruscher et al., 2009), and MRSP-infected animals are often difficult to treat or not treatable at all with antibiotics (Ruscher et al., 2010).

At present, two major clonal MRSP lineages are widely disseminated in Europe (ST71) and North America (ST68) (Perreten et al., 2010; Ruscher et al., 2010), but the underlying driving forces are not fully understood. Initial findings suggest that prior hospitalization and/or antibiotic therapy are presumably associated with MRSP carriage in dogs (Nienhoff et al., 2011). It seems likely that the establishment of MRSP in veterinary medicine is one of the major downsides of technical and therapeutic progress in this field of care. Companion animal owners and their animals can be colonized with indistinguishable *S. pseudintermedius* strains (Hanselman et al., 2009; Vincze et al., 2010), and it seems that owners of companion animals, in particular dogs, may be at higher risk for infections than other people (Vincze et al., 2010). Despite the rising number of reports about human infections with *S. pseudintermedius* (Tanner et al., 2000; Van Hoovels et al., 2006; Chuang et al., 2010; Riegel et al., 2011), including MRSP (Stegmann et al., 2010), little is known about the general frequency of transmission events between these different hosts and the resulting significance for public health.

Extended-spectrum beta-lactamases (ESBL)-producing *Enterobacteriaceae*

The production of extended-spectrum beta-lactamases (ESBL) confers resistance to the majority of the commonly used beta-lactam antimicrobials, including 3rd generation cephalosporins, but excluding beta-lactamase inhibitors (e.g. clavulanic acid). ESBLs confer resistance to beta-lactam antibiotics via cleavage of the beta-lactam ring system by hydrolysis. However, the main therapeutic burden results from the multidrug phenotype of these bacteria which is caused by a frequent genetic linkage with resistance mechanisms conferring additional resistance against other antimicrobial classes including fluoroquinolones and aminoglycosides (Pitout, 2010). The majority of beta-lactamases reported to date have been identified in clinical isolates of human sources (Bradford, 2001; Bonnet, 2004). Within the last decade there has been a shift in the detected ESBL enzymes from the classic TEM (Temoneira) and SHV (Sulfhydryl-variable) enzyme families, which were predominantly detected in the 1980s and 1990s, to the CTX-M (cefotaximase) family, which dominated the past ten years (Livermore et al., 2007).

Only recently, attention has been drawn to non-human sources as possible origins of infection. One important finding of these studies is that ESBL-producing bacteria and beta-lactamases are indeed frequently present in the microbiota and in clinical samples of livestock as well. In addition to this, initial findings affirm the occurrence of ESBLs in wild animals, such as birds and rodents (Li et al., 2007; Poeta et al., 2008; Bonnedahl et al., 2009; Guenther et al., 2010a,b; Literak et al., 2010; Simoes et al., 2010; Smet et al., 2010; Ho et al., 2011). Direct transmission of ESBL-producing Gram-negative bacteria between food-producing animals and humans has also been reported in recent years (Guardabassi et al., 2004; Bertrand et al., 2006; Smet et al., 2010).

Although the growing burden of extended-spectrum beta-lactam resistance among *Enterobacteriaceae* isolated from companion animals is increasingly recognized (Ewers et al., 2011b; Woodford et al., 2011), our understanding of the contribution of these animals to transmission scenarios is still limited. While the detection of the human pandemic clonal group of B2-O25b:H4-ST131-CTX-M-15-type ESBL-producing *E. coli* in dogs, cats, and horses proves the existence of these strains in companion animals, the role in the epidemiology and microevolution of ESBLs is unknown so far (Nicolas-Chanoine et al., 2008; Pomba et al., 2009; Ewers et al., 2010; Naseer and Sundsfjord, 2011; Platell et al., 2011; Rogers et al., 2011).

The first reports on ESBL-producing *Enterobacteriaceae* date back to the late 1980s, and the first CTX-M-type enzyme (FEC-1: Fujisawa *E. coli*-1) ever described for animals was discovered in a cefotaxime-resistant *E. coli* strain isolated from the fecal flora of a laboratory dog which was kept for pharmacokinetic studies of beta-lactam antimicrobials (Matsumoto et al., 1988). At the same time, nosocomial outbreaks by CTX-M-1-type ESBL-producing *E. coli* were recorded in hospitals in France and Germany (Kitzis et al., 1988; Bauernfeind et al., 1989). In the following ten years several studies reported about an explosive dissemination of ESBLs in human clinical settings worldwide (Bernard et al., 1992; Radice et al., 2002; Canton and Coque, 2006). Whereas to the best of our knowledge the very first clinical ESBL-producing strain from a companion animal was an SHV-12-type beta-lactamase-producing *E. coli* isolated from a dog with recurrent urinary tract infection in Spain in 1998 (Teshager et al., 2000). Subsequent studies followed,

describing the detection of ESBL-producing *E. coli* (mostly TEM and SHV) in dogs from Italy and Portugal (Feria et al., 2002; Carattoli et al., 2005). Current data report on relevant numbers of companion animals serving as hosts of ESBL-producing *E. coli* worldwide, whereas highest rates were observed for healthy cats (12.1%) and healthy dogs (7.8%) in Portugal (Vo et al., 2007; Carattoli et al., 2008; Costa et al., 2008; O'Keefe et al., 2010; Smet et al., 2010).

Since about 2000, the CTX-M enzymes have formed a rapidly growing family of ESBLs in human clinical and community settings (Bonnet, 2004; Pitout and Laupland, 2008; Mshana et al., 2009). Although based only on a limited number of available studies, one might assume that a similar development is taking place in companion animals as well. Several studies reported on clinical as well as commensal isolates which predominantly harbored enzymes of the CTX-M type (ranging between 2.6% and 5.6% of all investigated isolates and between 25% and 76.5% of all ESBLs detected (Smet et al., 2010; Ewers et al., 2011a,b)). The co-emergence of the pandemic B2-O25b:H4-ST131-CTX-M-15 clonal group in humans and companion animals raises the important question whether, similar to MRS, EHSGs of ESBL producers exist? If this were true, these EHSGs in ESBL-producing *Enterobacteriaceae* could also have a particular zoonotic potential. Although ESBLs are mainly encoded on plasmids, particular genomic lineages like the pandemic ST131 might harbor features fostering their pandemicity. Clearly, initial molecular typing by highly reproducible, unambiguous and globally comparable conservative typing tools like MLST will give first insight into this important field.

Apart from this successfully emerging multi-resistant clonal group of the ST131 lineage, several other *E. coli* STs, which obviously accumulate strains carrying ESBL plasmids, seemed to have made their way into different hosts, such as humans, livestock, companion animals or even wildlife. Currently, ST648, ST167, ST410, ST224, ST405, ST10 and ST23 can be listed as potential EHSGs in this context. Although ESBL-producing *E. coli* of these STs have predominantly been described from human sources, single findings already prove their occurrence in the animals mentioned above as well (Coque et al., 2008a,b; Bonnedahl et al., 2009; Hrabak et al., 2009; Naseer et al., 2009; Oteo et al., 2009; Sidjabat et al., 2009; Coelho et al., 2010; Cortes et al., 2010; Fam et al., 2011; Guenther et al., 2010a,b; Peirano et al., 2010; Simoes et al., 2010; Zong and Yu, 2010; Rodriguez-Villalobos et al., 2011).

Interestingly, our preliminary data on ESBL-producing *E. coli* from a collection of more than 200 European clinical isolates from companion animals provide strong evidence that humans and companion animals share the same ESBL-producing *E. coli*-STs. These data also point towards the occurrence of a novel putative EHSG, as ESBL-producing *E. coli* of ST648 have recently been recognized in humans (Sidjabat et al., 2009; Zong and Yu, 2010; Mshana et al., 2011; van der Bij et al., 2011), wild birds (Guenther et al., 2010a), livestock and companion animals (unpublished data) (Cortes et al., 2010). Thus, ST131 and ST648 might serve as appropriate model lineages to study the existence of EHSGs in ESBL-producing *E. coli*.

Whereas the number of studies on ESBL-producing *E. coli* from companion animals is continuously rising over the last few years, knowledge about the occurrence of ESBLs in other *Enterobacteriaceae* spp. is very limited. There are single reports on CTX-M-type, SHV-12 or OXA-10 enzymes in *Citrobacter* spp. (Ewers et al., 2011a,b), *Enterobacter* spp. (Sidjabat et al., 2007; Ma et al., 2009; SVARM, 2009), *Klebsiella* spp. (Vo et al., 2007; Ma et al., 2009; SVARM, 2009), and in *Salmonella enterica* ssp. enterica serovars (Rankin et al., 2005; Frye and Fedorka-Cray, 2007). Although limited in number, these data implicate a rather small diversity of broad-spectrum beta-lactamases in *Enterobacteriaceae* of animal origin compared to what has been documented for human strains (Machado et al., 2007; Coque et al., 2008a,b; Ko et al., 2008).

Conclusions

In 2010, 15 million households in Germany owned companion animals. In view of the apparently changing social role of these animals towards household members, the increasing proportion of risk-animals and the presumptive transmission and infection routes associated with this emerging development, actions unraveling the evolution and transmission mechanisms of multi-resistant bacterial pathogens are warranted. A two-track approach, including sufficient health care for pets as well as education and adequate behavior of companion animal owners, in compliance with a previous recommendation by the Robert Koch-Institute in 2003 (Weber and Schwarzkopf, 2003), is urgently needed to facilitate prevention of zoonotic transmission events, including multi-resistant pathogens like ESBL-producing *Enterobacteriaceae*, MRSA or MRSP.

We therefore envision initial surveillance and monitoring programs for those multi-resistant bacteria not only in livestock, but also particularly in companion animals. The small-scale monitoring programs, currently realized in a limited number of countries only (e.g. Danish DANMAP, German GE*RM*-Vet and Swedish SVARM) do not fulfill these needs. As a first step, analysis of mandatory documentation data concerning antimicrobial consumption according to the directive 2001/82/EC of the European parliament with respect to antimicrobial class, host species and underlying disease may provide deeper insight into dependencies of antibiotic quantities in association with increased appearance of certain resistance phenotypes in bacteria of animal origin.

The potential impact of MRS (MRSA and MRSP)-colonized and/or -infected companion animals as a source of infection in the community has not yet been investigated. The obvious genetic relationship of certain EHSG MRSA and ESBL-producing *Enterobacteriaceae* strains of human and companion animal origin hampers the identification of the original source in case of animal-to-human transmission and vice versa. Therefore, the major molecular or functional driving forces facilitating interspecies transferability of EHSG strains need to be investigated with respect to the different genetic lineages frequently appearing in this EHSG context.

Additionally, consequent basic hygiene measures as well as suitable and effective infection prevention and control strategies based on different requirements of various specialized veterinary clinics should be developed. Prudent use of antimicrobials in companion animal medicine according to appropriate antimicrobial guidelines is necessary to avoid further uninhibited spread of MDR pathogens in veterinary medicine. In particular, consequent efforts regarding implementation of antibiotic stewardship, especially in veterinary teaching hospitals, is inevitable for long-term and continuing education of veterinarians, regardless of whether student or permanently employed staff.

In order to define the specific impact of interspecies transmission of multi-resistant bacteria on public health, a general interdisciplinary effort including human and veterinary experts ("one health") is urgently needed to develop reliable investigation procedures with respect to the current reality of animal owners and their pets. Based on these data, implementation of evidence-based preventative methods e.g. in the form of general recommendations and/or requirements is possible. Needless to say that sound risk factor identification through epidemiological studies is the key issue in applying evidence-based intervention strategies.

Acknowledgements

This work was supported by grants 01KI1012A (BMBF network "FBI-Zoo") and 01KI1014F (BMBF network "MedVet-Staph").

Sebastian Guenther was financed by grant AIF KF2267301MD9. We thank Torsten Semmler and Ines Diehl for indispensable help in data analyses and Esther-Maria Antão for critical reading of the manuscript.

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