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Reflection paper on the risk of antimicrobial resistance transfer from companion animals

Summary

Antimicrobials are important tools for the therapy of infectious bacterial diseases in companion animals. Loss of efficacy of available antimicrobial substances can seriously compromise animal health and welfare. The need for the development of new antimicrobials for the therapy of multi-resistant infections, particularly those caused by Gram-negative bacteria, has been acknowledged in human medicine. For the future a corresponding need in veterinary medicine is to be expected.

A unique and critical aspect related to antimicrobial resistance in companion animals is their close contact with humans. This creates opportunities for interspecies transmission of (multidrug) resistant bacteria. Use of antimicrobials that are critically important for human health in companion animals is an additional risk factor for emergence and transmission of antimicrobial resistance. Yet, the current knowledge of many aspects of this field is limited and no assessment of this specific risk is performed when approving new veterinary antimicrobials.

Public health risks of transfer of resistance from bacteria from companion animals are reviewed in this document. The aim is to discuss the possible need for data in applications for new veterinary medicinal products for companion animals. The following aspects were considered:

- i. The use and indications of antimicrobials in companion animals.
- ii. Drug-resistant bacteria of concern among companion animals.
- iii. Risk factors for colonisation of companion animals with resistant bacteria.
- iv. Transmission of antimicrobial resistance (bacteria and/or resistance determinants) between animals and humans.

Microbiological hazards of concern were defined as the drug resistant bacteria and resistance genes originating from companion animals that directly or indirectly may cause adverse health effects in humans. The focus of this reflection paper is methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus pseudintermedius*, vancomycin-resistant enterococci, extended-spectrum beta-lactamase producing Enterobacteriaceae and carbapenem-resistant Gram-negative bacteria.

A risk assessment tool could be applied in applications for marketing authorisation for medicinal products for companion animals. With the principles of Codex and VICH it would be possible to meet the need for new treatment options for infections caused by multiresistant bacteria in companion animals by approving veterinary medicinal products for which risk levels are estimated as acceptable.

CVMP Recommendations for action

Antimicrobials are essential for the treatment of infectious diseases in humans and companion animals and there is substantial overlap between humans and animal species in the classes of antimicrobials used. The close contact between companion animals and their owners offers an opportunity for transfer of antimicrobial resistance about which there is limited knowledge, but which may have been under-estimated. It is now known that several problematic resistant organisms (e.g. MRSA) are shared between companion animals and humans and owing to the current concern about the emergence of multi-drug resistant infections and paucity of novel treatments under development, the CVMP concludes that the following recommendations should be considered in order to assess and limit the public health risk arising from the use of antimicrobials in companion animals:

1. Risk assessment guidelines should be developed to address the risk to public health from antimicrobial resistance due to antimicrobial use in companion animals.

An abbreviated risk assessment model consistent with the principles of Codex (Codex Alimentarius, 2011) or OIE Terrestrial Code (Vose et al., 2001) and CVMP/VICH GL27 (EMA, 2004) could be applied for applications relating to new compounds or new species or indications for existing compounds. The microbiological hazards identified in the reflection paper should be characterised in relation to the compound in question and the applicant could be requested to provide data similar to what is requested in VICH GL 27. An abbreviated estimate of the risk for exposure could be based on the number of animals to be treated with the antimicrobial in question. The indication and target population for the product should be justified taking into account the risk assessment and demonstrating that the intended use is compliant with responsible use principles. Possible risk mitigation measures should be proposed.

Responsible body: CVMP and its working parties.

2. Use in companion animals of substances regarded as critically important antimicrobials (CIA) for human medicine, especially last resort (life-saving) antimicrobials, should be carefully assessed considering the importance of those substances for public health.

Responsible body: In regards to applications for and approval of new Marketing Authorisations, it is the responsibility of applicants, CVMP and National Competent Authorities to ensure that a risk assessment is undertaken and appropriate guidance is given in the SPC and product literature. In regards to prescribing, it is the responsibility of professional bodies, universities and veterinary practitioners to develop and apply responsible use guidelines. The EMA, as part of the request from the European Commission for advice on the impact on public and animal health of the use of antibiotics in animals, is considering advice on the risk mitigation options related to the use of certain classes of antimicrobials that are of critical importance in human medicine¹.

Notwithstanding the recommendations above, the CVMP is of the opinion that transfer of AMR from companion animals should not be considered in isolation but a global approach is needed. Therefore, the CVMP, in addition to the recommendations above, strongly supports the two following suggestions in order to better understand and to limit the potential for transfer of antimicrobial resistance between companion animals and humans. It is recognised that these suggestions are outside the remit of the CVMP and that a significant amount of time and resources would be required for their implementation.

3. It would be desirable for the cascade use of antimicrobials in companion animals to be recorded and monitored, especially in regards to use of human-authorised antimicrobials.

¹ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142070.pdf

84 Responsible body: Competent Authorities.

85 4. It would be desirable to extend AMR surveillance programmes to include organisms of public health
86 significance isolated from companion animals.

87 Responsible body: Member States.

88 **Knowledge gaps**

89 The following knowledge gaps have been identified:

90 1. Risk factors and transmission routes involved in the transfer of antimicrobial resistance between
91 companion animals, between companion animals and humans and vice versa.

92 2. Extent and patterns of antimicrobial usage in companion animals.

93 3. The ecology of drug-resistant bacteria in companion animals and their environments, and the
94 relative importance of such bacteria in contributing to the burden of human disease.

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1. Introduction

During the last fifty years, the number of companion animals in modern society has substantially increased and a change in their social role has occurred. Attention to their welfare has increased as a consequence of the close contact between owners and their pets. Humans may acquire antimicrobial resistant bacteria or the corresponding resistance genes not only from food-producing animals but also via contact with their companion animals.

Methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus pseudintermedius* (MRSP), extended-spectrum beta-lactamases (ESBL, AmpC), producing Enterobacteriaceae and multidrug-resistant non-fermenting Gram-negative bacteria have emerged in healthy and sick dogs and cats (Ewers et al., 2012; Weese and van Duijkeren, 2010a; Wieler et al., 2011) implying a potential risk of transmission of these bacteria to humans from infected or colonized companion animals. In addition there is the possibility of transfer of genetic material coding for resistance.

In order to assess the emerging risks within the context of applications for new veterinary antimicrobials for companion animals, there might be a need for additional data requirements with respect to antimicrobial resistance. The currently available guidance on pre-approval information for registration of new veterinary medicinal products -VICH Topic GL27- is a guideline applicable to all new applications containing new active ingredients or existing substances for food producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01-FINAL) (EMA, 2004). It does not provide guidance on this issue for companion animals. Issues related to risk from direct contact with companion animals are not covered by any guidance document of the EMA.

2. Mandate and objectives

The CVMP mandated the SAGAM (currently the AWP) to draft a reflection paper and indicated that the main focus should comprise the selection in companion animals of multidrug-resistant bacteria that could carry risks for public health and transmission these bacteria from companion animals to humans.

Consequently the objective of the AWP was to review the current knowledge about zoonotic drug-resistant bacteria in companion animals, the risk of transmission of antimicrobial resistance between bacteria from companion animals and those from humans, and to identify the need for new data in order to register new antimicrobials for companion animal use.

In this document the term companion animals applies primarily to dog, cats, and pleasure or pet horses, although from a regulatory point-of-view, horses are classified as a food producing species and data requirements of products for horses are covered by GL27. Horses are included in this document because they are commonly kept in close contact with people. In addition, advanced veterinary procedures with intensive use of antimicrobials are performed in horses and multidrug resistant organisms have been recorded in this species. While it is acknowledged that emergence of multidrug-resistance among animals also represents loss of effectiveness of antimicrobials, the main focus of this reflection paper is on the zoonotic risks.

3. Use of antimicrobials

Antimicrobials are used in everyday practice for therapeutic and prophylactic purposes in companion animals. Antimicrobial consumption data for companion animals are often incomplete and usually refers to drug manufacturer sales. Although sales data provide an estimate of magnitude of

antimicrobial consumption, in general they do not contain data on the use of antimicrobials in different species. In the United Kingdom, there are examples of surveillance systems, such as VetCompass (<http://www.rvc.ac.uk/VetCOMPASS/>) and SAVSNET (<http://www.liv.ac.uk/SAVSNET/>) that may be used for monitoring of antimicrobial use in companion animals. In these data are electronically collected from volunteering veterinary practices. The data allow monitoring at prescription level. They could provide an important insight of the patterns and trends of antimicrobial usage as well as prevalence of common conditions in small animal populations. At present these systems do not include horses.

Widespread use of broad-spectrum antimicrobials has been reported in small animal practice in Europe (ESVAC, 2012). The most commonly used antimicrobials for dogs and cats in Denmark, Finland, Italy, Sweden, Norway and UK are beta lactams such as amoxicillin and amoxicillin combined with clavulanic acid (Escher et al., 2011; Kvaale et al., 2012; Mateus et al., 2011; Odensvik et al., 2001; Radford et al., 2011; Rantala et al., 2004a; Thomson et al., 2009). First generation cephalosporins are also frequently used, especially in dogs (Hill et al., 2006; Mateus et al., 2011; Odensvik et al., 2001; Rantala et al., 2004a; Thomson, 2010). Increased use of third generation cephalosporins in cats has been reported in the UK after the authorisation of cefovecin (Mateus et al., 2011) in Europe in 2006 (EMA, 2006). Lincosamides (clindamycin), fluoroquinolones, macrolides, tetracyclines (doxycycline), nitroimidazoles and trimethoprim-sulfonamides have also been reported to be routinely used in small animal practice but on a smaller scale than beta-lactams (DANMAP, 2010; Escher et al., 2011; Mateus et al., 2011; Radford et al., 2011; Rantala et al., 2004a; Thomson et al., 2009).

Data on antimicrobial usage in horses are scarce. A recent study conducted in Finland reported that antimicrobials are used mainly to treat skin infections and to a lesser extent, genito-urinary infections (endometritis, placental retention) in this species. The most common antimicrobials used to treat horses are penicillins or trimethoprim-sulphonamides (Thomson, 2010). In horses combinations of benzylpenicillin with either gentamicin or with trimethoprim-sulfonamides are often used in treatment (Thomson, 2010).

Current SPC guidance for the responsible use of antimicrobials in veterinary medicine recommends the restriction of the use of fluoroquinolones and third and fourth generation cephalosporins to clinical cases and whenever possible supported by antimicrobial susceptibility testing (AST) (EMA/CVMP/SAGAM, 2007; EMA/CVMP/SAGAM, 2009b; Official Journal of the European Union, 2012). In some countries national prescribing guidance have been developed for companion animals (BSAVA, 2012; BVA, 2009). Findings from a study in Italy revealed that only 5% of antimicrobial prescriptions in a veterinary teaching hospital were supported by results of culture and ASTs (Escher et al., 2011). Lack of confirmed diagnosis could lead to the misuse of antimicrobials. Antimicrobials administration has been reported to treat acute diarrhoea in dogs (German et al., 2010) and feline lower urinary tract disease (Thomson et al., 2009), for which conditions antimicrobial treatment is usually not recommended (Guardabassi et al., 2008). In the United States, a study in a canine intensive care unit from a tertiary University referral hospital, reported that the antimicrobial choices were appropriate only in 19% of the patients admitted (Black et al., 2009). A cross-sectional study on antimicrobial prescribing patterns in the UK showed that approximately 2% of prescriptions for dogs and cats were for products not authorised in those species (Hughes et al., 2012). Dose regimes in excess of that recommended in the SPC were also found to be common in dogs and cats in Switzerland (Regula et al., 2009).

In UK equine veterinary practice 11% of prescriptions were for antimicrobial drugs not licensed for use in horses (Hughes et al., 2013). In Switzerland, a study involving 8 veterinary mixed practices reported that the dosage corresponded to the manufacturer's recommendation was employed only in 45% of the analysed prescriptions. Critically important antimicrobials such as fluoroquinolones, third- and fourth-generation cephalosporins and macrolides were used in 9% of the prescriptions (Regula et al., 2009).

4. Drug-resistant bacteria of concern

4.1. Introduction

Multidrug resistant organisms have been reported in companion animals, sometimes severely compromising the treatment outcome. Because of limited surveillance and awareness of the zoonotic transmission of antimicrobial resistance between companion animals and humans, the extent of transmission and importance of it for public health are poorly understood. In the following paragraphs the most relevant drug-resistant bacteria are reviewed as well as the evidence for their transmission between companion animals and humans.

4.2. Methicillin-resistant staphylococci

4.2.1. Methicillin-resistant *Staphylococcus aureus* (MRSA)

MRSA is one of the most significant bacteria causing both hospital- and community-acquired infections in humans. MRSA has acquired the *mecA* gene, resulting in production of an altered penicillin-binding protein (PBP2a or PBP2') which cause resistance to all β -lactam antimicrobials. MRSA occurs also in companion animals as recently reviewed by SAGAM (Catry et al., 2010; EMA/CVMP/SAGAM, 2009a). Since the first companion animal-related outbreak of MRSA in a rehabilitation geriatric ward was reported in 1988, the number of reports on infections and colonization with MRSA in companion animals has been described with increasing frequency (Boag et al., 2004; Catry et al., 2010; Leonard and Markey, 2008; Rich and Roberts, 2006; Scott et al., 1988; Tomlin et al., 1999; Weese et al., 2007). MRSA have been isolated from a variety of conditions in animals such as skin and soft tissue infections, postsurgical wound infections, urinary tract infections, and pneumonia (Catry et al., 2010). MRSA has also been associated with outbreaks in veterinary hospitals and other animal facilities (Wieler et al., 2011).

The majority of MRSA strains isolated from small animal patients are identical to human hospital-acquired strains and belong to certain genetic MRSA lineages such as ST254, ST8 and ST22, that are shared with animals and humans (Wieler et al., 2011). Animals may become colonized with MRSA although the frequency and duration of colonization is unknown (Loeffler et al., 2005; Loeffler et al., 2010; Weese et al., 2007). So far, studies on the overall prevalence of MRSA colonization state that it remains low in dogs and cats (Catry et al., 2010; Leonard and Markey, 2008). MRSA have been frequently isolated from horses in Europe, Asia and North America from wound and post-operative infections and also from healthy animals (Catry et al., 2010). There are also several reports concerning MRSA outbreaks in equine hospitals (Catry et al., 2010). MRSA can be passed between pet animals (dogs, cats and horses) and owners with the possibility for zoonotic infections (Manian, 2003; van Duijkeren et al., 2004; van Duijkeren et al., 2011e; Weese et al., 2006a). One case report described the same Panton–Valentine leukocidin (PVL) toxin-positive MRSA strain in a dog and a human (Rankin et al., 2005).

In the veterinary context transmission of MRSA is usually considered to be human-to-animal. Although colonization of persons in contact with infected or colonized horses has been extensively documented, reports of clinical MRSA infections of humans associated with horse contact are rare (Catry et al., 2010; van Duijkeren et al., 2010; Weese and van Duijkeren, 2010b). These were cases of skin infections. A suspected transmission of MRSA ST398 between a horse and a girl has been described (van Duijkeren et al., 2011e). Potential differences between the human epidemiology of MRSA and the dynamics of MRSA colonization in animals and the risk factors may exist and these are inadequately documented (Catry et al., 2010). Veterinary staff and veterinary practitioners are at a higher risk of colonization with MRSA than the general population (Baptiste et al., 2005; Catry et al., 2010; Lefebvre et al., 2006; Loeffler et al., 2005; Moodley et al., 2008; O'Mahony et al., 2005).

4.2.2. Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP)

Since 2006, methicillin-resistant *S. pseudintermedius* (MRSP) (Bannoehr et al., 2007) has been reported as causing disease in canine and feline patients and has emerged as a significant animal health problem (Kadlec et al., 2010; Loeffler et al., 2007; Perreten et al., 2010; Sasaki et al., 2007a; Schwarz et al., 2008; Weese and van Duijkeren, 2010b). The methicillin resistance in MRSP is mediated by the *mecA* gene as in MRSA. Although methicillin-susceptible *S. pseudintermedius* isolates are genetically diverse, a limited number of MRSP clones have spread worldwide, resembling the worldwide MRSA dissemination (Perreten et al., 2010; Ruscher et al., 2010; van Duijkeren et al., 2011b). Compared to MRSA, the emergence of MRSP is a greater concern to veterinary patients as *S. pseudintermedius* is the primary staphylococcal species colonizing healthy dogs and cats. MRSP can cause a plethora of infections in dogs and cats such as skin and ear infections, post-operative wound infections, gingivitis, hepatitis, urinary tract infections, respiratory infections, arthritis, peritonitis and septicemia (van Duijkeren et al., 2011b). In Europe and North America the multidrug resistance profile of MRSP includes resistance to all oral and most parenteral antimicrobials approved for veterinary use (van Duijkeren et al., 2011a). MRSP colonisation is more common in dogs than in cats (Couto et al., 2011; Hanselman et al., 2009). The prevalence of MRSP colonisation in various dog populations in different countries has been reported to be 0–7% depending on study population. It is the highest in dogs suffering from chronic skin infections (van Duijkeren et al., 2011c; Weese and van Duijkeren, 2010b). While MRSA strains isolated from companion animals are evolutionarily related to different human-associated MRSA clones the scenario for MRSP is different. MRSP originates from an animal reservoir. Diverse SCCmec elements occur among the different MRSP genetic lineages suggesting that the *mecA* gene has been acquired by different *S. pseudintermedius* strains on multiple occasions (van Duijkeren et al., 2011c; Weese and van Duijkeren, 2010b). Evidence suggests that the origin of the MRSP SCCmec elements is *S. aureus* (Kania et al., 2009). The transfer of SCCmec elements between different staphylococcal species is a concern. Although colonization or infection with MRSP is rare in humans, the potential transfer of new SCCmec elements from MRSP and/or other MRSP associated antimicrobial resistance genes to other staphylococcal species like *S. aureus* is possible.

Data on the zoonotic transmission of MRSP is limited. Veterinary hospitals and clinics play a role in the dissemination of MRSP between the patients, to the personnel at a veterinary practice as well as to the environment and society (van Duijkeren et al., 2008; van Duijkeren et al., 2011d). Colonisation of humans with MRSP seems to be uncommon and transient, as reported for MSSP (Laarhoven et al., 2011; van Duijkeren et al., 2011b). Owners of infected pets and veterinarians in contact with infected animals seem to have a higher risk of being MRSP positive (van Duijkeren et al., 2011b; van Duijkeren et al., 2011c). Although there are low numbers of reports of MRSP colonisation of veterinarians, it could be considered an occupational hazard (Boost et al., 2011; Ishihara et al., 2010; Jordan et al., 2011; Paul et al., 2011; Sasaki et al., 2007b). Recently, a 4% MRSP carriage rate was found among

small animal dermatologists (Paul et al., 2011). While reports on MRSP colonization of humans are rare (Soedarmanto et al., 2011; van Duijkeren et al., 2011b), case reports on MRSP infection in humans have been reported. In some cases this has been associated with dog contact (Hatch et al., 2012; Savini et al., 2013; Stegmann et al., 2010), in other cases there has been no contact or this has not been investigated (Atalay et al., 2005; Campanile et al., 2007; Gerstadt et al., 1999).

4.3. Enterococci

Enterococci are Gram-positive cocci colonizing the mammalian gastrointestinal tract. *Enterococcus faecium* and *Enterococcus faecalis* are the most common enterococci causing infections in people. They are generally considered to be of a relatively low virulence but are capable of causing a wide range of infections including sepsis (Linden, 2008). Vancomycin-resistant enterococci (VRE) first appeared in human hospitals in the late 1980s in a few European countries (Werner et al., 2008). At present, six types of acquired vancomycin resistance genes in enterococci are known; however, only *VanA* and to a lesser extent *VanB* are widely prevalent (Werner et al., 2008). During the period of avoparcin use in food animals in Europe high rates of VRE carriage in dogs (e.g. 48% vancomycin resistance among canine enterococci in the Netherlands) were reported (van Belkum et al., 1996). A subsequent Dutch study, performed 5 years after the ban on avoparcin use, reported no VRE in 100 dogs (Wagenvoort et al., 2003). Healthy dogs and cats can be colonized by VRE (Damborg et al., 2008; Ossiprandi et al., 2008; Rice et al., 2003) and 13% of healthy dogs were found positive on faecal culture in one Spanish study (Herrero et al., 2004). *VanA*-type VRE have been described in healthy horses in Italy, Poland, and Hungary (de Niederhäusern et al., 2007).

In Europe acquired ampicillin resistance is a major phenotypic marker of hospital-acquired *E. faecium* and experience has shown that the appearance of such resistance often precedes increasing rates of VRE with a delay of several years (Werner et al., 2008). Ampicillin-resistant *E. faecium* were detected in 42 (23%) of 183 dogs screened in a cross-sectional study in the United Kingdom and in 19 (76%) of 25 dogs studied longitudinally in Denmark. In the latter study the carriage was intermittent (Damborg et al., 2009).

Evidence of gene exchange between human and animal enterococci was described in the U.S.A. (Simjee et al., 2002). A particular form of the Tn1546 transposon which has only been described in human clinical vancomycin-resistant enterococci was found in a vancomycin-resistant *E. faecium* uropathogenic isolate from a dog. These data demonstrate that exchange of resistance determinants between human and canine enterococcal strains can occur (Simjee et al., 2002). In addition, VRE of dogs have been shown to be the same genetic lineages which cause hospital acquired infections in humans (Herrero et al., 2004; Manson et al., 2003; Simjee et al., 2002). This applies also to ampicillin resistant enterococci (Damborg, Top et al 2009). Inclusion of dogs should in surveillance programs of VRE has been suggested (Herrero, Fernandez-Garayzabal et al 2004).

4.4. Enterobacteriaceae

Enterobacteriaceae group includes many species such as *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp. and *Salmonella* spp. Many organisms belonging to these species are commensals of the gastrointestinal tract. Increasing antimicrobial resistance among *Enterobacteriaceae* is emerging as a significant public health concern in human medicine (Pitout and Laupland, 2008). Of particular note are the *Enterobacteriaceae*, which produce extended-spectrum beta-lactamases (ESBLs), extended-spectrum cephalosporinases (ESCs) and plasmid-mediated AmpC beta-lactamases (henceforth referred

as ESBLs). Reports of ESBL- producing bacteria in veterinary patients are limited (Ewers et al., 2011; Gurnee et al., 2006; Leonard and Markey, 2008; Pomba et al., 2009; Sanchez et al., 2002; Sidjabat et al., 2006).

Klebsiella pneumoniae from the ST11 human epidemic clone was isolated from dogs and cats in Spain. It was found to be highly resistant to aminoglycosides due to the ArmA methyltransferase (Hidalgo et al., 2013).

4.4.1. *Escherichia coli*

FEC-1 (Fujisawa *E. coli*-1) was the first CTX-M-type ESBL enzyme discovered in a cefotaxime-resistant *E. coli* strain isolated from the feces of a laboratory dog in Japan in 1986 (Matsumoto et al., 1988). During the following decade, ESBLs have disseminated in human clinical settings worldwide. The first report of an ESBL-producing uropathogenic *E. coli* from companion animals is from 1998 in Spain (Teshager et al., 2000). This was followed by the detection of ESBL-producing *E. coli* in healthy dogs from Italy (mostly TEM and SHV derived), and dogs with urinary tract infection in Portugal (chromosomal AmpC hyperproduction) (Feria et al., 2002); (Carattoli et al., 2005). CTX-M enzymes have formed a rapidly growing family of ESBLs in bacteria from human infections (Canton and Coque, 2006; Poirel et al., 2012). In companion animals both clinical and commensal isolates of *E. coli* produce often CTX-M-type β -lactamases (2.6% and 5.6% of all investigated Enterobacteriaceae isolates and between 25% and 76.5% of all ESBLs reported)(Ewers, Grobbel et al. 2011).

Multidrug-resistant *Escherichia coli* sequence type 131 (ST131) has recently emerged as a worldwide pandemic clone in humans (Rogers et al., 2010). Reports of clinical infections in animals caused by ST131 are scant, which may be because its detection requires genotypic methods (Platell et al., 2011). The first reported ST131 isolate of animal origin was from a Portuguese study in which 61 fluoroquinolone-resistant *E. coli*, isolated from 2004 to 2006 from dogs (n = 41) and cats (n = 20) were screened for ESBLs (Pomba et al., 2009). Many clinical ST131 *E. coli* isolates from companion animals are similar to human clinical ST131 *E. coli* isolates based on their virulence genotype, resistance characteristics, plasmid content and PFGE profile (Ewers et al., 2011). Recently a study conducted in an Australian veterinary referral centre found fluoroquinolone-resistant extraintestinal pathogenic *E. coli*, including O25b-ST131, isolated from faeces of hospitalized dogs (Guo et al., 2013). Other ESBL-producing *E. coli* sequence types (ST405 and ST648) also can be found both in companion animals and humans (Wieler et al., 2011). The detection of identical clones in humans and a number of nonhuman species (e.g. dogs, cats, horses and poultry) as well as in food may suggest their transmission through animal contact or food. Such transmission may be also contributory factor the rapid and successful dissemination of *E. coli* (Platell et al., 2011), although among humans the most important route of transmission is probably person-to-person (Ewers et al., 2012).

4.4.2. Other Enterobacteriaceae

Multidrug-resistant *Salmonella* Typhimurium have been associated with outbreaks of gastrointestinal nosocomial infections in companion animals in veterinary clinics and an animal shelter (Wright et al., 2005). One such outbreak involved also veterinary staff and other persons contacted with animals (Cherry et al., 2004). Multidrug-resistant *S. Typhimurium* definitive phagetype (DT) 104 has been described to be causative organism in some of these. Companion animal facilities may serve as foci of transmission for salmonellae between animals and humans if adequate infection control measures are not followed (Wright et al., 2005).

As with *E. coli*, ESBL producing strains of salmonellae are of concern. Ceftiofur resistance was identified in 9.8% of feline, 19.2% of equine and 20.8% of canine *Salmonella* isolates in one United States study and CTX-M group III, SHV, TEM and CMY-2 β -lactamases were detected among these (Frye and Fedorka-Cray, 2007).

Knowledge of ESBLs other than *E. coli* of companion animals is limited. The presence of different ESBL (CTX-M, SHV-12 or OXA-10) enzymes has been reported in *Citrobacter* isolates from dogs, cats and horses (Ewers et al., 2011; Ewers et al., 2010), *Enterobacter* isolates from dogs and cats (Gibson et al., 2010; Ma et al., 2009; Sidjabat et al., 2007; SVARM, 2010), and *Klebsiella* isolates from dogs, cats and horses (Haenni et al., 2012; Ma et al., 2009; SVARM, 2010; Vo et al., 2007).

Recently, the emergence and clonal spread of *K. pneumoniae* and *E. coli* producing carbapenemase OXA-48 in dogs was reported (Stolle et al., 2013).

4.5. *Campylobacter*

Campylobacter is a well-known causative organism of diarrhea in humans. Most often the source of infection is improperly cooked meat or contaminated drinking water. *Campylobacter jejuni* is the species usually isolated in human infections. Other *Campylobacter* species are also becoming more common, especially in young children and immunocompromised individuals (Man, 2011). *Campylobacter* are frequent inhabitants of intestinal microbiota in many animal species including dogs. A longitudinal study of the excretion patterns of thermophilic *Campylobacter* spp. in young pet dogs in Denmark found that they excreted *Campylobacter* spp. during the majority of their young age and adolescent period. *Campylobacter upsaliensis* was excreted for months, with short-term interruptions by or co-colonization with other transitory *Campylobacter* spp., predominantly *C. jejuni*. *C. jejuni* was more prevalent in dogs between 3 months and 1 year of age than in dogs between 1 and 2 years of age (Hald et al., 2004). One study reports the occurrence of *C. jejuni* in pets living with human patients infected with *C. jejuni*. In this work *C. jejuni* was recovered from four dogs (11%) and four cats (33%) living with Danish human patients infected with *C. jejuni* (Damborg et al., 2004a). There is evidence that pet ownership is a significant risk factor for *Campylobacter* infections in humans (Adak et al., 2005; Kapperud et al., 1992; Neimann et al., 2003).

In dogs the role of *Campylobacter* as a cause of diarrhoea or other gastrointestinal infections is contradictory. Such organisms may have a role in diarrhoea in young dogs, but in cats they are not considered as intestinal pathogens (Marks et al., 2011). Dogs and cats can be source of infection for humans. Two studies have demonstrated *C. jejuni* dog-human transmission. One reported a case of neonatal *C. jejuni* sepsis in a 3-week-old infant who acquired the infection through transmission from a recently acquired household puppy (Wolfs et al., 2001). The second study revealed the occurrence of the same quinolone-resistant *C. jejuni* strain in a girl and her dog (Damborg et al., 2004b). Companion animals may play an important role in the dissemination of this pathogen in the environment, particularly in urban areas, where direct pet-to-pet contact or exposure to faeces from other pets is likely to occur.

4.6. *Pseudomonas* and *Acinetobacter*

Pseudomonas aeruginosa is a Gram-negative bacterium that is ubiquitous in the environment. In veterinary medicine *Pseudomonas* is commonly related to otitis and pyoderma, but also nosocomial infections have been reported (Fine and Tobias, 2007). Antimicrobial treatment generally involves

combination protocols although evidence on their superiority is lacking (Nuttall and Cole, 2007). In veterinary medicine multidrug resistance is a common problem in *Pseudomonas*. Pan-resistant *Pseudomonas aeruginosa* (resistance to all antimicrobials) has been reported in humans but as yet not in animals (Deplano et al., 2005). In a study of isolates from canine ear and skin infections, acquired resistance to gentamicin (7%) and amikacin (3%) was uncommon but resistance to fluoroquinolones was frequent with 16% of the isolates resistant to ciprofloxacin, 31% resistant to enrofloxacin and 52% resistant to orbifloxacin (Rubin et al., 2008). Comparable antimicrobial resistance patterns were reported in other reports in Denmark (Pedersen et al., 2007) and in USA (Wildermuth et al., 2007), and recently a study in Croatia showed a marked increase in gentamicin resistance (Mekić et al., 2011).

Acinetobacter spp. are Gram-negative aerobic coccobacilli. *A. baumannii* is a common species in hospital-acquired infections in humans. It can be found on the skin and in the oral cavity of healthy dogs, but is also ubiquitous in the environment (Francey et al., 2000). Only a few studies have described infections due to *A. baumannii* in animals (Boerlin et al., 2001; Brachelente et al., 2007; Francey et al., 2000). In 2000 Francey and collaborators described clinical characteristics of several pets with various *A. baumannii* infections (i.e. urinary, respiratory, wound and bloodstream infections), reporting an overall attributable mortality of 47%. *A. baumannii* isolates collected in 1998–2000 from pets and horses belonged into two main PFGE clones, and the majority of *A. baumannii* infections were hospital-acquired (Boerlin et al., 2001; Brachelente et al., 2007; Francey et al., 2000). Treatment options are often limited. A recent study showed that *A. baumannii* isolates from pets and horses shared common phenotypic and genotypic characteristics with those described in humans (Endimiani et al., 2011). The spread of such *A. baumannii* strains in companion animals is very concerning because of the multiple mechanisms of antimicrobial resistance, especially to carbapenems and colistin (Higgins et al., 2010; Perez et al., 2010).

4.7. *Clostridium difficile*

Clostridium difficile infection has been described in many animal species including horses and dogs (Keessen et al., 2011). The role of this organism as a pathogen in dogs is not clear although in one report a significant association between the presence of diarrhea and the detection of *C. difficile* toxins was observed (Marks et al., 2002). A small animal experiment using six dogs could not fulfil Koch's postulates for *C. difficile* as a pathogen in dogs (Marks et al., 2002). Cats can also be colonized with *C. difficile* without any signs of diarrhoea (Keessen et al., 2011). *C. difficile* colonization rates in healthy dogs and cats range from 1.4% to 21% (Keessen et al., 2011; Weese et al., 2010). A higher prevalence of *C. difficile* has been reported - varying from 18% to 40% - in companion animals attending veterinary clinics (Keessen et al., 2011). *C. difficile* can be found in the environment of veterinary practices (Weese et al., 2000). Very high rates of *C. difficile* colonization have been described in dogs that visit human hospitals (Lefebvre et al., 2006).

Antibiotic associated diarrhea, colitis and pseudomembranous colitis caused by *C. difficile* are common nosocomial infections increasing incidence and severity in humans worldwide (Keessen et al., 2011). This is related to the emergence of certain hyper-virulent strains of *C. difficile*, such as ribotypes 027 and 078. *C. difficile* often colonizes the gastrointestinal tract of many mammals, birds and reptiles. It is also common in the environment where it survives by forming spores. A zoonotic role of *C. difficile* has been suggested because that animals often carry strains with the same ribotypes as strains which cause infections in humans (Hensgens et al., 2012).

5. Factors associated with acquisition of drug-resistant bacteria

The administration of antimicrobials is a common risk factor for acquiring drug resistant bacteria in humans (Canton and Bryan, 2012a; Canton and Bryan, 2012b). Antimicrobial use in small animals has also been identified as one of the risk factors for colonisation or infection with resistant pathogens (Rantala et al., 2004b; Soares Magalhães et al., 2010). Antimicrobial administration within 30 days before admission to a veterinary teaching hospital or ceftiofur or aminoglycosides administration during hospitalization were associated with MRSA colonization in horses (Weese and Lefebvre, 2007; Weese et al., 2006b). Antimicrobial therapy may also constitute a risk factor for MRSP infections in dogs (Weese et al., 2009). Healthy dogs treated with oral enrofloxacin have been shown to be more effectively colonized with multidrug-resistant *E. coli* than control dogs (Trott et al., 2004). Oral treatment of dogs with cephalexin has been proposed as a selector of CMY-2 producing *E. coli* in the faecal microbiota of dogs. The study design did not permit evaluation of the presence of CMY-2 producers before the treatment and possible selection or persistence in intestinal microbiota thus remains to be elucidated (Damborg et al., 2011). One study carried out in a veterinary ICU showed that the proportion of dogs carrying resistant *E. coli* increased with duration of hospitalization and with the use of antimicrobial drugs (Ogeer-Gyles et al., 2006).

Other factors associated with antimicrobial resistance in humans are prolonged hospitalisation, gastrointestinal surgery or transplantation; exposure to invasive devices of all types, especially central venous catheters, underlying diseases and severity of illness, advanced age (Safdar and Maki, 2002). Studies concerning factors others than antimicrobials (Baptiste et al., 2005; Weese et al., 2007) in companion animals are scarce. Risk factors for MRSA colonization of horses have been determined to be previous colonization, presence of colonized horses on the same farm, admission to the neonatal ICU and admission to a service other than the surgical service (Weese and Lefebvre, 2007). Owners from MRSA-positive households or healthcare workers, exposure to medical hospitals, extensive wounds, prolonged hospitalization and immunosuppression also constitute possible risk factors (Catry et al., 2010). Apart from antimicrobial therapy, hospitalisation (Nienhoff et al., 2011) and surgical interventions could also be risk factors for acquiring MRSP in dogs (Weese et al., 2009). Concerning *C. difficile* risk factors for colonisation in dogs are as follows: living with an immunocompromised owner, antimicrobial administration to a dog or to an owner, contact with children, and visiting human hospitals (Marks et al., 2011).

6. Discussion

Available data show that resistant bacteria emerge in the companion animals and several problematic resistant organisms are shared between companion animals and humans. These organisms spread between animals and humans, although the direction of transfer is often difficult to prove. Nevertheless, the use of antimicrobials in companion animals with the corresponding selection and potential spread of drug resistance constitutes a potential risk to public health.

Of special concern is the situation whereby the use of antimicrobials in companion animals contributes to resistance against last resort antimicrobials used in human medicine. Problems of resistance development and of infection control in companion animal hospitals are mimicking those in human hospitals (ECDC et al., 2009). Hospitals in both scenarios are facilities of intensive use of antimicrobials and high density of patients and are therefore high risk environments for the occurrence and spread of nosocomial infections and resistant bacteria (Johnson, 2002; Morley, 2004). With increasing demand

498 for advanced therapy coupled with the spread of multidrug-resistant bacteria one may foresee the
499 need for new antimicrobials for the future in veterinary medicine.

500 As part of the approval of new antimicrobial agents there is a need to address the concerns related to
501 spread of resistant bacteria and resistance genes to humans. The risk, of transmission of resistance
502 from companion animals to humans cannot be fully quantified. Overall, companion animal derived
503 antimicrobial resistance transmission to humans is complex and needs further investigation.

504 Risk assessment methodology should be used to evaluate new antimicrobial treatment options for
505 infections caused by bacteria in companion animals. The new antimicrobial products would be those for
506 which risk levels are estimated as acceptable. Microbiological hazards of concern may directly or
507 indirectly cause adverse health effects in humans. Direct hazards for human health are defined as
508 antimicrobial-resistant bacteria that are transmitted from animals to humans under natural conditions
509 and potentially cause disease in humans (zoonoses). Indirect hazards are the transmission of
510 resistance genes from companion animals to humans and the consequences for health care and public
511 health. Based on the data in this document, the most important microbiological hazards emerging from
512 companion animals are summarized in Table 1.

513 Table 1 – Selected microbiological hazards identified in this document

	Type of hazard	Sources
Methicillin-resistant <i>Staphylococcus aureus</i>	Direct hazard	Dogs, cats, horses
Methicillin-resistant <i>Staphylococcus pseudintermedius</i>	Direct hazard ^a	Dogs, cats, horses
Vancomycin-resistant enterococci	Indirect hazard ^b	Dogs, horses
ESBL producing Enterobacteria	Indirect hazard	Dogs, cats, horses
Carbapenem-resistant Gram-negative bacteria	Indirect hazard ^b	Dogs

514 ^alow number of cases of human infections originating from companion animals

515 ^bno human infections originating from companion animals have been reported

516

517 Based on available data major food-borne zoonotic bacteria such *Salmonella* and *Campylobacter* do not
518 constitute an urgent direct hazard in respect of antimicrobial resistance emerging from companion
519 animals. The same rationale applies to *Clostridium difficile*. It is not possible to evaluate the
520 microbiological hazard constituted by *Pseudomonas aeruginosa*.

521 The microbiological hazards identified in this document need to be characterized in relation to the
522 compound in question. Then, an abbreviated risk assessment model consistent with the principles of
523 Codex (Codex Alimentarius, 2011) and VICH GL27 (EMA, 2004) could be applied in case of
524 applications for marketing authorisation for medicinal products for companion animals. A predictable
525 and transparent assessment should facilitate the process of approval for new VMPs for use in
526 companion animals. Risk mitigation measures to reduce AMR risks could be applied. Availability of
527 approved VMPs on the market would ensure use according to the SPC and reduce the need for the
528 cascade use of human products.

529 For new compounds or new species or indications for existing compounds the applicant could be
530 requested to provide data similar to what is requested in GL27 tailored to the organisms identified
531 above. With regard to exposure assessment, it is questionable to what extent it would be feasible or
532 desirable to request from an applicant to fully map the selection pressure and link that to likelihood of
533 spread of resistance to humans. Alternatively, the risk assessment could be based only on the hazard
534 characterisation, a rough estimate of the risk for exposure and the number of animals to be treated

with the antimicrobial in question. The applicant could be asked to provide an expert report where the risk is discussed. One important element of this report would be to justify their suggested indication and target population, demonstrating that the intended use is compliant with responsible use principles considering any hazards of concern for the product.

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