# Chapter 17
# Infections With Multidrug-Resistant Bacteria—Has the Post-Antibiotic Era Arrived in Companion Animals?

**Lothar H. Wieler, Birgit Walther, Szilvia Vincze, Sebastian Guenther and Antina Lübke-Becker**

**Abstract** The increasing prevalence of infectious diseases caused by drug- and multidrug-resistant pathogenic bacteria in companion animals (dogs, cats, horses), particularly in veterinary hospitals, is a worrisome development. Regarding companion animals, currently the four clinically most important groups of multidrug-resistant pathogenic bacteria are methicillin-resistant *Staphylococcus* (*S.*) *aureus* (MRSA), methicillin-resistant *S. pseudintermedius* (MRSP), Extended-ß-lactamase-producing (ESBL) Enterobacteriaceae and multidrug-resistant *Acinetobacter* (*A.*) *baumannii*. Infections caused by these bacteria are often associated with clinical settings and involve mostly wound, skin, ear or urinary tract infections. *S. pseudintermedius* is a typical cause of canine skin infections and until recently regarded as being host-specific. However, the epidemic spread of MRSP together with the changing socio-cultural interaction between companion animals and humans has already resulted in human cases of MRSP infections. Just the opposite development was observed with MRSA. Here, typical hospital-associated (HA) genotypes originating from humans spread into companion animals, now being a substantial cause of disease. In both cases, typical non-zoonotic bacteria turned into zoonotic agents. These findings are just the tip of the iceberg when it comes to the influence of antimicrobial drug usage and multidrug-resistance in speeding up microbial evolution. Concerted action is urgently needed to slow down these processes.

## 17.1 The Role of Socio-Cultural Developments for the Transmission of Multidrug-Resistant Bacteria Between Man and Companion Animals

The domestication of wild animals is regarded as a pivotal threshold in human evolution, a well-known fact that gives evidence for the prehistoric human relationships with companion animals (Zeder 2006). In this chapter we concentrate on the

L. H. Wieler (✉) · B. Walther · S. Vincze · S. Guenther · A. Lübke-Becker
Free University Berlin, Berlin, Germany
e-mail: Lothar.Wieler@fu-berlin.de



A. Sing (ed.), *Zoonoses–Infections Affecting Humans and Animals,*
DOI 10.1007/978-94-017-9457-2_17

importance of three companion animals, i.e. dogs, cats and horses, as sources or targets of infections with four multidrug-resistant zoonotic bacterial pathogens. We consider the ongoing socio-cultural changes in the relationship between companion animals and humans as a highly important matter in this respect. Here we briefly describe the domestication of dogs as one example of this ongoing development. This is meant to just give a flavor of our vision in terms of the possibility of an exchange of zoonotic pathogens between companion animals and their owners. We envision that the ever closer relationship will increase the risk of exchange of microbiota, and thus also of pathogens.

Although the dog was the first domesticated animal the idea based on molecular clock estimates from mitochondrial DNA that domestication started about 135,000 years (Vilà et al. 1997) is not without controversy. More circumspect estimates of zooarcheologists lead to the conclusion that dog domestication began about 15,000 years ago. Since even a broad analysis of 49,024 autosomal SNPs in 1375 dogs (representing 35 breeds) and 19 wolves failed in unraveling the history of dog domestication, next-generation sequencing of modern and ancient dog genomes is needed to settle this debate (Larson et al. 2012). Nevertheless, DNA analysis revealed that American dogs were more similar to dogs from the Old World than to gray wolves of North America. This outcome supports the idea that dogs accompanied humans crossing the Bering Strait in the late Pleistocene (Leonard et al. 2002), who consequently availed from the dogs abilities in hunting, protection and as pack animals. Moreover, during the process of domestication, dogs have been selected for a set of social-cognitive abilities that enable them to communicate with humans in unique ways (Hare et al. 2002). The archeological finds of canine bones revealed distinctions against contemporary wolves that were pronounced in both skulls and dentition and could be interpreted as results of human intervention in natural selection or may be markers of an early commensal relationship with humans as so called "camp-follower scavengers" (Murugaiyan et al. 2014; Zeder 2006). Skull shape modifications were probably the result of changes in dogs' brain morphology with a decrease of overall size relative to that of wolves and an increase in brain-to-body-size ratio (Schoenebeck and Ostrander 2013; Zeder et al. 2012).

In 2010, the estimated percentage of European households owning at least one dog or one cat was 27 and 24 %, respectively, a demonstration of the tight bond between mankind and domesticated animals, particularly canides, in postindustrial societies. Moreover, if it comes to numbers, 73.643.400 dogs and 84.705.500 cats were counted for European households (fediaf.org 2010). Since people are willing to spend a lot of money for their beloved companions not only for costly extensive medical treatments of seriously ill or elderly patients, but also for a wide range of unusual consumer products and services, pet animals contribute significantly to the economy (Walsh 2009). In 2010 the estimated combined annual turnover of pet food industry and related supply and services throughout Europe reached about € 24 billion (fediaf.org 2010).

It seems to be common knowledge that the human-animal interactions possess the potential to benefit human mental and physical health and wellbeing (O'Haire 2010). However, study results towards the association between pet ownership and

human health were frequently found contradictory (McNicholas et al. 2005). Regarding the psychological part, the most important benefit of pet ownership was identified in terms of companionship (Duvall Antonacopoulos and Pychyl 2010). Nonetheless, a closer look at the complex psychological nature of human and companion animal relationships revealed that the degree of attachment (to the animal) is a stronger predictor of psychological distress than gender, marital status, age, and number of people within a household. However, the causal direction of this association remains unknown at present and needs to be further investigated (Peacock et al. 2012). Pet ownership in elderly people (≥65 years) is frequently discussed as a possibility to avoid loneliness and depression, a rising problem due to population aging in Western societies. Interestingly, only for those people who were both, divorced and living alone, pet ownership demonstrated the potential for being associated with greater satisfaction with life (Himsworth and Rock 2013). Thus, chronically disconnected people tend to substitute social contacts by companion animals (Serpell 2003; Zeder 2006). Moreover, a number of studies confirmed the positive impact of interactions with companion animals on physical health, particularly in patients with heart disease and chronic diseases like cancer (Friedmann and Thomas 1995; Johnson et al. 2003 ). Anderson et al. (1992) correlated pet ownership with cardiovascular benefits, e. g. lower systolic blood pressure, plasma cholesterol (men only) and triglyceride levels (Anderson et al. 1992).

The socio-cultural background including traditions seems to influence the orientation of companion animal owners towards their animal: Study results by Blouin et al. (2013) suggest that among dog owners, one group values mostly the usefulness of their dog (e.g. protection), another provide the status of surrogate humans, and the third group views the dogs as valuable companions including own (animal) interests (Blouin (2013). The second group uses anthropomorphism, a term which can be defined as the attribution of human mental states (thoughts, feelings, motivations and beliefs) to non-human creatures (Serpell 2003). Moreover, anthropomorphism induces a certain kind of evolutionary selection pressure and a variety of corresponding adaptations, which were not exclusively linked to animal welfare, resulting in a novel ecological niche (Serpell 2003). Beside the socio-cultural effects of this equalization of humans and companion animals, the transmission risk for pathogens rises as a result of offering certain human privileges to companion animals. This should be highlighted by the following study results: Of 102 dog owners, who attended a dog show event in 2009, 88.9% reported to allow at least one dog in the house, 68.5% allow the dog(s) to rest on the sofa, 39.8% allow their dogs to come onto the bed, 93.5% let them lick their hands and 52.8% let them lick their face (Walther et al. 2012b). These exemplarily co-habitation and behavioral pattern give cause to concern with respect to the fact that 60% of all human pathogens were generally regarded as zoonotic (Cleaveland et al. 2001; Woolhouse and Gowtage-Sequeria 2005) and a rising number of opportunistic bacteria exhibit multidrug resistance (Chuang et al. 2010; Stegmann et al. 2010; Wieler et al. 2011). Recent work published by Song et al. proving that family members share microbiota with their dogs, in particular regarding skin microbiota, gives further evidence on the extensive exchange of microbes (Song et al. 2013).

When new zoonotic pathogens emerge, a frequently chosen strategy is to search for the most important infections source, ignoring other species that might strongly influence transmission (Brisson et al. 2011). A considerable problem arises when scientists use the term "reservoir" in this context. Although "reservoir" is defined as the natural permanent infection source of a certain pathogen, some scientists assign rather deliberately any infection source identified as reservoir. This implies that eradication of the respective pathogen in this reservoir will be the key for intervention. This can be illustrated with the emergence of so-called "livestock-associated" (LA-) MRSA. The first report of colonized members of a farmer family and their pigs in the Netherlands in 2004 (Voss et al. 2005) was followed by a rush of scientists from different disciplines in stables, flocks and cages. Early focusing on a limited number of possible host species as infection source can delay biological understanding. This may cause misguiding public health interventions as the important host species of either amplifying or transmissing the pathogen are overlooked (Brisson et al. 2011; Walther et al. 2012a). In case of LA-MRSA, a broad spread took place since 2005, including infections of horses, dogs, cats and many other species. Similarly, the new MRSA variant harboring *mec*C, initially described for humans and ruminants, was subsequently also found in diseased companion animals (Walther et al. 2012a). The finding that particular genetic lineages of Staphylococci are able to infect several host species led to the introduction of the paradigma of extended host spectrum genotypes (EHSG) (Walther et al. 2009).

Knowledge concerning the risks associated with infections of companion animals with multidrug-resistance bacteria is rather limited (Stull et al. 2012). In consequence, interdisciplinary efforts are required to fulfill the demands of zoonotic disease information for both companion animal and non-owning households (Stull et al. 2012). We consider surveillance efforts in terms of a "One health" umbrella as the key starting point. Here we summarize knowledge on four multidrug-resistant bacterial species. We highlight the knowledge gaps of these increasing important in terms of disease burden in companion animals and their zoonotic potential.

## 17.2 Methicillin-Resistant *Staphylococcus aureus* in Companion Animals

The natural habitat of *Staphylococcus (S.) aureus*, a Gram-positive coccus, is the skin and the anterior nares of humans. Approximately 30% of humans are permanently while up to 50% are transiently colonized. Besides, various animals can be carriers. As an opportunistic pathogen, *S. aureus* plays an important role in both human and veterinary medicine, affecting a broad range of animals.

Methicillin-resistant *S. aureus* (MRSA) are resistant against all ß-lactam antibiotics mediated by the acquisition of the Penicillin-binding protein 2a (PBP2a) encoding *mec*A- or *mec*C-gene. PBP2 is expressed by all *S. aureus* and catalyzes two enzymatic reactions (transpeptidation and transglycosilation). By binding ß-lactam antibiotics, the transpeptidase of PBP2 loses its function which mediates

the bactericidal effect. PBP2a acts as an additional transpeptidase and shows, unlike the native PBP2, a low affinity to ß-lactam antibiotics, thus it compensates the loss of function in PBP2 after therapy with ß-lactams.

Only a short time after the introduction of methicillin, MRSA-infections were reported with an increasing number in hospitals as well as other healthcare settings. This observed restriction led to the denomination of those genotypes as hospital-associated (HA-) MRSA. Along with methicillin-resistance, *S. aureus* frequently acquire resistance against various antimicrobials, leading to reduced therapeutic options. In human medicine, MRSA is one of the most important nosocomial pathogens that provides a significant burden to healthcare settings due to extended therapy, prolonged hospital stay and higher costs (Köck et al. 2010). During the 1990s the MRSA epidemiology changed, as MRSA-infections were no longer restricted to healthcare settings, but were increasingly observed in humans outside the hospital. In comparison to well-characterized HA-MRSA, these strains belonged to different genetic lineages and were termed as community-associated (CA-) MRSA (Chambers 2001). Nowadays, MRSA are important pathogens in both healthcare settings and surroundings without exposure to hospital environments (Köck et al. 2014).

It was not until the late 1990s that the awareness of MRSA as cause of infections in animals increased based on several case reports. In 2004, MRSA of a specific genetic lineage, namely CC398-MRSA, emerged as frequent colonizers of pigs and farmers in close contact. The initial assumed host restriction to swine and other livestock resulted in the denomination as Livestock-associated (LA-) MRSA. Since then, CC398-MRSA have been reported in humans and several other animal species (Köck et al. 2014).

Meanwhile, MRSA have been detected in a wide range of animals. In particular companion animals are regularly identified to be colonized and/or infected with MRSA. The main infection sites in dogs and cats include wounds, urogenital tract, skin and mucosa as well as ears (Walther et al. 2008). Data concerning colonization in dogs and cats are rare and difficult to compare due to heterogeneous study settings. However, these surveys describe colonization in dogs and cats with rates from zero to 4 % in healthy dogs and cats without clinical background and up to 9 % for dogs at a veterinary clinic (Weese 2010). Although there is a lack of knowledge concerning the colonization length, first evidence exists that MRSA-carriage is transient in dogs and cats (Loeffler et al. 2010b). The genotypes of canine and feline MRSA mirror predominant human HA-associated MRSA-lineages within the same geographic region like clonal complexes (CC)8 in France (Haenni et al. 2012), CC5 and CC22 in Germany (Vincze et al. 2013) and CC22 and CC30 in the United Kingdom (Loeffler et al. 2010a), indicating a spill-over from human hospitals to dogs and cats. In addition, CC398-MRSA can be detected in dogs and cats on a regular basis, underlining the potential of this lineage to colonize and infect not only livestock and humans but dogs and cats as well (Köck et al. 2014; Vincze et al. 2014).

In horses, MRSA-infections were described only occasionally after the first report in 1989 and it was not before the mid-1990s that an increasing number of equine MRSA-cases demonstrated the importance of this pathogen. Infections can be associated with both horses in clinical environments and without exposure to

clinics. While nosocomial outbreaks in equine clinics occur on a regular basis resulting in a large number of surgical site infections, MRSA-infections also have a serious impact in sporadic outbreaks without clinical background. Common infections without hospital background include joint, incision, and skin or soft tissue infections (Weese 2010). Similar to colonization studies in dogs and cats, data for horses are difficult to compare and range, depending on the investigated population, from 0 to 5% in horses from farms, up to 11% in horses admitted to equine clinics (van Duijkeren et al. 2010). In contrast to strains from dogs and cats, equine MRSA-lineages do not mirror common regional human lineages. Instead, CC8-MRSA, a prior human epidemic clone with sparse occurrence currently in humans, was reported as most common lineage in horses, leading to speculations on putative advantages of this lineage in equine colonization and infection (Weese 2010). Only recently, CC398-MRSA were reported in several horses from different European countries like Belgium, France and The Netherlands (Van den Eede et al. 2009; van Duijkeren et al. 2010). Recent data point towards the microevolution of a horse-adapted sublineage of ST398 (Abdelbary et al. 2014).

Transmission events between companion animals and humans have been described regularly, showing either humans as infection or colonization source for dogs, cats and horses or vice versa (Faires et al. 2009; Ferreira et al. 2011; Köck et al. 2014; Manian 2003; Weese et al. 2005). Even though, there is evidence for zoonotic transmission between companion animals and humans, longitudinal studies that address the frequency and impact of these events are still missing. Since dogs and cats are regularly infected with MRSA-lineages similar to prevalent regional genotypes causing infections in humans, transmission might be an important factor for colonization and/or infection in both directions. These events need to be unraveled, therefore longitudinal studies as well as case-control studies are urgently needed. The above discussed changes in the socio-cultural relationship between humans and companion animals clearly provide more opportunities for transmission (Walther et al. 2012b). Consequently, owners of MRSA-infected dogs were found more often nasally colonized with MRSA than the average population in Great Britain. Thus, MRSA-infected dogs are already identified as a risk factor for human colonization (Loeffler et al. 2010a).

So far, genetic lineages that were recognized as cause of infections in dogs, cats and horses did not show specific restrictions to one or a limited number of hosts. In contrast, MRSA of these genotypes seem to possess the potential to infect and/or colonize humans as well. Genotypes with the ability to infect a broad host spectrum were termed as extended host spectrum genotypes (EHSG) (Köck et al. 2014; Walther et al. 2009). With the knowledge that (i) MRSA is an important pathogen in companion animal medicine, (ii) MRSA from companion animals are EHSG, (iii) ownership of an MRSA-infected companion animal results in a higher risk of human colonization, and (iv) epidemiology changes over time as proven for MRSA in horses, monitoring and surveillance utilizing molecular typing of MRSA in companion animals is crucial to understand dynamics and spread of MRSA in companion animals.

## 17.3 Extended-Spectrum Beta-Lactamase (ESBL)-Producing Enterobacteriaceae

Extended-spectrum beta-Lactamases (ESBL) are a diverse group of hydrolyzing enzymes produced by Gram-negative bacteria that inactivate a wide range of beta-lactam antibiotics including broad-spectrum penicillin and cephalosporin up to the 3rd generation. ESBL enzymes in general are encoded on plasmids. They can still be inhibited by clavulanic acid which separates ESBL from AmpC, another type group of beta-lactamases. The *ampC* genes are often chromosomally encoded and occur frequently in Enterobacteriaceae. Their overexpression due to mutations confers broad-spectrum beta-lactam resistance as well.

As carbapenems are not inactivated by ESBL-or AmpC producers, they often present the last treatment opportunity. This is due to the fact that ESBL-producing Enterobacteriaceae often display additional resistances to several other classes of antimicrobial substances, resulting in multidrug-resistant phenotypes. Therefore, ESBLs are a worrying global public health issue as infections caused by these multidrug-resistant organisms are associated with a higher morbidity and mortality and a greater fiscal burden (Dhillon and Clark 2012). Taking into account the increasing worldwide prevalence (central Europe approx. 10% of clinical *E. coli*) and an ever diminishing supply in the antibiotic armamentarium, ESBLs represent a clear and present danger to public health (Dhillon and Clark 2012). Although ESBLs are often commensals, they represent primary or secondary pathogens in healthy individuals in a wide range of diseases such as urinary tract infections, wound infections, pneumonia and septicaemia (Canton and Coque 2006). Cephalosporins are among the most commonly used antimicrobial classes in companion animal medicine, therefore increasing resistance against this class also presents an emerging problem for veterinarians.

Initially ESBL-producing Enterobacteriaceae were only observed in clinical settings where the first nosocomial outbreaks were recorded in clinics in Central Europe in the late 1980s. Since then an explosive worldwide proliferation of ESBLs in human clinical settings has been observed (Ewers et al. 2012). Within the last decade a community-associated onset has taken place. In between ESBL-producing Enterobacteriaceae are isolated from a wide range of companion animals, livestock, environmental samples and wildlife all over the world (Guenther et al. 2011). These ESBL-producing Enterobacteriaceae of animal origin did not only present resistant commensals, but included strains relevant to human health underlining the zoonotic character of ESBL (Carattoli 2008; Ewers et al. 2011a; Hasman et al. 2005; Overdevest et al. 2011; Smet et al. 2010). Considering that horizontally acquired plasmids are encoding these resistances, it is obvious that these developments further enrich the resistome (Gaze et al. 2013).

ESBL-production in companion animals is primarily associated with *Escherichia coli*, but can also occur in other pathogenic Enterobacteriaceae such as *Citrobacter*, *Proteus*, *Salmonella* and *Klebsiella* (Ewers et al. 2011b). About a decade after

the increased numbers of nosocomial infections in human medicine the numbers of ESBL involved in nosocomial infections of companion animals is also rising.

At present over 200 ESBL types are known and have been classified into three major classes: CTX-M, SHV and TEM. These ESBL-encoding genes are frequently located on plasmids, which harbour additional resistance genes and can be transmitted between different Enterobacteriaceae species. Amongst companion animals, ESBLs are mostly described in dogs, cats and horses, whereas their prevalence in other companion animals still remains unknown yet (Ewers et al. 2012). ESBL-producing Enterobacteriaceae are mostly spread by the faecal-oral route and transmission can occur either by direct contact or indirect by contaminated food and water.

As mentioned above different enzymes encode for ESBL-production and the ones present in companion animals are basically the same than the ones, which have been found in human isolates. The first descriptions in companion animals date back to the late 1990's and these early studies reported the presence of mainly TEM and SHV genes in clinical isolates from dogs in Spain, Portugal and Italy (Feria et al. 2002; Teshager et al. 2000).

However, similar to the situation in humans also in companion animals a shift towards CTX-M-genes seems to have taken place over the last decade. These CTX-M-genes have been detected in 2.6–5.6% of all reported clinical and commensal Enterobacteriaceae and overall this gene type accounts for about 25–76% of all Extended-spectrum beta-lactamases originating from companion animals (Ewers et al. 2011b). $Bla_{\text{CTX-M}}$-genes are particularly common in companion animal isolates from Europe, but can also often be found in isolates originating from America, Australia and Asia (Ewers et al. 2012). The most frequent CTX-M-types reported in companion animals are CTX-M-15 and CTX-M-1 (Damborg et al. 2011; Damborg et al. 2012; Dierikx et al. 2012, Dolejska et al. 2011; Ewers et al. 2010; Schink et al. 2011).

Extensive studies on risk factors concerning ESBL-carriage in companion animals are missing yet. However, risk factors identified in human medicine seem to be relevant in the veterinary context as well. Indeed, some studies showed that hospitalization and antimicrobial treatment—in particular with cephalosporins—appear to select for ESBL in horses and dogs (Damborg et al. 2011; Damborg et al. 2012; Dolejska et al. 2011; Maddox et al. 2012). Taking into account these main risk factors, general infection control measures and rational antibiotic use appear to be important steps in the prevention of an intra- and interspecies spread of ESBL-producing Enterobacteriaceae.

Regarding the zoonotic risk of ESBL-bacteria there is currently only limited evidence for a transmission between closely interacting humans and companion animals. One study reported the presence of the same *E. coli* clone harbouring a CTX-M-1 type beta-lactamase in a human and several horses in the same riding centre (Dolejska et al. 2011). Nevertheless, potentially zoonotic ESBL-strains exist in companion animals. One example is the pandemic multidrug-resistant and virulent *E. coli* lineage B2-O25b:H4-ST131-CTX-M15, which represents the dominant ESBL-isolate in most European countries and all over the world (Livermore et al. 2007). Recent studies have reported this lineage to be occurring in companion

animals as well as—also in association with CTX-M-15– among *E. coli* isolates from dogs, cats and horses worldwide (Albrechtova et al. 2012; Ewers et al. 2010; Timofte et al. 2011).

This illustrates that besides the same genes, identical clonal lineages are also shared between humans and companion animals. Thus it seems that transmission of this recently evolved clone has taken place between humans and companion animals or vice versa, either directly or indirectly. Research is needed to assess and prevent the human health risk associated with the companion animals, especially in consideration of the frequent use of cephalosporins in small animal medicine.

Summing up the role of companion animals in human infections caused by ESBL-producing Enterobacteriaceae is currently impossible. There is strong evidence that a decade after these bacteria have established in human medicine we observe an identical epidemiology in companion animals. ESBLs in between have established in commensal and potentially pathogenic Enterobacteriaceae of companion animals. Undoubtedly, this could be a valuable source of human infections and vice versa.

## 17.4 Multidrug-Resistant *Acinetobacter baumannii* and Methicillin-Resistant *Staphylococcus pseudintermedius* (MRSP)

This chapter briefly summarizes trends in infections with two bacterial pathogens, as multidrug-resistant variants of these have only recently been detected in animals. Only initial evidence exists about their zoonotic potential. However, as multidrug-resistance is a potent driver towards bacteria successfully entering new habitats (Gaze et al. 2013; Guenther et al. 2011; Holt et al. 2012), we consider an increasing incidence of infections with multidrug-resistant variants of *Acinetobacter* (*A.*) *baumannii* as well as *Staphylococcus* (*S.*) *pseudintermedius* in the near future. *S. pseudintermedius* until recently was regarded as a non-zoonotic pathogen of dogs and horses. However, case reports in humans encouraged us to include this pathogen (Vincze et al. 2010). This even more as both pathogens display multidrug-resistant types which in the case of infections can hardly be treated by antibiotics. Furthermore, both species are of high tenacity, thus survive in the environment for considerable long time periods. Both form biofilms on abiotic surfaces. This leads to increased survival within human and veterinary clinics. These features are a prerequisite for both microbes to act as nosocomial agents, therefore large-scale desinfections are needed in case of nosocomial outbreaks.

*A. baumannii* is a facultative pathogen that is isolated both from humans and in animals from different diseases such as pneumonia, catheter-associated genital tract infections, septicemia, skin and soft tissues infections. It is mostly seen in immunocompromised patients (Karah et al. 2012; Kim et al. 2013; O'Shea 2012; Qiu et al. 2012; Renckens et al. 2006). As well-known nosocomial pathogen it is associated

with increased morbidity and mortality in the medical field. Infections in companion animals have only recently been reported (Boerlin et al. 2001; Endimiani et al. 2011; Francey et al. 2000; Müller et al. 2014; Vaneechoutte 2000; Zordan et al. 2011). This is why crucial knowledge on the epidemiology is lacking.

Over the last 20 years multidrug-resistant *Acinetobacter* (*A*.) *baumannii*- strains are increasingly isolated from medical patients, mostly associated with infections in clinical settings. Mortalities of 40–75 % for ventilator-associated pneumonia and septicemia in 28–43 % have been reported for humans (McConnell et al. 2013; Qiu et al. 2012). Some 2–10 % of all nosocomial infections in intensive care units are caused by *A. baumannii*. The rate of multidrug-resistant *A. baumannii* isolates increased during 2002–2006 from 2.1 to 7.9 % (Wadl et al. 2010). In between increased isolation rates of multidrug-resistant *A. baumannii* are also observed in veterinary clinics. In cats and dogs *A. baumannii* has been reported to mainly cause wound and urinary tract infections. The latter ones are often associated with catheterized animals in veterinary hospitals therefore nosocomial origins are most probable (Zordan et al. 2011). An identical development is envisioned as already experienced with MRSA, namely the appearance of this multidrug-resistant pathogen first in human medicine and then with a decades' time lag in veterinary settings (Ewers et al. 2012; Ewers et al. 2011b; Vincze et al. 2014; Wieler et al. 2011).

However, substantial epidemiological data are lacking. Even the reservoir of *A. baumannii* is still unknown, but most probably it is the environment as it can be isolated from soil, water and food. Although pathogenic *A. baumannii* are isolated from skin or surfaces or in stool samples, in general the ubiquitous apathogenic *Acinetobacter spp*. are isolated (Mortensen and Skaar 2012; Peleg et al. 2008). Acinetobacter may be part of the physiological microbiota of animals. However, still this hypothesis needs to be falsified. The question of the transmission direction between humans and animals is therefore also open and needs to be further ascertained (Hamouda et al. 2011; Müller et al. 2014; Peleg et al. 2008). As it is currently not possible to unequivocally identify *A. baumannii* by phenotypical or MALDI-TOF methods it is not always clear whether actually *A. baumannii* was identified or an isolate belonging to the *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex (*Acb* complex) (Dijkshoorn et al. 2007; Peleg et al. 2008). Therefore molecular methods like analysis of the 16S-23S rRNA-gene spacer region, *bla*-OXA-51-like gene, *rpo*B gene or whole genome sequence analysis are increasingly implemented (Chang et al. 2005). As each of the four species belonging to the Acb complex differ in clinical course and thus in different treatment options a correct species identification is of utmost importance (Espinal et al. 2012).

*A. baumannii* are naturally resistant against trimethoprim. In addition, they have a tendency to develop resistance extremely rapidly by up-regulation of efflux pumps or acquisition of resistant determinants. The intrinsic resistance mechanisms include the small number of porins, the AmpC cephalosporinase (Hamouda et al. 2011) and the multidrug efflux pump AbeABC. Different classes of antibiotics such as aminoglycosides, chloramphenicol, tetracyclines, fluoroquinolones, trimethoprim, and beta-lactams including Carbapenemene can be ejected as substrates (Gootz and Marra 2008; Müller et al. 2014). Resistance to fluoroquinolones is based primarily on mutations in the genes *gyrA* and *parC*, which encode a DNA gyrase

and topoisomerase IV (Peleg et al. 2008). Genomic analysis of multidrug-resistant *A. baumannii* strains demonstrated that the genes that mediate resistance are usually encoded on so-called resistance islands. The 86-kb AbaR1 Island encoding 45 resistance genes is the largest island of resistance described (Fournier et al. 2006). *A. baumannii* has mechanisms that favor horizontal gene transfer and thus the rapid development of multidrug resistant (MDR=multidrug resistant) strains (Dijkshoorn et al. 2007; Giamarellou 2008; Müller et al. 2014; O'Shea 2012). This is why *A. baumannii* genomes harbor a large number of mobile genetic elements such as transposons, integrons class I or insertion sequences (Overdevest et al. 2011; Peleg et al. 2008). Thus in *A. baumannii* isolates ESBLs and Oxacillinases are seen, some even being carbapenemases (Gootz and Marra 2008; Peleg et al. 2008). Carbapenems are currently the most effective antibiotic in the treatment of *A. baumannii* infections. Resistance to these antibiotics significantly reduces therapeutic options. Meanwhile *A. baumannii* strains have been isolated that are resistant to all classes of commercially available antibiotics, which for both medical and veterinary doctors is a tremendous challenge (Dijkshoorn et al. 2007). Some authors argue that regarding *A. baumannii* we are closer to the end of the antibiotic era as with MRSA (Giamarellou et al. 2008; Müller et al. 2014).

Most infections in humans are caused by the so-called EU or international clones I-III. These are characterized by a high level of antibiotic resistance (Dijkshoorn et al. 2007; Giamarellou et al. 2008; Karah et al. 2012; Seifert et al. 2005). *A. baumannii* isolates belonging to these EU clones have also been responsible for outbreaks in German veterinary clinics and veterinary practices (Endimiani et al. 2011; Müller et al. 2014; Vaneechoutte et al. 2000; Zordan et al. 2011). It is clear that *A. baumannii* is a pathogen with zoonotic potential.

A totally different perspective is given by *S. pseudintermedius*. The bacterial species has previously been known as *S. intermedius*, one of the most important causes of pyodermia and otitis, particularly in dogs. In 2005, Devriese et al. described a novel coagulase positive staphylococcal (CPS) species, denominated as *S. pseudintermedius* (Devriese et al. 2005). In the following years, molecular taxonomic investigations revealed that *S. pseudintermedius*, *S. delphini* and *S. intermedius* are closely related CPS species referred to as staphylococci of the intermedius group (SIG). While *S. intermedius* seems to be commonly associated with pigeons, *S. pseudintermedius* is not only a common colonizer of the canine skin, but also an opportunistic pathogen frequently isolated from clinical specimens of dogs, and, to a lesser extent, of cats and various other host species (Bannoehr et al. 2007; Bannoehr and Guardabassi 2012; Kadlec et al. 2010; Ruscher et al. 2008; Sasaki et al. 2007; Solyman et al. 2013). These findings have led to the realization that most canine isolates previously identified as *S. intermedius* should have been classified as *S. pseudintermedius* (Bannoehr et al. 2009; Sasaki et al. 2007). While biochemical features seem to vary among isolates of the same SIG species, sequence based methods, analysis by MALDI-TOF (Matrix Assisted Laser Desorption Ionisation-Time Of Flight Mass Spectrometry) and polymerase chain reaction-restriction length polymorphism (PCR-RFLP) are considered as reliable identification tools for *S. pseudintermedius* (Bannoehr and Guardabassi 2012; Murugaiyan et al. 2014; Savini et al. 2012).

The first methicillin resistant variants of *S. pseudintermedius* were reported sporadically in the late 1990s (Gortel et al. 1999; Piriz et al. 1996). Only a few years later, a sudden rise of MRSP reports followed and meanwhile MRSP are among the most important therapeutic challenges due to their frequent multi-drug resistance phenotype world-wide (Bemis et al. 2009; Perreten et al. 2010; Ruscher et al. 2010). Moreover, MRSP are of particular concern with respect to the increase of nosocomial infections in veterinary medicine and their potential transferability to humans and other animals in the household (Perreten et al. 2010; Perreten et al. 2010; Wieler et al. 2011). Consequently, owners of dogs suffering from *S. pseudintermedius*-infections and veterinarians seem to be at higher risk for nasal colonization and/or contamination than other people. Dog owners who keep more than two dogs also have a significantly higher chance to harbor *S. pseudintermedius* in the nose cavity (Frank et al. 2009; Ishihara et al. 2010; Paul et al. 2011; Vincze et al. 2010; Walther et al. 2012b). A high level of domestic MRSP-contamination, probably mediated by loss of hair and epithelia cells of the infected animal patient, may lead to a higher risk of developing MRSP infections in case of surgical or non-surgical wounds for pet owners (van Duijkeren et al. 2011). A sudden increase of reports concerning cases of severe *S. pseudintermedius*-infection in humans is noticeable and seems to reflect these changes in infection ecology (Riegel et al. 2010; Savini et al. 2013; Stegmann et al. 2010; Van Hoovels et al. 2006). The public health impact of the sudden emergence of a multidrug resistant zoonotic pathogen frequently occurring in companion animals like MRSP needs to be the subject of more detailed molecular and epidemiological studies (Loeffler et al. 2010a).

## 17.5 Conclusions and Outlook

Human interventional therapeutic use and misuse of antimicrobial drugs both in veterinary and human medicine is a major driver for the enrichment of the bacterial resistome. The increasing isolation of multidrug-resistant bacteria from clinical infections, be they zoonotic or non-zoonotic, is a direct consequence of this recent development. While initially key multidrug-resistant bacteria like MRSA, ESBLs or *A. baumannii* have been isolated from medical clinics, their spread into the community was followed by infections in companion animals. In between, first cases of euthanasia due to failing therapy have been reported. These cases are vivid proof of a post-antibiotic era. Besides the clinical failure of antimicrobial drugs, multidrug-resistant bacteria show a change in habitat specificity in that they enable the bacteria to spread into previously unavailable habitats (Guenther et al. 2011; Holt et al. 2012). One particularly worrisome outcome of this development is the proven spread of MRSA into companion animals, leading not only to nosocomial infections in veterinary hospitals, but also to ongoing transmission between companion animals and their owners (Fig. 17.1). Similar trends are evidenced regarding ESBL-producing Enterobacteriaceae and multidrug-resistant *A. baumannii*. These worrisome developments have fostered the initiation of the EU-wide project CALLISTO to give

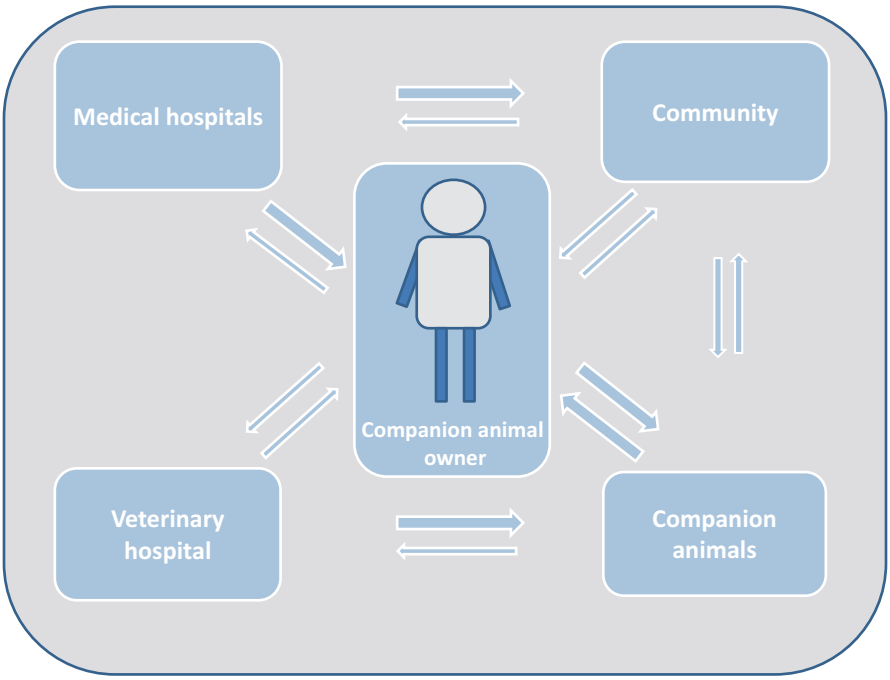


**Fig. 17.1** Transmission routes of multi-resistant bacteria between companion animals and humans

ground on further scientific steps in developing strategies against these zoonotic agents (http://www.callistoproject.eu/joomla/). In the case of *S. pseudintermedius* a tendency is observed that this naturally species-specific facultative pathogen is able to infect humans by gaining multidrug resistance. The socio-cultural changes in the co-existence between humans and their companion animals foster these developments. The link between multidrug-resistance and increased zoonotic potential of bacterial pathogens is a key evolutionary challenge we have to tackle. The only way of success is a multi- and interdisciplinary approach, the start of which is a global molecular driven surveillance of multidrug-resistant bacteria. This can only be successful when implemented by a "One health" approach. Such a surveillance will unravel both the microevolution of these bacteria and the directionality of transmission. These data are needed as a base for future intervention studies. However, regardless of these larger research efforts—prudent use of antimicrobial drugs must be a prerequisite for each and everyone in the world of antimicrobial drug usage.

There is a lack of knowledge on their prevalence in veterinary medicine based on the fact that no surveillance is in place. Clearly, effective preventive measures can only be installed based on unequivocal identification and representative epidemiological studies. Here the lack of knowledge is immense. As potential source of zoonotic transmission, data concerning colonization and infection should be determined and monitored continuously. Further, interdisciplinary studies are needed to determine the frequency of colonization and/or infection in owners and their

animals with the same clone. These data can help to identify the impact of companion animals as source of human infection and/or colonization and could raise the owner's awareness that companion animals can be a source of pathogen transmission in general, and in particular for MRSA.

## References

Abdelbary MM, Wittenberg A, Cuny C, Layer F, Kurt K, Wieler LH, Walther B, Skov R, Larsen J, Hasman H, Fitzgerald JR, Smith TC, Wagenaar JA, Pantosti A, Hallin M, Struelens MJ, Edwards G, Böse R, Nübel U, and WW (2014) Phylogenetic analysis of *Staphylococcus aureus* CC398 reveals a sub-lineage epidemiologically associated with infections in horses. PLoS ONE 9(2):e88083

Albrechtova K, Dolejska M, Cizek A, Tausova D, Klimes J, Bebora L, Literak I (2012) Dogs of nomadic pastoralists in Northern Kenya are reservoirs of plasmid-mediated cephalosporin- and quinolone-resistant *Escherichia coli*, including pandemic clone B2-O25-ST131. Antimicrob Agents Chemother 56:4013–4017

Anderson WP, Reid CM, Jennings GL (1992) Pet ownership and risk factors for cardiovascular disease. Med J Aust 157:298–301

Bannoehr J, Guardabassi L (2012) *Staphylococcus pseudintermedius* in the dog: taxonomy, diagnostics, ecology, epidemiology and pathogenicity. Vet Dermatol 23:253–e252

Bannoehr J, Ben Zakour NL, Waller AS, Guardabassi L, Thoday KL, van den Broek AH, Fitzgerald JR (2007) Population genetic structure of the *Staphylococcus intermedius* group: insights into *agr* diversification and the emergence of methicillin-resistant strains. J Bacteriol 189:8685–8692

Bannoehr J, Franco A, Iurescia M, Battisti A, Fitzgerald JR (2009) Molecular diagnostic identification of *Staphylococcus pseudintermedius*. J Clin Microbiol 47:469–471

Bemis DA, Jones RD, Frank LA, Kania SA (2009) Evaluation of susceptibility test breakpoints used to predict mecA-mediated resistance in *Staphylococcus pseudintermedius* isolated from dogs. J Vet Diagn Invest 21:53–58

Blouin DD (2013) Are dogs children, companions, or just animals? Understanding variations in people's orientations toward animals. Anthrozoos 26:279–294

Boerlin P, Eugster S, Gaschen F, Straub R, Schawalder P (2001) Transmission of opportunistic pathogens in a veterinary teaching hospital. Vet Microbiol 82:347–359

Brisson D, Brinkley C, Humphrey PT, Kemps BD, Ostfeld RS (2011) It takes a community to raise the prevalence of a zoonotic pathogen. Interdisciplinary perspectives on infectious diseases 2011

Canton R, Coque TM (2006) The CTX-M beta-lactamase pandemic. Curr Opin Microbiol 9:466–475

Carattoli A (2008) Animal reservoirs for extended spectrum beta lactamase producers. Clin Microbiol Infect 14:117–123

Chambers HF (2001) The changing epidemiology of *Staphylococcus aureus*? Emerg Infect Dis 7:178–182

Chang HC, Wei YF, Dijkshoorn L, Vaneechoutte M, Tang CT, Chang TC (2005) Species-level identification of isolates of the *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex by sequence analysis of the 16S-23S rRNA gene spacer region. J Clin Microbiol 43:1632–1639

Chuang CY, Yang YL, Hsueh PR, Lee PI (2010) Catheter-related bacteremia caused by *Staphylococcus pseudintermedius* refractory to antibiotic-lock therapy in a hemophilic child with dog exposure. J Clin Microbiol 48:1497–1498

Cleaveland S, Laurenson MK, Taylor LH (2001) Diseases of humans and their domestic mammals: pathogen characteristics, host range and the risk of emergence. Philos Trans R Soc Lond B Biol Sci 356:991–999

Damborg P, Gaustad IB, Olsen JE, Guardabassi L (2011) Selection of CMY-2 producing *Escherichia coli* in the faecal flora of dogs treated with cephalexin. Vet Microbiol 151:404–408

Damborg P, Marskar P, Baptiste KE, Guardabassi L (2012) Faecal shedding of CTX-M-producing *Escherichia coli* in horses receiving broad-spectrum antimicrobial prophylaxis after hospital admission. Vet Microbiol 154:298–304

Devriese LA, Vancanneyt M, Baele M, Vaneechoutte M, De Graef E, Snauwaert C, Cleenwerck I, Dawyndt P, Swings J, Decostere A, Haesebrouck F (2005) *Staphylococcus pseudintermedius* sp nov., a coagulase-positive species from animals. Int J Syst Evol Microbiol 55:1569–1573

Dhillon RH, Clark J (2012) ESBLs: a clear and present danger? Crit Care Res Pract 2012:625170

Dierikx CM, Duijkeren E van, Schoormans AH, van Essen-Zandbergen A, Veldman K, Kant A, Huijsdens XW, van der Zwaluw K, Wagenaar JA, Mevius DJ (2012) Occurrence and characteristics of extended-spectrum-beta-lactamase- and AmpC-producing clinical isolates derived from companion animals and horses. J Antimicrob Chemother 67:1368–1374

Dijkshoorn L, Nemec A, Seifert H (2007) An increasing threat in hospitals: multidrug-resistant *Acinetobacter baumannii*. Nat Rev Microbiol 5:939–951

Dolejska M, Duskova E, Rybarikova J, Janoszowska D, Roubalova E, Dibdakova K, Maceckova G, Kohoutova L, Literak I, Smola J, Cizek A (2011) Plasmids carrying blaCTX-M-1 and qnr genes in *Escherichia coli* isolates from an equine clinic and a horseback riding centre. J Antimicrob Chemother 66:757–764

Duvall Antonacopoulos NM, Pychyl TA (2010) An examination of the potential role of pet ownership, human social support and pet attachment in the psychological health of individuals living alone. Anthrozoos 23:37–54

Endimiani A, Hujer KM, Hujer AM, Bertschy I, Rossano A, Koch C, Gerber V, Francey T, Bonomo RA, Perreten V (2011) *Acinetobacter baumannii* isolates from pets and horses in Switzerland: molecular characterization and clinical data. J Antimicrob Chemother 66:2248–2254

Espinal P, Seifert H, Dijkshoorn L, Vila J, Roca I (2012) Rapid and accurate identification of genomic species from the *Acinetobacter baumannii* (Ab) group by MALDI-TOF MS. Clin Microbiol Infect 18:1097–1103

Ewers C, Grobbel M, Stamm I, Kopp PA, Diehl I, Semmler T, Fruth A, Beutlich J, Guerra B, Wieler LH, Guenther S (2010) Emergence of human pandemic O25:H4-ST131 CTX-M-15 extended-spectrum-beta-lactamase-producing *Escherichia coli* among companion animals. J Antimicrob Chemother 65:651–660

Ewers C, Bethe A, Wieler LH, Guenther S, Stamm I, Kopp PA, Grobbel M (2011a) Companion animals: a relevant source of extended-spectrum beta-lactamase-producing fluoroquinolone-resistant *Citrobacter freundii*. Int J Antimicrob Agents 37:86–87

Ewers C, Grobbel M, Bethe A, Wieler LH, Guenther S (2011b) Extended-spectrum beta-lactamases-producing gram-negative bacteria in companion animals: action is clearly warranted! Berl Munch Tierarztl Wochenschr 124:94–101

Ewers C, Bethe A, Semmler T, Guenther S, Wieler LH (2012) Extended-spectrum beta-lactamase-producing and AmpC-producing *Escherichia coli* from livestock and companion animals, and their putative impact on public health: a global perspective. Clin Microbiol Infect 18:646–655

Faires MC, Tater KC, Weese JS (2009) An investigation of methicillin-resistant *Staphylococcus aureus* colonization in people and pets in the same household with an infected person or infected pet. J Am Vet Med Assoc 235:540–543

fediaf.org (2010) Posting date. [Online]

Feria C, Ferreira E, Correia JD, Goncalves J, Canica M (2002) Patterns and mechanisms of resistance to beta-lactams and beta-lactamase inhibitors in uropathogenic *Escherichia coli* isolated from dogs in Portugal. J Antimicrob Chemother 49:77–85

Ferreira JP, Anderson KL, Correa MT, Lyman R, Ruffin F, Reller LB, Fowler VG Jr (2011) Transmission of MRSA between companion animals and infected human patients presenting to outpatient medical care facilities. PLoS ONE 6:e26978

Fournier PE, Vallenet D, Barbe V, Audic S, Ogata H, Poirel L, Richet H, Robert C, Mangenot S, Abergel C, Nordmann P, Weissenbach J, Raoult D, Claverie JM (2006) Comparative genomics of multidrug resistance in *Acinetobacter baumannii*. PLoS Genet 2:e7

Francey T, Gaschen F, Nicolet J, Burnens AP (2000) The role of *Acinetobacter baumannii* as a nosocomial pathogen for dogs and cats in an intensive care unit. J Vet Intern Med/Am Coll Vet Intern Med 14:177–183

Frank LA, Kania SA, Kirzeder EM, Eberlein LC, Bemis DA (2009) Risk of colonization or gene transfer to owners of dogs with meticillin-resistant *Staphylococcus pseudintermedius*. Vet Dermatol 20:496–501

Friedmann E, Thomas SA (1995) Pet ownership, social support, and one-year survival after acute myocardial infarction in the cardiac arrhythmia suppression trial (CAST). Am J Cardiol 76:1213–1217

Gaze WH, Krone SM, Larsson DG, Li XZ, Robinson JA, Simonet P, Smalla K, Timinouni M, Topp E, Wellington EM, Wright GD, Zhu YG (2013) Influence of humans on evolution and mobilization of environmental antibiotic resistome. Emerg Infect Dis 19

Giamarellou H, Antoniadou A, Kanellakopoulou K (2008) *Acinetobacter baumannii*: a universal threat to public health? Int J Antimicrob Agents 32:106–119

Gootz TD, Marra A (2008) *Acinetobacter baumannii*: an emerging multidrug-resistant threat. Expert Rev Anti Infect Ther 6:309–325

Gortel K, Campbell KL, Kakoma I, Whittem T, Schaeffer DJ, Weisiger RM (1999) Methicillin resistance among staphylococci isolated from dogs. Am J Vet Res 60:1526–1530

Guenther S, Ewers C, Wieler LH (2011) Extended-spectrum beta-lactamases producing *E. coli* in wildlife, yet another form of environmental pollution? Front Microbiol 2:246

Haenni M, Saras E, Chatre P, Medaille C, Bes M, Madec JY, Laurent F (2012) A USA300 variant and other human-related methicillin-resistant *Staphylococcus aureus* strains infecting cats and dogs in France. J Antimicrob Chemother 67:326–329

Hamouda A, Findlay J, Al Hassan L, Amyes SG (2011) Epidemiology of *Acinetobacter baumannii* of animal origin. Int J Antimicrob Agents 38:314–318

Hare B, Brown M, Williamson C, Tomasello M (2002) The domestication of social cognition in dogs. Science 298:1634–1636

Hasman H, Mevius D, Veldman K, Olesen I, Aarestrup FM (2005) beta-Lactamases among extended-spectrum beta-lactamase (ESBL)-resistant *Salmonella* from poultry, poultry products and human patients in The Netherlands. J Antimicrob Chemother 56:115–121

Himsworth CG, Rock M (2013) Pet ownership, other domestic relationships, and satisfaction with life among seniors: results from a Canadian national survey. Anthrozoos 26:295–305

Holt KE, Baker S, Weill FX, Holmes EC, Kitchen A, Yu J, Sangal V, Brown DJ, Coia JE, Kim DW, Choi SY, Kim SH, da Silveira WD, Pickard DJ, Farrar JJ, Parkhill J, Dougan G, Thomson NR (2012) *Shigella sonnei* genome sequencing and phylogenetic analysis indicate recent global dissemination from Europe. Nat Genet 44:1056–1059

Ishihara K, Shimokubo N, Sakagami A, Ueno H, Muramatsu Y, Kadosawa T, Yanagisawa C, Hanaki H, Nakajima C, Suzuki Y, Tamura Y (2010) Occurrence and molecular characteristics of methicillin-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus pseudintermedius* in an academic veterinary hospital. Appl Environ Microbiol 76:5165–5174

Johnson RA, Meadows RL, Haubner JS, Sevedge K (2003) Human-animal interaction: a complementary/alternative medical (CAM) intervention for cancer patients. Am Behav Sci 47:55–69

Kadlec K, Schwarz S, Perreten V, Andersson UG, Finn M, Greko C, Moodley A, Kania SA, Frank LA, Bemis DA, Franco A, Iurescia M, Battisti A, Duim B, Wagenaar JA, Duijkeren E van, Weese JS, Fitzgerald JR, Rossano A, Guardabassi L (2010) Molecular analysis of methicillin-resistant *Staphylococcus pseudintermedius* of feline origin from different European countries and North America. J Antimicrob Chemother 65:1826–1828

Karah N, Sundsfjord A, Towner K, Samuelsen O (2012) Insights into the global molecular epidemiology of carbapenem non-susceptible clones of *Acinetobacter baumannii*. Drug Resist Updat Rev Comment Antimicrob Anticancer Chemother 15:237–247

Kim CH, Jeong YJ, Lee J, Jeon SJ, Park SR, Kang MJ, Park JH (2013) Essential role of toll-like receptor 4 in *Acinetobacter baumannii*-induced immune responses in immune cells. Microb Pathog 54:20–25

Köck R, Becker K, Cookson B, Gemert-Pijnen JE van, Harbarth S, Kluytmans J, Mielke M, Peters G, Skov RL, Struelens MJ, Tacconelli E, Navarro Torne A, Witte W, Friedrich AW (2010) Methicillin-resistant *Staphylococcus aureus* (MRSA): burden of disease and control challenges in Europe. Euro Surveill 15:19688

Köck R, Ballhausen B, Bischoff M, Cuny C, Eckmanns T, Fetsch A, Harmsen D, Goerge T, Oberheitmann B, Schwarz S, Selhorst T, Tenhagen B-A, Walther B, Witte W, Ziebuhr W, Becker K (2014) The burden of zoonotic MRSA colonization and infection in Germany. Berl Münch Tierärztl Wochenschr 127 (in press)

Larson G, Karlsson EK, Perri A, Webster MT, Ho SYW, Peters J, Stahl PW, Piper PJ, Lingaas F, Fredholm M, Comstock KE, Modiano JF, Schelling C, Agoulnik AI, Leegwater PA, Dobney K, Vigne JD, Vilà C, Andersson L, Lindblad-Toh K (2012) Rethinking dog domestication by integrating genetics, archeology, and biogeography. Proc Natl Acad Sci U S A 109:8878–8883

Leonard JA, Wayne RK, Wheeler J, Valadez R, Guillén S, Vilà C (2002) Ancient DNA evidence for old world origin of new world dogs. Science 298:1613–1616

Livermore DM, Canton R, Gniadkowski M, Nordmann P, Rossolini GM, Arlet G, Ayala J, Coque TM, Kern-Zdanowicz I, Luzzaro F, Poirel L, Woodford N (2007) CTX-M: changing the face of ESBLs in Europe. J Antimicrob Chemother 59:165–174

Loeffler A, Pfeiffer DU, Lloyd DH, Smith H, Soares-Magalhaes R, Lindsay JA (2010a) Meticillin-resistant *Staphylococcus aureus* carriage in UK veterinary staff and owners of infected pets: new risk groups. J Hosp Infect 74:282–288

Loeffler A, Pfeiffer DU, Lindsay JA, Soares-Magalhaes R, Lloyd DH (2010b) Lack of transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) between apparently healthy dogs in a rescue kennel. Vet Microbiol 141:178–181

Maddox TW, Pinchbeck GL, Clegg PD, Wedley AL, Dawson S, Williams NJ (2012) Cross-sectional study of antimicrobial-resistant bacteria in horses. Part 2: risk factors for faecal carriage of antimicrobial-resistant *Escherichia coli* in horses. Equine Vet J 44:297–303

Manian FA (2003) Asymptomatic nasal carriage of mupirocin-resistant, methicillin-resistant *Staphylococcus aureus* (MRSA) in a pet dog associated with MRSA infection in household contacts. Clin Infect Dis 36:e26–e28

McConnell MJ, Actis L, Pachon J. 2013. *Acinetobacter baumannii*: human infections, factors contributing to pathogenesis and animal models. FEMS Microbiol Rev 37:130–155

McNicholas J, Gilbey A, Rennie A, Ahmedzai S, Dono JA, Ormerod E (2005) Pet ownership and human health: a brief review of evidence and issues. BMJ 331:1252–1254

Mortensen BL, Skaar EP. 2012. Host-microbe interactions that shape the pathogenesis of *Acinetobacter baumannii* infection. Cell Microbiol 14:1336–1344

Müller S, Janßen T, Wieler LH. 2014. Multidrug resistant *Acinetobacter baumannii* in veterinary medicine—emergence of an underestimated pathogen? Berl Münch Tierärztl Wochenschr 127 (in press)

Murugaiyan J, Walther B, Stamm I, Abou-Elnaga Y, Brueggemann-Schwarze S, Vincze S, Wieler LH, Lübke-Becker A, Semmler T, and RU (2014) Species differentiation within the *Staphylococcus intermedius* group using a refined MALDI-TOF MS database. Clin Microbiol Infect. doi: 10.1111/1469–0691.12662 [Epub ahead of print]

O'Shea MK (2012) Acinetobacter in modern warfare. Int J Antimicrob Agents 39:363–375

O'Haire M (2010) Companion animals and human health: benefits, challenges, and the road ahead. J Vet Behav Clin Appli Res 5:226–234

Overdevest I, Willemsen I, Rijnsburger M, Eustace A, Xu L, Hawkey P, Heck M, Savelkoul P, Vandenbroucke-Grauls C, Zwaluw K van der, Huijsdens X, Kluytmans J (2011) Extended-spectrum beta-lactamase genes of *Escherichia coli* in chicken meat and humans, The Netherlands. Emerg Infect Dis 17:1216–1222

Paul NC, Moodley A, Ghibaudo G, Guardabassi L (2011) Carriage of methicillin-resistant *Staphylococcus pseudintermedius* in small animal veterinarians: indirect evidence of zoonotic transmission. Zoonoses and public health

Peacock J, Chur-Hansen A, Winefield H (2012) Mental health implications of human attachment to companion animals. J Clin Psychol 68:292–303

Peleg AY, Seifert H, Paterson DL. (2008) *Acinetobacter baumannii*: emergence of a successful pathogen. Clin Microbiol Rev 21:538–582

Perreten V, Kadlec K, Schwarz S, Gronlund Andersson U, Finn M, Greko C, Moodley A, Kania SA, Frank LA, Bemis DA, Franco A, Iurescia M, Battisti A, Duim B, Wagenaar JA, Duijkeren E van, Weese JS, Fitzgerald JR, Rossano A, Guardabassi L (2010) Clonal spread of methicillin-resistant *Staphylococcus pseudintermedius* in Europe and North America: an international multicentre study. J Antimicrob Chemother 65:1145–1154

Piriz S, Valle J, Mateos EM, la Fuente R de, Cid D, Ruiz-Santaquiteria JA, Vadillo S (1996) In vitro activity of fifteen antimicrobial agents against methicillin-resistant and methicillin-susceptible *Staphylococcus intermedius*. J Vet Pharmacol Ther 19:118–123

Qiu H, KuoLee R, Harris G, Rooijen N Van, Patel GB, Chen W (2012) Role of macrophages in early host resistance to respiratory *Acinetobacter baumannii* infection. PLoS ONE 7:e40019

Renckens R, Roelofs JJ, Knapp S, Vos AF de, Florquin S, Poll T van der (2006) The acute-phase response and serum amyloid A inhibit the inflammatory response to *Acinetobacter baumannii* Pneumonia. J Infect Dis 193:187–195

Riegel P, Jesel-Morel L, Laventie B, Boisset S, Vandenesch F, Prevost G (2010) Coagulase-positive *Staphylococcus pseudintermedius* from animals causing human endocarditis. Int J Med Microbiol 301:237–239

Ruscher C, Lübke-Becker A, Wieler LH, Walther B (2008) Prävalenz Methicillin-resistenter *Staphylococcus pseudintermedius* (MRSP) in diagnostischem Probematerial 2007. Berliner und Münchener Tierärztliche Wochenschrift (BMTW)

Ruscher C, Lübke-Becker A, Semmler T, Wleklinski CG, Paasch A, Soba A, Stamm I, Kopp PA, Wieler LH, Walther B (2010) Widespread rapid emergence of a distinct methicillin- and multidrug-resistant *Staphylococcus pseudintermedius* (MRSP) genetic lineage in Europe. Vet Microbiol 144:340–346

Sasaki T, Kikuchi K, Tanaka Y, Takahashi N, Kamata S, Hiramatsu K (2007) Reclassification of phenotypically identified *Staphylococcus intermedius* strains. J Clin Microbiol 45:2770–2778

Savini V, Polilli E, Polakowska K, Marrollo R, Bialecka A, Kasprowicz A, Fazii P, D'Antonio D, Carretto E, Miedzobrodzki J (2012) Arginine dehydrolase and beta-gentiobiose cannot discriminate within the *Staphylococcus intermedius* group. Vet Microbiol 161:236–237 (author reply 235)

Savini V, Barbarini D, Polakowska K, Gherardi G, Bialecka A, Kasprowicz A, Polilli E, Marrollo R, Di Bonaventura G, Fazii P, D'Antonio D, Miedzobrodzki J, Carretto E (2013) Methicillin-resistant *Staphylococcus pseudintermedius* infection in a bone marrow transplant recipient. J Clin Microbiol 51:1636–1638

Schink AK, Kadlec K, Schwarz S (2011) Analysis of bla(CTX-M)-carrying plasmids from *Escherichia coli* isolates collected in the BfT-GermVet study. Appl Environ Microbiol 77:7142–7146

Schoenebeck JJ, Ostrander EA (2013) The genetics of canine skull shape variation. Genetics 193:317–325

Seifert H, Dolzani L, Bressan R, Reijden T van der, Strijen B van, Stefanik D, Heersma H, Dijkshoorn L (2005) Standardization and interlaboratory reproducibility assessment of pulsed-field gel electrophoresis-generated fingerprints of *Acinetobacter baumannii*. J Clin Microbiol 43:4328–4335

Serpell JA (2003) Anthropomorphism and anthropomorphic selection—beyond the "cute response". Soc Anim 11:83–100

Smet A, Martel A, Persoons D, Dewulf J, Heyndrickx M, Herman L, Haesebrouck F, Butaye P (2010) Broad-spectrum beta-lactamases among *Enterobacteriaceae* of animal origin: molecular aspects, mobility and impact on public health. FEMS Microbiol Rev 34:95–316

Solyman SM, Black CC, Duim B, Perreten V, van Duijkeren E, Wagenaar JA, Eberlein LC, Sadeghi LN, Videla R, Bemis DA, Kania SA (2013) Multilocus Sequence Typing for Characterization of *Staphylococcus pseudintermedius*. J Clin Microbiol 51:306–310

Song SJ, Lauber C, Costello EK, Lozupone CA, Humphrey G, Berg-Lyons D, Caporaso JG, Knights D, Clemente JC, Nakielny S, Gordon JI, Fierer N, Knight R (2013) Cohabiting family members share microbiota with one another and with their dogs. eLife 2:e00458

Stegmann R, Burnens A, Maranta CA, Perreten V (2010) Human infection associated with methicillin-resistant *Staphylococcus pseudintermedius* ST71. J Antimicrob Chemother 65:2047–2048

Stull JW, Peregrine AS, Sargeant JM, Weese JS (2012) Household knowledge, attitudes and practices related to pet contact and associated zoonoses in Ontario, Canada. BMC Public Health 12:553

Teshager T, Dominguez L, Moreno MA, Saenz Y, Torres C, Cardenosa S (2000) Isolation of an SHV-12 beta-lactamase-producing *Escherichia coli* strain from a dog with recurrent urinary tract infections. Antimicrob Agents Chemother 44:3483–3484

Timofte D, Dandrieux J, Wattret A, Fick J, Williams NJ (2011) Detection of extended-spectrum-beta-lactamase-positive *Escherichia coli* in bile isolates from two dogs with bacterial cholangiohepatitis. J Clin Microbiol 49:3411–3414

Van den Eede A, Martens A, Lipinska U, Struelens M, Deplano A, Denis O, Haesebrouck F, Gasthuys F, Hermans K (2009) High occurrence of methicillin-resistant *Staphylococcus aureus* ST398 in equine nasal samples. Vet Microbiol 133:138–144

van Duijkeren E, Moleman M, Sloet van Oldruitenborgh-Oosterbaan MM, Multem J, Troelstra A, Fluit AC, van Wamel WJ, Houwers DJ, de Neeling AJ, Wagenaar JA (2010) Methicillin-resistant *Staphylococcus aureus* in horses and horse personnel: an investigation of several outbreaks. Vet Microbiol 141:96–102

van Duijkeren E, Kamphuis M, Mije IC van der, Laarhoven LM, Duim B, Wagenaar JA, Houwers DJ (2011) Transmission of methicillin-resistant *Staphylococcus pseudintermedius* between infected dogs and cats and contact pets, humans and the environment in households and veterinary clinics. Vet Microbiol 150:338–343

Van Hoovels L, Vankeerberghen A, Boel A, Van Vaerenbergh K, De Beenhouwer H (2006) First case of *Staphylococcus pseudintermedius* infection in a human. J Clin Microbiol 44:4609–4612

Vaneechoutte M, Devriese LA, Dijkshoorn L, Lamote B, Deprez P, Verschraegen G, Haesebrouck F (2000) *Acinetobacter baumannii*-infected vascular catheters collected from horses in an equine clinic. J Clin Microbiol 38:4280–4281

Vilà C, Savolainen P, Maldonado JE, Amorim IR, Rice JE, Honeycutt RL, Crandall KA, Lundeberg J, Wayne RK (1997) Multiple and ancient origins of the domestic dog. Science 276:1687–1689

Vincze S, Paasch A, Walther B, Ruscher C, Lubke-Becker A, Wieler LH, Barbara K (2010) Multidrug- and methicillin resistant *Staphylococcus pseudintermedius* as a cause of canine pyoderma: a case report. Berl Munch Tierarztl Wochenschr 123:353–358

Vincze S, Stamm I, Monecke S, Kopp PA, Semmler T, Wieler LH, Lubke-Becker A, Walther B (2013) Molecular analysis of human and canine *Staphylococcus aureus* strains reveals distinct extended-host-spectrum genotypes independent of their methicillin resistance. Appl Environ Microbiol 79:655–662

Vincze S, Brandenburg AG, Espelage W, Stamm I, Wieler LH, Kopp PA, Lübke-Becker A, Walther B (2014) Risk factors for MRSA infection in companion animals: results from a case-control study within Germany. Int J Med Microbiol doi:10.1016/j.ijmm.2014.07.007

Voss A, Loeffen F, Bakker J, Klaassen C, Wulf M (2005) Methicillin-resistant *Staphylococcus aureus* in Pig Farming. Emerg Infect Dis 11:1965–1966

Wadl M, Heckenbach K, Noll I, Ziesing S, Pfister W, Beer J, Schubert S, Eckmanns T (2010) Increasing occurrence of multidrug-resistance in *Acinetobacter baumannii* isolates from four German University Hospitals, 2002–2006. Infection 38:47–51

Walsh F (2009) Human-animal bonds I: the relational significance of companion animals. Fam Process 48:462–480

Walther B, Wieler LH, Friedrich AW, Hanssen AM, Kohn B, Brunnberg L, Lubke-Becker A (2008) Methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from small and exotic animals at a university hospital during routine microbiological examinations. Vet Microbiol 127:171–178

Walther B, Monecke S, Ruscher C, Friedrich AW, Ehricht R, Slickers P, Soba A, Wleklinski CG, Wieler LH, Lubke-Becker A (2009) Comparative molecular analysis substantiates zoonotic potential of equine methicillin-resistant *Staphylococcus aureus*. J Clin Microbiol 47:704–710

Walther B, Wieler LH, Vincze S, Antao EM, Brandenburg A, Stamm I, Kopp PA, Kohn B, Semmler T, Lubke-Becker A (2012a) MRSA variant in companion animals. Emerg Infect Dis 18:2017–2020

Walther B, Hermes J, Cuny C, Wieler LH, Vincze S, Abou Elnaga Y, Stamm I, Kopp PA, Kohn B, Witte W, Jansen A, Conraths FJ, Semmler T, Eckmanns T, Lubke-Becker A (2012b) Sharing more than friendship—nasal colonization with coagulase-positive staphylococci (CPS) and co-habitation aspects of dogs and their owners. PLoS ONE 7:e35197

Weese JS (2010) Methicillin-resistant *Staphylococcus aureus* in animals. ILAR J/Natl Res Counc, Inst of Lab Anim Resour 51:233–244

Weese JS, Archambault M, Willey BM, Hearn P, Kreiswirth BN, Said-Salim B, McGeer A, Likhoshvay Y, Prescott JF, Low DE (2005) Methicillin-resistant *Staphylococcus aureus* in horses and horse personnel, 2000–2002. Emerg Infect Dis 11:430–435

Wieler LH, Ewers C, Guenther S, Walther B, Lubke-Becker A (2011) Methicillin-resistant staphylococci (MRS) and extended-spectrum beta-lactamases (ESBL)-producing Enterobacteriaceae in companion animals: nosocomial infections as one reason for the rising prevalence of these potential zoonotic pathogens in clinical samples. Int J Med Microbiol 301:635–641

Woolhouse MEJ, Gowtage-Sequeria S (2005) Host range and emerging and reemerging pathogens. Emerg Infect Dis 11:1842–1847

Zeder MA (2006) Central questions in the domestication of plants and animals. Evol Anthropol 15:105–117

Zeder MA (ed) (2012) Pathways to animal domestication. Cambridge University, Cambridge

Zordan S, Prenger-Berninghoff E, Weiss R, Reijden T van der, Broek P van den, Baljer G, Dijkshoorn L (2011) Multidrug-resistant *Acinetobacter baumannii* in veterinary clinics, Germany. Emerg Infect Dis 17:1751–1754