15 January 2015
EMA/CVMP/AWP/401740/2013
Committee for Medicinal Products for Veterinary Use (CVMP)

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

Draft agreed by Antimicrobials Working Party (AWP)	26 September 2013
Adopted by CVMP for release for consultation	10 October 2013
Start of public consultation	21 October 2013
End of consultation (deadline for comments)	31 January 2014
Agreed by AWP	19 November 2014
Adopted by CVMP	15 January 2015

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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 antimicrobial substances can seriously compromise animal health and welfare. Necessity of new antimicrobials for the therapy of multi-resistant infections, particularly those caused by Gram-negative bacteria has been acknowledged in human medicine. A corresponding need in veterinary medicine is to be expected in the near future.

A unique aspect related to antimicrobial resistance in companion animals is their close contact with humans providing 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 relating to many aspects of this field is limited and no risk assessment is performed when approving veterinary antimicrobials for companion animals.

Public health risks associated with transfer of antimicrobial resistance from companion animals are reviewed in this document. The aim is to discuss the possible need for data in applications relating to new compounds, new species or indications for existing compounds, for this target group of animals. The following aspects are considered: i) the use 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, and extended-spectrum beta-lactamase and carbapenemase producing Gram-negative bacteria.

CVMP Recommendations for action

Antimicrobials are essential for the treatment of infectious diseases in humans and companion animals and there is substantial overlap in the classes of antimicrobials used in these two areas of medicine. 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. meticillin-resistant *Staphylococcus aureus*) are shared between companion animals and humans and owing to the current concern about the emergence of multidrug-resistant infections and the 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, 2001) and CVMP/VICH GL27 (EMEA 2004) could be applied for applications relating to new compounds, new species or new indications for existing compounds. It is recognised that owing to extensive knowledge gaps (see below), a qualitative approach would need to be taken. 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 related data similar to that requested in VICH GL 27. An abbreviated estimate of the risk for exposure could be provided taking account of the conditions of use of the product. The hazard characterisation would consider the relative importance of the antimicrobial to human medicine. 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. The use in companion animals of substances regarded as critically important antimicrobials (CIA) for human medicine should be carefully assessed considering the importance of those substances for public health, and possible limitations on the use of human last resort (life-saving) antimicrobials for treatment of companion animals should be considered.

   Responsible body: In regards to applications for and approval of 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 summary of product characteristics (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, of which many examples already exist (FECAVA[1,2], 2013). As also addressed in the response to the request from the European Commission for advice on the impact on public and animals health of the use of antibiotics in animals, consideration could be given in the intended new legislation of veterinary medicinal products to provide flexible tools to allow banning or

[1] http://www.fecava.org/sites/default/files/files/FECAVA%20Recommendations%20for%20Appropriate%20Antimicrobial%20Therapy.pdf

[2] http://www.fecava.org/sites/default/files/files/FECAVA%20Advice%20on%20Responsible%20use%20of%20Antimicrobials.pdf

limitations on the use of human last resort (life-saving) antimicrobials for treatment of companion animals.

Notwithstanding the recommendations above, the CVMP is of the opinion that transfer of antimicrobial resistance (AMR) from companion animals should not be considered in isolation but a One Health approach is needed. Therefore, the CVMP, in addition to the recommendations above, strongly supports the following suggestions in order to better understand and to limit the potential for transfer of antimicrobial resistance between companion animals and humans. The list is limited to actions related to veterinary medicine and includes (but is not limited to) specific recommendations for companion animals. 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 off-label use of human CIAs in companion animals to be recorded and monitored, especially in regards to use of human-only authorised antimicrobials.

   Responsible body: Competent Authorities

4. It would be desirable to extend AMR surveillance programmes to include organisms of public health significance that are present in companion animals.

   Responsible body: Member States

5. A global approach should be taken to limiting the need for use of antimicrobial agents in companion animals. This includes: training of veterinary personnel in responsible use of antibiotics; improved communication with clients on rational use of antibiotics; strengthening infection prevention and control in veterinary hospitals and clinics and hygiene in the home and developing alternative treatment and management strategies, especially for chronic infections.

Knowledge gaps

The following knowledge gaps have been identified:

1. Risk factors and transmission routes involved in the transfer of antimicrobial resistance between companion animals, food-producing animals and humans and vice versa.
2. Extent and patterns of antimicrobial usage in companion animals, including off-label use.
3. The ecology of drug-resistant bacteria in companion animals and their environments, and the relative importance of such bacteria in contributing to the burden of human disease.

Table of contents

Summary **2**

CVMP Recommendations for action **3**

Knowledge gaps **4**

1. Introduction **6**

2. Mandate and objectives **6**

3. Use of antimicrobials **7**

4. Drug-resistant bacteria of concern **8**

4.1. Introduction 8

4.2. Methicillin-resistant staphylococci 8

4.2.1. Methicillin-resistant *Staphylococcus aureus* (MRSA) 8

4.2.2. Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) 9

4.3. Enterococci 10

4.4. Enterobacteriaceae 11

4.4.1. Escherichia coli 11

4.4.2. Other *Enterobacteriaceae* 12

4.5. Campylobacter 12

4.6. Pseudomonas and Acinetobacter 13

4.7. Clostridium difficile 13

5. Factors associated with acquisition of drug-resistant bacteria **14**

6. Discussion **15**

7. References **16**

1. Introduction

During the last fifty years, the number of companion animals in modern society has substantially increased and their societal role has changed. Attention to their welfare has increased as a consequence of the close contact between owners and their pets. Humans may acquire resistant bacteria or 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 dogs and cats (Ewers et al., 2012; Weese and van Duijkeren, 2010a; Wieler et al., 2011), thereby presenting a potential risk of transmission of these bacteria to humans from infected or colonised companion animals. In addition there is the possibility of transfer of genetic material coding for resistance to antimicrobials.

In order to assess these risks within the context of applications relating to new compounds, new species or indications for existing compounds for companion animals, there might be a need for additional data requirements with respect to antimicrobial resistance. The 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) (EMEA, 2004). It does not provide guidance on this issue for companion animals. The risk of transfer of antimicrobial resistance to humans from direct contact with companion animals is not covered by any guidance document of the European Medicines Agency.

2. Mandate and objectives

The CVMP mandated the AWP (previously SAGAM) in January 2011 to draft a reflection paper and indicated that the main focus should be upon multidrug-resistant (MDR) bacteria of companion animals that could create a public health risk by transmission of these bacteria or their resistance determinants 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 antimicrobial products, new species or indications for existing compounds for companion animal use.

In this document the term companion animals apply primarily to dogs, cats, and horses not intended for human consumption. 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 herewith because they are commonly kept in close contact with people. In addition, advanced veterinary procedures involving extensive use of antimicrobials are performed in horses and MDR organisms have been recorded in this species. While it is acknowledged that emergence of MDR among animals also represents loss of effectiveness of antimicrobials, the main focus of this reflection paper is on the public health risk.

3. Use of antimicrobials

Antimicrobials are frequently used for therapeutic and prophylactic purposes in companion animals. Antimicrobial consumption data are often incomplete and usually refer to drug manufacturer sales. Although sales data provide an estimate of the magnitude of antimicrobial consumption, in general data on the use of antimicrobials in different species is lacking. In the United Kingdom, there are examples of surveillance systems, such as VetCompass[3] and SAVSNET[4] that may be used for monitoring of antimicrobial use in companion animals. In these systems data are electronically collected from volunteering veterinary practices. The data allow monitoring at prescription level. They could provide an important insight into 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. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project was launched in 2009 by the European Medicines Agency. The fourth ESVAC report presents data on the sales of veterinary antimicrobial agents from 26 EU/EEA countries as provided at package level according to a standardised protocol and template (EMA/ESVAC, 2014). It has special emphasis on food-producing animals. Data presented in the ESVAC report on sales of veterinary antimicrobial agents for companion animals are solely based on the sales of tablets. Antimicrobial products marketed for human use are also used in companion animals, in application of the 'cascade' (Article 10 of Directive 2001/82/EC of the European Parliament and of the Council). Additionally all injectable veterinary antimicrobial products are included in the sales for food-producing animals in the ESVAC report (EMA/ESVAC, 2014). Therefore, the data on sales of veterinary antimicrobial agents for companion animals presented in the ESVAC report underestimate the actual sales.

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 (EMEA, 2006). Lincosamides (clindamycin), fluoroquinolones, macrolides, tetracyclines (doxycycline), nitroimidazoles and trimethoprim-sulfonamides have also been reported to be 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 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 empiric antimicrobial therapy (Thomson, 2010). In UK equine veterinary practice 11% of prescriptions were for antimicrobial drugs not authorised for use in horses (Hughes et al., 2013).

Current SPC guidance for the responsible use of antimicrobials in veterinary medicine recommends the reservation of the use of fluoroquinolones and third and fourth generation cephalosporins for treatment when other options are likely to fail which should whenever possible supported by antimicrobial susceptibility testing (AST) (EMA/CVMP/SAGAM, 2007; EMEA/CVMP/SAGAM, 2009b; Official Journal of

[3] http://www.rvc.ac.uk/VetCOMPASS
[4] http://www.savsnet.co.uk/

the European Union, 2012). In some countries national prescribing guidance has been developed for companion animals (BSAVA, 2012; BVA, 2009; Evira, 2009; Schipper et al., 2013; SVF, 2009). Additionally, the Federation of Veterinarians (FVE)[5] and the Federation of European Companion Animal Veterinary Associations (FECAVA) have produced guidance notes on prudent prescribing of antimicrobials [6,7]. Recently, the Heads of Medicines Agencies and the FECAVA undertook a survey on antimicrobial prescribing habits by Veterinarians which was completed by 1.5 per cent of active veterinary practitioners in Europe. (De Briyne et al., 2013). There were differences between the frequency of performing sensitivity testing amongst the different types of practitioners, and for the seven countries studied. Antimicrobial therapy was found to be mainly empirical rather than being based on culture and AST (reserved for cases of poor responses or complicated cases). The findings from a study in Italy revealed that only 5% of antimicrobial prescriptions in a veterinary teaching hospital were supported by results of microbial culture and antimicrobial susceptibility testing (Escher et al., 2011). Lack of confirmed diagnosis can lead to the misuse of antimicrobials. Antimicrobial treatment has been reported of conditions such as in diarrhoea in dogs (German et al., 2010) and feline lower urinary tract disease (Thomson et al., 2009), which may not have bacterial aetiology. 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 admitted patients (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). Higher doses than recommended in the SPC were also found to be common in dogs and cats in Switzerland (Regula et al., 2009). A Swiss study involving 8 mixed veterinary practices reported that the dosage corresponding 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

MDR organisms have been reported in companion animals, sometimes severely compromising the treatment outcome. In the following paragraphs relevant MDR 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 frequent causes of bacterial healthcare-associated (HCA) infections in humans. MRSA occurs also in companion animals as reviewed by the CVMP Scientific Advisory Group on Antimicrobials (Catry et al., 2010; EMEA/CVMP/SAGAM, 2009a). Since the first companion animal-related outbreak of MRSA in a geriatric rehabilitation ward, reported in 1988, the number of reports on

[5] http://www.fve.org/veterinary/medicines.php

[6] http://www.fecava.org/sites/default/files/files/FECAVA%20Recommendations%20for%20Appropriate%20Antimicrobial%20Therapy.pdf

[7] http://www.fecava.org/sites/default/files/files/FECAVA%20Advice%20on%20Responsible%20use%20of%20Antimicrobials.pdf

infections and colonization with MRSA in companion animals has increased (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 companion 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 MRSA strains belonging to certain genetic MRSA lineages such as ST254, ST8 and ST22 (Wieler et al., 2011). The transmission of livestock- associated MRSA (LA-MRSA) ST398 from companion animals to humans has been described (van Duijkeren et al., 2011e).

Animals may become colonised with MRSA, although the frequency and duration of colonisation needs to be further studied (Loeffler et al., 2005; Loeffler et al., 2010; Weese et al., 2007). So far, studies on the overall prevalence of MRSA colonisation have indicated that MRSA prevalence is 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 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).

Transmission of MRSA is usually considered to be predominantly from humans to animals. Although colonisation of humans in contact with infected or colonised horses has been extensively documented, reports of clinical MRSA infections of humans associated with horse contact are rare and are so far restricted to skin infections (Catry et al., 2010; van Duijkeren et al., 2010; Weese and van Duijkeren, 2010b). Veterinary staff and veterinary practitioners are at a higher risk of colonisation 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, MRSP (Bannoehr et al., 2007) has emerged as a significant health problem in canine and feline patients (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). Identical to MRSA, methicillin resistance in MRSP is mediated by the *mecA* gene. 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 colonising 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 septicaemia (van Duijkeren et al., 2011b). In Europe and North America the MDR 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, being 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 mainly related to different human-associated MRSA clones, the scenario for MRSP is different. MRSP originates from an animal reservoir. Diverse

staphylococcal cassette chromosome mec (SCC*mec*) 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). The transfer of SCC*mec* elements between different staphylococcal species is a concern. Although colonisation or infection with MRSP is rare in humans, the potential transfer of SCC*mec* elements from MRSP and/or other MRSP associated antimicrobial resistance genes to other staphylococcal species like *Staphylococcus aureus* is possible.

Data on the zoonotic transmission of MRSP are limited. Veterinary hospitals and clinics play a role in the dissemination of MRSP between the animal patients, to the personnel at veterinary practices 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 methicillin susceptible *Staphylococcus pseudintermedius* (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, such colonisation 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). A 4% MRSP carriage rate was found among small animal dermatologists (Paul et al., 2011). While reports on MRSP colonisation of humans in daily contact with companion animals are rare (Soedarmanto et al., 2011; van Duijkeren et al., 2011b), case reports of MRSP infection in humans associated with dog contact (Hatch et al., 2012; Savini et al., 2013; Stegmann et al., 2010), or even no apparent contact with dogs, have increased (Atalay et al., 2005; Campanile et al., 2007; Gerstadt et al., 1999).

4.3. Enterococci

Enterococci are Gram-positive cocci colonising the mammalian gastrointestinal tract. *Enterococcus faecium* and *Enterococcus faecalis* are the most common enterococci causing infections in humans. They are generally considered to be harmless commensals 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-encoding resistance genes in enterococci are known; of these 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 vancomycin-resistant enterococci (VRE) carriage in dogs (e.g. 48% VRE 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 colonised 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). 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 *Enterococcus faecium* and experience has shown that the appearance of such resistance often precedes the increasing prevalence of VRE with a delay of several years (Werner et al., 2008). Ampicillin-resistant *Enterococcus 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 (Damborg et al., 2009). 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 United States (Simjee et al., 2002). A particular form of the Tn*1546* transposon which has only been described in human clinical VRE was found in a vancomycin-resistant *Enterococcus faecium* uropathogenic isolate from a dog (Simjee, White et al. 2002). This indicates that exchange of resistance determinants between human and canine enterococci can occur (Simjee et al., 2002). In addition, VRE from 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). It has been suggested that dogs should be included in VRE surveillance programs (Herrero, Fernandez-Garayzabal et al 2004).

4.4. Enterobacteriaceae

Members of the family *Enterobacteriaceae* include 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, extended-spectrum cephalosporinases (ESCs) and plasmid-mediated AmpC beta-lactamases (henceforth referred as ESBLs). There are few reports of ESBL- producing bacteria in veterinary patients (Ewers et al., 2011a; Gurnee et al., 2006; Leonard and Markey, 2008; Pomba et al., 2009; Sanchez et al., 2002; Sidjabat et al., 2006).

4.4.1. Escherichia coli

Fujisawa *Escherichia coli*-1 (FEC-1) was the first CTX-M-type ESBL enzyme discovered in a cefotaxime-resistant *Escherichia coli* strain isolated from the faeces of a laboratory dog in Japan in 1986 (Matsumoto et al., 1988). During the following decade ESBLs disseminated in human clinical settings worldwide. The first report of an ESBL-producing uropathogenic *Escherichia coli* from companion animals is from 1998 in Spain (Teshager et al., 2000). This was followed by the detection of ESBL-producing *Escherichia coli* in healthy dogs from Italy (mostly TEM and SHV genes 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 (Canton and Coque, 2006; Poirel et al., 2012). In companion animals both clinical and commensal isolates of *Escherichia coli* often produce CTX-M-type beta-lactamases (2.6% and 5.6% of all investigated *Enterobacteriaceae* isolates and between 25% and 76.5% of all ESBLs reported) (Ewers et al., 2011b).

MDR *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, maybe 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 *Escherichia 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 *Escherichia coli* isolates from companion animals are similar to human clinical ST131 *Escherichia coli* isolates based on their virulence genotype, resistance characteristics, plasmid content and PFGE profile (Ewers et al., 2011a). Recently a study conducted in an Australian veterinary referral centre found fluoroquinolone-resistant extraintestinal pathogenic *Escherichia coli (ExPEC)*, including O25b-ST131, isolated from faeces of hospitalized dogs (Guo et al., 2013). Other ESBL-producing *Escherichia coli* sequence types (ST156, ST405, ST410 and ST648) also

can be found both in companion animals and humans (Wieler et al., 2011). Detection of identical clones in humans and a number of animals (e.g. dogs, cats, horses and poultry may suggest their transmission through animal contact. Such transmission may also be a contributory factor to the rapid and successful dissemination of *Escherichia coli* (Platell et al., 2011), although among humans the most important route of transmission is probably person-to-person (Ewers et al., 2012).

Additionally, a global emergence of carbapenemase resistance in companion animals has occurred. NDM-1 and OXA-48 producing *Escherichia coli* have been detected from clinical infections in dogs and cats in the United States and in dogs in Europe, respectively (Shaheen et al., 2013; Stolle et al., 2013).

4.4.2. Other *Enterobacteriaceae*

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

ESBL- or AmpC-producing strains of *salmonellae* isolated in companion animals are of concern in the United States. Ceftiofur resistance was reported 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 beta-lactamases were detected among these (Frye and Fedorka-Cray, 2007).

Knowledge of ESBLs in other *Enterobacteriaceae* 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., 2011a; 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). K*lebsiella pneumoniae* from the ST11 human epidemic clone was isolated from dogs and cats in Spain (Hidalgo et al., 2013).

4.5. Campylobacter

Campylobacter is a well-known causative organism of diarrhoea in humans. Most often the source of infection is improperly cooked meat (principally poultry) or contaminated drinking water. *Campylobacter jejuni* is the species usually isolated in human infections. Other *Campylobacter* species may also become more common, (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 the juvenile and adolescent period. *Campylobacter upsaliensis* was excreted for months, with short-term interruptions by or co-colonisation with other transitory *Campylobacter* spp., predominantly *Campylobacter jejuni* (Hald et al., 2004). One study reports the occurrence of *Campylobacter jejuni* in pets living with human patients infected with *Campylobacter jejuni.* In a limited study *Campylobacter jejuni* was recovered from dogs and cats living with Danish human patients infected with *Campylobacter jejuni* (Damborg et al., 2004a). There is

evidence that pet ownership is a 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 a*s a cause of diarrhoea is contradictory. *Campylobacter* may have a role in diarrhoea in young dogs, but in cats is not considered to be an intestinal pathogen (Marks et al., 2011). Dogs and cats can be a source of infection for humans. Two studies have demonstrated *Campylobacter jejuni* dog-human transmission. One reported a case of neonatal *Campylobacter 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 *Campylobacter 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 in dogs, but also nosocomial infections have been reported (Fine and Tobias, 2007). Antimicrobial treatment generally involves combination protocols although evidence of their efficacy is lacking (Nuttall and Cole, 2007). MDR is a common problem in *Pseudomonas* (Buckley et al., 2013). 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 and amikacin was uncommon but resistance to fluoroquinolones was frequent with 16% of the isolates resistant to ciprofloxacin(Rubin et al., 2008). Comparable antimicrobial resistance figures were described in other reports in Denmark (Pedersen et al., 2007) and in United States (Wildermuth et al., 2007). Recently, a study in Croatia showed a marked increase in gentamicin resistance in *Pseudomonas aeruginosa* from canine otitis (Mekic et al., 2011).

Acinetobacter spp. are Gram-negative aerobic *coccobacilli*. *Acinetobacter 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 *Acinetobacter baumannii* in animals (Boerlin et al., 2001; Brachelente et al., 2007; Francey et al., 2000). In 2000, Francey and collaborators described the clinical characteristics of several pets with various *Acinetobacter baumannii* infections (i.e. urinary, respiratory, wound and bloodstream infections), reporting an overall attributable mortality of 47%. *Acinetobacter baumannii* isolates collected in 1998–2000 from pets and horses belonged to two clones, and the majority of *Acinetobacter 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 *Acinetobacter 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 *Acinetobacter baumannii* strains in companion animals is particularly 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 often colonises the gastrointestinal tract of many mammals, birds and reptiles. It is also common in the environment where it survives by forming spores. Antibiotic associated diarrhea,

colitis and pseudomembranous colitis caused by *Clostridium difficile* are common nosocomial infections of increasing incidence and severity in humans worldwide (Keessen et al., 2011). This is related to the emergence of certain hyper-virulent strains of *Clostridium difficile*, such as ribotypes 027 and 078 (Mulvey et al., 2010). A zoonotic role of *Clostridium 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).

Clostridium difficile infections have been described in many animal species including horses and dogs (Keessen et al., 2011). *Clostridium difficile* is intrinsically resistant to many antimicrobial agents, and thus may survive during therapy leading to unexpected complications (Rupnik et al., 2009). 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 *Clostridium difficile* toxins was observed (Marks et al., 2002). A small animal experiment using six dogs could not fulfil Koch's postulates for *Clostridium difficile* as a pathogen in dogs (Marks et al., 2002). Cats can also be colonised with *Clostridium difficile* without any signs of diarrhea (Keessen et al., 2011). *Clostridium difficile* colonisation rates in healthy dogs and cats have been reported to range from 1.4% to 21% (Keessen et al., 2011; Weese et al., 2010). *Clostridium difficile* has been reported as a cause of diarrhoea in horses (Diab et al., 2013). A higher prevalence of *Clostridium difficile* has been reported - varying from 18% to 40% - in companion animals attending veterinary clinics (Keessen et al., 2011). *Clostridium difficile* can be found in the environment of veterinary practices (Weese et al., 2000). High rates of *Clostridium difficile* colonisation (58%) have been described in dogs that visit human hospitals (Lefebvre et al., 2006).

5. Factors associated with acquisition of drug-resistant bacteria

The administration of antimicrobials is a common risk factor for selection of 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 colonisation in horses (Weese and Lefebvre, 2007; Weese et al., 2006b). Antimicrobial therapy may also be a risk factor for MRSP infections in dogs (Weese et al., 2009). Healthy dogs treated with oral enrofloxacin were shown to be more effectively colonised with MDR *Escherichia coli* than control dogs (Trott et al., 2004). Oral treatment of dogs with cephalexin has been proposed as a selector of CMY-2 producing *Escherichia 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 the possible selection or persistence in intestinal microbiota thus remains to be elucidated (Damborg et al., 2011). One study carried out in a veterinary intensive care unit (ICU) showed that the proportion of dogs carrying resistant *Escherichia coli* increased with duration of hospitalization and with the use of antimicrobial drugs (Ogeer-Gyles et al., 2006).

Other risk 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, and old 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 colonisation of horses were previous colonisation, presence of colonised 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 healthcare settings, extensive wounds, prolonged hospitalization and immunosuppression also constituted 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). Risk factors for colonisation with *Clostridium difficile* in dogs were reported to be living with an immunocompromised owner, antimicrobial treatment of the dog or the owner, contact with children and visiting human hospitals (Marks et al., 2011). Contact with pet animals as well as travelling have been reported as risk factors for colonisation with ESBL-producing *Escherichia coli* in healthy infection control personnel (Meyer et al., 2012).

6. Discussion

Available data have shown that resistant bacteria emerge in companion animals. Furthermore, several MDR pathogenic bacteria 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 implies the selection and potential spread of drug resistance, which in turn constitutes a potential risk to public health. Furthermore, the lack of effective antimicrobials in the future, can facilitate the development and transmission of resistance (due to ineffective treatment, which can lead to more longer infection episodes of even chronic infections).

Of special concern is the situation in which 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 for advanced therapy coupled with the spread of MDR bacteria one may foresee the future need for new antimicrobials in veterinary medicine.

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

Risk assessment methods should be used to evaluate new antimicrobial treatment options for bacterial infections in companion animals. The new antimicrobial products would be those for which risk levels due to AMR are estimated as acceptable in the context of an overall benefit-risk assessment for the product. Microbiological hazards of concern may directly or indirectly cause adverse health effects in humans. Direct hazards for human health are defined as antimicrobial-resistant bacteria that are transmitted from animals to humans and cause disease in humans (zoonoses). Indirect hazards relate to the transmission of resistance genes from companion animal bacteria to bacteria in humans and subsequently having consequences for public health. Based on the data in this document, the most important microbiological hazards emerging from companion animals are summarized in **Table 1**.

Table 1. Selected microbiological hazards identified in this document

	Type of hazard	**Sources**
Methicillin-resistant *Staphylococcus aureus*	Direct hazard	Dogs, cats, horses

Methicillin-resistant *Staphylococcus pseudintermedius*	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, cats

[a]low number of cases of human infections originating from companion animals
[b]no human infections originating from companion animals have been reported

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

When considering applications for new compounds, new species or indications for existing veterinary antimicrobials for companion animals, the microbiological hazards identified in this document need to be considered in relation to the substance in question. Then, an abbreviated risk assessment model consistent with the principles of Codex (Codex Alimentarius, 2011), OIE (Vose et al., 2001) and VICH GL27 (EMEA, 2004) could be applied. A predictable and transparent assessment should facilitate the process of Marketing Authorisation approval for new VMPs for use in companion animals. Risk mitigation measures to reduce AMR risks could be applied dependent on the outcome of the assessment. Availability of approved VMPs on the market would ensure use according to the SPC and reduce the need for the off-label use of human products.

Owing to extensive knowledge gaps, a qualitative approach would need to be taken to the risk assessment. For new compounds, or new species or indications for existing compounds, the applicant could be requested to provide data similar to what is requested in GL27 tailored to the organisms identified above. With regard to exposure assessment, it is questionable to what extent it would be feasible or desirable to request from an applicant to fully map the selection pressure and link that to likelihood of spread of resistance to humans; however, account could be taken of risk factors such as the duration of treatment, route of administration, prevalence of the indication, etc. The hazard characterisation would consider the relative importance of the antimicrobial to human medicine. The applicant could be asked to provide an expert report where the AMR risk is discussed. One important element of this report would be to justify the suggested indication and target population for the product, demonstrating that the intended use is compliant with responsible use principles considering any hazards of concern.

7. References

Adak, G.K., J.M. Cowden, S. Nicholas, and H.S. Evan. 2005. The public health laboratory service national case-control study of primary indigenous sporadic cases of Campylobacter infection. *Epidemiol. Infect.* 115:15-22.

Atalay, B., F. Ergin, M. Cekinmez, H. Caner, and N. Altinors. 2005. Brain abscess caused by Staphylococcus intermedius. *Acta neurochirurgica* 147:347-348; discussion 348.

Bannoehr, J., N.L. Ben Zakour, A.S. Waller, L. Guardabassi, K.L. Thoday, A.H.M. van den Broek, and J.R. Fitzgerald. 2007. Population Genetic Structure of the Staphylococcus intermedius Group: Insights into agr Diversification and the Emergence of Methicillin-Resistant Strains. *Journal of bacteriology* 189:8685-8692.

Baptiste, K.E., K. Williams, N.J. Williams, A. Wattret, P.D. Clegg, S. Dawson, J.E. Corkill, T. O'Neill, and C.A. Hart. 2005. Methicillin-resistant staphylococci in companion animals *Emerging infectious diseases* 11:1942-1944.

Black, D.M., S.C. Rankin, and L.G. King. 2009. Antimicrobial therapy and aerobic bacteriologic culture patterns in canine intensive care unit patients: 74 dogs (January–June 2006). *Journal of Veterinary Emergency and Critical Care* 19:489-495.

Boag, A.K., A. Loeffler, and D.H. Lloyd. 2004. Methicillin-resistant Staphylococcus aureus isolates from companion animals. *Veterinary Record* 154:411.

Boerlin, P., S. Eugster, F. Gaschen, R. Straub, and P. Schawalder. 2001. Transmission of opportunistic pathogens in a veterinary teaching hospital. *Veterinary microbiology* 82:347-359.

Boost, M., S. So, and V. Perreten. 2011. Low Rate of Methicillin -resistant Coagulase po Staphylococcal Colonization of Veterinary Personnel in Hong Kong. *Zoonoses and public health* 58:36-40.

Brachelente, C., D. Wiener, Y. Malik, and D. Huessy. 2007. A case of necrotizing fasciitis with septic shock in a cat caused by Acinetobacter baumannii. *Veterinary Dermatology* 18:432-438.

BSAVA. 2012. BSAVA/SAMSoc Antibiotics advice In http://www.bsava.com/LinkClick.aspx?fileticket=UD4scQIXfrA%3d&tabid=1500.

Buckley, L.M., N.A. McEwan, and T. Nuttall. 2013. Tris-EDTA significantly enhances antibiotic efficacy against multidrug-resistant Pseudomonas aeruginosa in vitro. *Veterinary dermatology* 24:519-e122.

BVA. 2009. RESPONSIBLE USE OF ANTIMICROBIALS IN VETERINARY PRACTICE: THE 8-POINT PLAN. In http://www.bva.co.uk/public/documents/bva_antimicrobials_poster.pdf

Campanile, F., D. Bongiorno, S. Borbone, M. Venditti, M. Giannella, C. Franchi, and S. Stefani. 2007. Characterization of a variant of the SCCmec element in a bloodstream isolate of Staphylococcus intermedius. *Microb Drug Resist* 13:7-10.

Canton, R., and J. Bryan. 2012a. Global antimicrobial resistance: from surveillance to stewardship. Part 1: surveillance and risk factors for resistance. *Expert Rev Anti Infect Ther* 10:1269-1271.

Canton, R., and J. Bryan. 2012b. Global antimicrobial resistance: from surveillance to stewardship. Part 2: stewardship initiatives. *Expert Rev Anti Infect Ther* 10:1375-1377.

Canton, R., and T.M. Coque. 2006. The CTX-M beta-lactamase pandemic. *Current opinion in microbiology* 9:466-475.

Carattoli, A., S. Lovari, A. Franco, G. Cordaro, P. Di Matteo, and A. Battisti. 2005. Extended-spectrum beta-lactamases in Escherichia coli isolated from dogs and cats in Rome, Italy, from 2001 to 2003. *Antimicrobial agents and chemotherapy* 49:833-835.

Catry, B., E. Van Duijkeren, M.C. Pomba, C. Greko, M.A. Moreno, P. S., M. Ruz Auskas, P. Sanders, E.J. Threlfall, F. Ungemach, K. Torneke, C. Munoz-Madero, J. Torren-Edo, and o.b.o.t.S.A.G.o.A. (SAGAM). 2010. Reflection paper on MRSA in food-producing and companion animals: epidemiology and control options for human and animal health. *Epidemiology and Infection.* 138:626-644.

Cherry, B., A. Burns, G.S. Johnson, H. Pfeiffer, N. Dumas, D. Barrett, P.L. Mcdonough, and M. Eidson. 2004. Salmonella Typhimurium outbreak associated with veterinary clinic. *Emerging infectious diseases* 10:2249–2251.

Codex Alimentarius. 2011. Guidelines for risk analysis of foodborne antimicrobial resistance (CAC/GL 77- 2011). In http://www.codexalimentarius.org/download/standards/11776/CXG_077e.pdf.

Couto, N., C. Pomba, A. Moodley, and L. Guardabassi. 2011. Prevalence of meticillin-resistant staphylococci among dogs and cats at a veterinary teaching hospital in Portugal. *Veterinary Record* 169:72.

Damborg, P., I.B. Gaustad, J.E. Olsen, and L. Guardabassi. 2011. Selection of CMY-2 producing Escherichia coli in the faecal flora of dogs treated with cephalexin. *Veterinary microbiology* 151:404-408.

Damborg, P., K.E. Olsen, E. Moller Nielsen, and L. Guardabassi. 2004a. Occurrence of Campylobacter jejuni in pets living with human patients infected with C. jejuni. *Journal of clinical microbiology* 42:1363-1364.

Damborg, P., K.E.P. Olsen, E. Møller Nielsen, and L. Guardabassi. 2004b. Occurrence of Campylobacter jejuni in Pets Living with Human Patients Infected with C. jejuni. *Journal of clinical microbiology* 42:1363-1364.

Damborg, P., A.H. Sørensen, and L. Guardabassi. 2008. Monitoring of antimicrobial resistance in healthy dogs: First report of canine ampicillin-resistant Enterococcus faecium clonal complex 17. *Veterinary microbiology* 132:190-196.

Damborg, P., J. Top, A.P.A. Hendrickx, S. Dawson, R.J.L. Willems, and L. Guardabassi. 2009. Dogs Are a Reservoir of Ampicillin-Resistant Enterococcus faecium Lineages Associated with Human Infections. *Applied and environmental microbiology* 75:2360-2365.

DANMAP. 2010. DANMAP 2010- Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Den¬mark. In H. Korsgaard, Y. Agersø, A. Hammerum, and L. Skøj-Rasmussen, editors. Statens Serum Institut, Danish Medicines Agency, National Veterinary Institute Technical University of Denmark, National Food Institute Technical University of Denmark, Copenhagen

De Briyne, N., J. Atkinson, L. Pokludova, S.P. Borriello, and S. Price. 2013. Factors influencing antibiotic prescribing habits and use of sensitivity testing amongst veterinarians in Europe. *The Veterinary record* 173:475.

de Niederhäusern, S., C. Sabia, P. Messi, E. Guerrieri, G. Manicardi, and M. Bondi. 2007. VanA-Type Vancomycin-Resistant Enterococci in Equine and Swine Rectal Swabs and in Human Clinical Samples. *Current Microbiology* 55:240-246.

Deplano, A., O. Denis, L. Poirel, D. Hocquet, C. Nonhoff, B. Byl, P. Nordmann, J.L. Vincent, and M.J. Struelens. 2005. Molecular Characterization of an Epidemic Clone of Panantibiotic-Resistant Pseudomonas aeruginosa. *Journal of clinical microbiology* 43:1198-1204.

Diab, S.S., G. Songer, and F.A. Uzal. 2013. Clostridium difficile infection in horses: a review. *Veterinary microbiology* 167:42-49.

ECDC, EFSA, and EMEA. 2009. Joint scientific report of ECDC, EFSA and EMEA on meticillin resistant Staphylococcus aureus (MRSA) in livestock, companion animals and food. Summary of the scientific Opinion of the Panel on Biological Hazards (EFSA/BIOHAZ) on “Assessment of the Public Health significance of meticillin resistant *Staphylococcus aureus* (MRSA) in animals and foods” and the Reflection paper of the Committee for Medicinal Products for Veterinary Use (EMEA/CVMP) on “MRSA in food producing and companion animals and in the European Union: Epidemiology and control options for human and animal health”. In http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004306.

EMA/CVMP/SAGAM. 2007. Public statement on the use of (fluoro)quinolones in food-producing animals in the european union: development of resistance and impact on human and animal health. In http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/10/WC500005152.pdf.

EMA/ESVAC. 2014. European Medicines Agency. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2012 (EMA/333921/2014). In http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/10/WC500175671.pdf.

EMEA. 2004. VICH GL27 Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance In CVMP, editor European Medicines Agency, London 11.

EMEA. 2006. EMEA/CVMP/215997/2006. Scientific discussion. Convenia. . In European Medicines Agency (EMA), London. 17.

EMEA/CVMP/SAGAM. 2009a. Reflection paper on MRSA in food producing and companion animals in the European Union: epidemiology and control options for human and animal health (EMEA/CVMP/SAGAM/68290/2009). In http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004311.pdf

EMEA/CVMP/SAGAM. 2009b. Revised reflection paper on the use of 3rd and 4th generation cephalosporins in food producing animals in the European Union: development of resistance and impact on human and animal health. In http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004307.pdf.

Endimiani, A., K.M. Hujer, A.M. Hujer, I. Bertschy, A. Rossano, C. Koch, V. Gerber, T. Francey, R.A. Bonomo, and V. Perreten. 2011. Acinetobacter baumannii isolates from pets and horses in Switzerland: molecular characterization and clinical data. *Journal of Antimicrobial Chemotherapy*

Escher, M., M. Vanni, L. Intorre, A. Caprioli, R. Tognetti, and G. Scavia. 2011. Use of antimicrobials in companion animal practice: a retrospective study in a veterinary teaching hospital in Italy. *Journal of Antimicrobial Chemotherapy* 66:920-927.

Evira. 2009. Mikrobilääkkeiden käyttösuositukset eläinten tärkeimpiin tulehdus- ja tartuntatauteihin. *Eviran julkaisuja*

Ewers, C., A. Bethe, T. Semmler, S. Guenther, and L.H. Wieler. 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. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 18:646-655.

Ewers, C., A. Bethe, L.H. Wieler, S. Guenther, I. Stamm, P.A. Kopp, and M. Grobbel. 2011a. Companion animals: a relevant source of extended-spectrum β-lactamase-producing fluoroquinolone-resistant Citrobacter freundii. *International journal of antimicrobial agents* 37:86-87.

Ewers, C., M. Grobbel, A. Bethe, L.H. Wieler, and S. Guenther. 2011b. Extended-spectrum beta-lactamases-producing gram-negative bacteria in companion animals: action is clearly warranted! *Berliner und Munchener tierarztliche Wochenschrift* 124:94-101.

Ewers, C., M. Grobbel, I. Stamm, P.A. Kopp, I. Diehl, T. Semmler, A. Fruth, J. Beutlich, B. Guerra, L.H. Wieler, and S. Guenther. 2010. Emergence of human pandemic O25:H4-ST131 CTX-M-15 extended-spectrum-β-lactamase-producing Escherichia coli among companion animals. *Journal of Antimicrobial Chemotherapy* 65:651-660.

Feria, C., E. Ferreira, J.D. Correia, J. Goncalves, and M. Canica. 2002. Patterns and mechanisms of resistance to beta-lactams and beta-lactamase inhibitors in uropathogenic Escherichia coli isolated from dogs in Portugal. *The Journal of antimicrobial chemotherapy* 49:77-85.

Fine, D.M., and A.H. Tobias. 2007. Cardiovascular Device Infections in Dogs: Report of 8 Cases and Review of the Literature. *Journal of Veterinary Internal Medicine* 21:1265-1271.

Francey, T., F. Gaschen, J. Nicolet, and A.P. Burnens. 2000. The Role of Acinetobacter baumannii as a Nosocomial Pathogen for Dogs and Cats in an Intensive Care Unit. *Journal of Veterinary Internal Medicine* 14:177-183.

Frye, J.G., and P.J. Fedorka-Cray. 2007. Prevalence, distribution and characterisation of ceftiofur resistance in Salmonella enterica isolated from animals in the USA from 1999 to 2003. *International journal of antimicrobial agents* 30:134-142.

German, A.J., L.J. Halladay, and P.-J.M. Noble. 2010. First-choice therapy for dogs presenting with diarrhoea in clinical practice. *Veterinary Record* 167:810-814.

Gerstadt, K., J.S. Daly, M. Mitchell, M. Wessolossky, and S.H. Cheeseman. 1999. Methicillin-resistant Staphylococcus intermedius pneumonia following coronary artery bypass grafting. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 29:218-219.

Gibson, J.S., R.N. Cobbold, P. Heisig, H.E. Sidjabat, M.T. Kyaw-Tanner, and D.J. Trott. 2010. Identification of Qnr and AAC(6′)-1b-cr plasmid-mediated fluoroquinolone resistance determinants in multidrug-resistant Enterobacter spp. isolated from extraintestinal infections in companion animals. *Veterinary microbiology* 143:329-336.

Guo, S., H.J. Brouwers, R.N. Cobbold, J.L. Platell, T.A. Chapman, V.R. Barrs, J.R. Johnson, and D.J. Trott. 2013. Fluoroquinolone-resistant extraintestinal pathogenic Escherichia coli, including O25b-ST131, isolated from faeces of hospitalized dogs in an Australian veterinary referral centre. *The Journal of antimicrobial chemotherapy* 68:1025-1031.

Gurnee, C.M., R.P. Groman, and S.C. Rankin. 2006. Molecular characterization of multiple-drug resistant Escherichia coli at a veterinary teaching hospital. In 24th Annual ACVIM Forum J.o.t.V.I. Medicine, editor Blackwell Publishing Ltd, Louisville. 697-802.

Haenni, M., C. Ponsin, V. Metayer, C. Medaille, and J.Y. Madec. 2012. Veterinary hospital-acquired infections in pets with a ciprofloxacin-resistant CTX-M-15-producing Klebsiella pneumoniae ST15 clone. *The Journal of antimicrobial chemotherapy* 67:770-771.

Hald, B., K. Pedersen, M. Wainø, J.C. Jørgensen, and M. Madsen. 2004. Longitudinal Study of the Excretion Patterns of Thermophilic Campylobacter spp. in Young Pet Dogs in Denmark. *Journal of clinical microbiology* 42:2003-2012.

Hanselman, B.A., S.A. Kruth, J. Rousseau, and J.S. Weese. 2009. Coagulase positive staphylococcal colonization of humans and their household pets. *Canadian Veterinary Journal* 50:954-958.

Hatch, S., A. Sree, S. Tirrell, B. Torres, and A.L. Rothman. 2012. Metastatic complications from Staphylococcus intermedius, a zoonotic pathogen. *Journal of clinical microbiology* 50:1099-1101.

Hensgens, M.P., E.C. Keessen, M.M. Squire, T.V. Riley, M.G. Koene, E. de Boer, L.J. Lipman, and E.J. Kuijper. 2012. Clostridium difficile infection in the community: a zoonotic disease? *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 18:635-645.

Herrero, I.A., J.F. Fernández-Garayzábal, M.A. Moreno, and L. Domínguez. 2004. Dogs Should Be Included in Surveillance Programs for Vancomycin-Resistant Enterococci. *Journal of clinical microbiology* 42:1384-1385.

Hidalgo, L., B. Gutierrez, C.M. Ovejero, L. Carrilero, S. Matrat, C.K.S. Saba, A. Santos-Lopez, D. Thomas-Lopez, A. Hoefer, G. Santurde, C. Martin-Espada, and B. Gonzalez-Zorn. 2013. Klebsiella pneumoniae ST11 from companion animals bearing ArmA methyltransferase, DHA-1 β-lactamase and QnrB4. *Published ahead of print 10 June 2013*

Higgins, P.G., C. Dammhayn, M. Hackel, and H. Seifert. 2010. Global spread of carbapenem-resistant Acinetobacter baumannii. *Journal of Antimicrobial Chemotherapy* 65:233-238.

Hill, P.B., A. Lo, C.A.N. Eden, S. Huntley, V. Morey, S. Ramsey, C. Richardson, D.J. Smith, C. Sutton, M.D. Taylor, E. Thorpe, R. Tidmarsh, and V. Williams. 2006. Survey of the prevalence, diagnosis and treatment of dermatological conditions in small animals in general practice. *Veterinary Record* 158:533-539.

Hughes, L.A., G. Pinchbeck, R. Callaby, S. Dawson, P. Clegg, and N. Williams. 2013. Antimicrobial prescribing practice in UK equine veterinary practice. *Equine veterinary journal* 45:141-147.

Hughes, L.A., N. Williams, P. Clegg, R. Callaby, T. Nuttall, K. Coyne, G. Pinchbeck, and S. Dawson. 2012. Cross-sectional survey of antimicrobial prescribing patterns in UK small animal veterinary practice. *Preventive veterinary medicine* 104:309-316.

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

Johnson, J.A. 2002. Nosocomial infections. *Veterinary Clinics of North America. Small Animal Practice* 32:1101-1026.

Jordan, D., J. Simon, S. Fury, S. Moss, P. Giffard, M. Maiwald, P. Southwell, M.D. Barton, J.E. Axon, S.G. Morris, and D.J. Trott. 2011. Carriage of methicillin-resistant Staphylococcus aureus by veterinarians in Australia. *Australian veterinary journal* 89:152-159.

Kadlec, K., S. Schwarz, V. Perreten, U. Grönlund Andersson, M. Finn, C. Greko, A. Moodley, S.A. Kania, L.A. Frank, D.A. Bemis, A. Franco, M. Iurescia, A. Battisti, B. Duim, J.A. Wagenaar, E. van Duijkeren, J.S. Weese, J.R. Fitzgerald, A. Rossano, and L. Guardabassi. 2010. Molecular analysis of methicillin-resistant Staphylococcus pseudintermedius of feline origin from different European countries and North America. *Journal of Antimicrobial Chemotherapy* 65:1826-1828.

Kapperud, G., E. Skjerve, N.H. Bean, S.M. Ostroff, and J. Lassen. 1992. Risk factors for sporadic Campylobacter infections: results of a case-control study in southeastern Norway. *Journal of clinical microbiology* 30:3117-3121.

Keessen, E.C., W. Gaastra, and L.J.A. Lipman. 2011. Clostridium difficile infection in humans and animals, differences and similarities. *Veterinary microbiology* 153:205-217.

Kvaale, M.K., K. Grave, A.B. Kristoffersen, and M. Norstrom. 2012. The prescription rate of antibacterial agents in dogs in Norway - geographical patterns and trends during the period 2004-2008. *Journal of veterinary pharmacology and therapeutics*

Laarhoven, L.M., P. de Heus, J. van Luijn, B. Duim, J.A. Wagenaar, and E. van Duijkeren. 2011. Longitudinal study on methicillin-resistant Staphylococcus pseudintermedius in households. *PloS one* 6:e27788.

Lefebvre, S.L., D. Waltner-Toews, A.S. Peregrine, R. Reid-Smith, L. Hodge, L.G. Arroyo, and J.S. Weese. 2006. Prevalence of zoonotic agents in dogs visiting hospitalized people in Ontario: implications for infection control. *Journal of Hospital Infection* 62:458-466.

Leonard, F.C., and B.K. Markey. 2008. Meticillin-resistant Staphylococcus aureus in animals: A review. *The Veterinary Journal* 175:27-36.

Linden, P.K. 2008. Enterococci: resistance update and treatment options In Antimicrobial resistance: problem pathogens and clinical countermeasures. J.R.C. Owens, and E. Lautenbach, editors. Informa Healthcare, New York. 89.

Loeffler, A., A.K. Boag, J. Sung, J.A. Lindsay, L. Guardabassi, A. Dalsgaard, H. Smith, K.B. Stevens, and D.H. Lloyd. 2005. Prevalence of methicillin-resistant Staphylococcus aureus among staff and pets in a small animal referral hospital in the UK. *Journal of Antimicrobial Chemotherapy* 56:692-697.

Loeffler, A., M. Linek, A. Moodley, L. Guardabassi, J.M.L. Sung, M. Winkler, R. Weiss, and D.H. Lloyd. 2007. First report of multiresistant, mecA-positive Staphylococcus intermedius in Europe: 12 cases from a veterinary dermatology referral clinic in Germany. *Veterinary Dermatology* 18:412-421.

Loeffler, A., D.U. Pfeiffer, J.A. Lindsay, R. Soares-Magalhaes, and D.H. Lloyd. 2010. Lack of transmission of methicillin-resistant Staphylococcus aureus (MRSA) between apparently healthy dogs in a rescue kennel. *Veterinary microbiology* 141:178-181.

Ma, J., Z. Zeng, Z. Chen, X. Xu, X. Wang, Y. Deng, D. Lü, L. Huang, Y. Zhang, J. Liu, and M. Wang. 2009. High Prevalence of Plasmid-Mediated Quinolone Resistance Determinants qnr, aac(6′)-Ib-cr, and qepA among Ceftiofur-Resistant Enterobacteriaceae Isolates from Companion and Food-Producing Animals. *Antimicrobial agents and chemotherapy* 53:519-524.

Man, S.M. 2011. The clinical importance of emerging Campylobacter species. *Nature reviews. Gastroenterology & hepatology* 8:669-685.

Manian, F.A. 2003. Asymptomatic Nasal Carriage of Mupirocin-Resistant, Methicillin-Resistant Staphylococcus aureus (MRSA) in a Pet Dog Associated with MRSA Infection in Household Contacts. *Clinical Infectious Diseases* 36:e26-e28.

Manson, J.M., S. Keis, J.M.B. Smith, and G.M. Cook. 2003. Characterization of a Vancomycin-Resistant Enterococcus faecalis (VREF) Isolate from a Dog with Mastitis: Further Evidence of a Clonal Lineage of VREF in New Zealand. *Journal of clinical microbiology* 41:3331-3333.

Marks, S.L., E.J. Kather, P.H. Kass, and A.C. Melli. 2002. Genotypic and Phenotypic Characterization of Clostridium perfringens and Clostridium difficile in Diarrheic and Healthy Dogs. *Journal of Veterinary Internal Medicine* 16:533-540.

Marks, S.L., S.C. Rankin, B.A. Byrne, and J.S. Weese. 2011. Enteropathogenic bacteria in dogs and cats: diagnosis, epidemiology, treatment, and control. *Journal of veterinary internal medicine / American College of Veterinary Internal Medicine* 25:1195-1208.

Mateus, A., D.C. Brodbelt, N. Barber, and K.D.C. Stärk. 2011. Antimicrobial usage in dogs and cats in first opinion veterinary practices in the UK. *Journal of Small Animal Practice* 52:515-521.

Matsumoto, Y., F. Ikeda, T. Kamimura, Y. Yokota, and Y. Mine. 1988. Novel plasmid-mediated beta-lactamase from Escherichia coli that inactivates oxyimino-cephalosporins. *Antimicrobial agents and chemotherapy* 32:1243-1246.

Mekic, S., K. Matanovic, and B. Seol. 2011. Antimicrobial susceptibility of Pseudomonas aeruginosa isolates from dogs with otitis externa. *The Veterinary record* 169:125.

Meyer, E., P. Gastmeier, A. Kola, and F. Schwab. 2012. Pet animals and foreign travel are risk factors for colonisation with extended-spectrum beta-lactamase-producing Escherichia coli. *Infection* 40:685-687.

Moodley, A., E.C. Nightingale, M. Stegger, S.S. Nielsen, R.L. Skov, and L. Guardabassi. 2008. High risk for nasal carriage of methicillin-resistant *Staphylococcus aureus* among Danish veterinary practitioners. *Scandinavian Journal of Work, Environment & Health* 34:151–157.

Morley, P.S. 2004. Surveillance for nosocomial infections in veterinary hospitals. *The Veterinary clinics of North America. Equine practice* 20:561-576.

Mulvey, M.R., D.A. Boyd, D. Gravel, J. Hutchinson, S. Kelly, A. McGeer, D. Moore, A. Simor, K.N. Suh, G. Taylor, J.S. Weese, M. Miller, and P. Canadian Nosocomial Infection Surveillance. 2010. Hypervirulent Clostridium difficile strains in hospitalized patients, Canada. *Emerging infectious diseases* 16:678-681.

Neimann, J., J. Engberg, K. Mølbak, and H.C. Wegener. 2003. A case-control study of risk factors for sporadic campylobacter infections in Denmark. *Epidemiol. Infect.* 130:353–366.

Nienhoff, U., K. Kadlec, I.F. Chaberny, J. Verspohl, G.F. Gerlach, L. Kreienbrock, S. Schwarz, D. Simon, and I. Nolte. 2011. Methicillin-resistant Staphylococcus pseudintermedius among dogs admitted to a small animal hospital. *Veterinary microbiology* 150:191-197.

Nuttall, T., and L.K. Cole. 2007. Evidence-based veterinary dermatology: a systematic review of interventions for treatment of Pseudomonas otitis in dogs. *Veterinary Dermatology* 18:69-77.

O'Mahony, R., Y. Abbott, F.C. Leonard, B.K. Markey, P.J. Quinn, P.J. Pollock, S. Fanning, and A.S. Rossney. 2005. Methicillin-resistant Staphylococcus aureus (MRSA) isolated from animals and veterinary personnel in Ireland. *Veterinary microbiology* 109:285-296.

Odensvik, K., K. Grave, and C. Greko. 2001. Antibacterial Drugs Prescribed for Dogs and Cats in Sweden and Norway 1990-1998. *Acta Veterinaria Scandinavica* 42:189 - 198.

Official Journal of the European Union. 2012. Summary of European Union decisions on marketing authorisations in respect of medicinal products from 1 January 2012 to 31 January 2012 (2012/C 78/02). Cephalosporins. In http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1420644411495&uri=CELEX:52012XC0316%2804%29.

Ogeer-Gyles, J., K.A. Mathews, W. Sears, J.F. Prescott, J.S. Weese, and P. Boerlin. 2006. Development of antimicrobial drug resistance in rectal Escherichia coli isolates from dogs hospitalized in an intensive care unit. *Journal of the American Veterinary Medical Association* 229:694-699.

Ossiprandi, M.C., E. Bottarelli, F. Cattabiani, and E. Bianchi. 2008. Susceptibility to vancomycin and other antibiotics of 165 Enterococcus strains isolated from dogs in Italy. *Comparative Immunology, Microbiology and Infectious Diseases* 31:1-9.

Paul, N.C., A. Moodley, G. Ghibaudo, and L. Guardabassi. 2011. Carriage of Methicillin-Resistant Staphylococcus pseudintermedius in Small Animal Veterinarians: Indirect Evidence of Zoonotic Transmission. *Zoonoses and public health* 58:533-539.

Pedersen, K., K. Pedersen, H. Jensen, K. Finster, V.F. Jensen, and O.E. Heuer. 2007. Occurrence of antimicrobial resistance in bacteria from diagnostic samples from dogs. *Journal of Antimicrobial Chemotherapy* 60:775-781.

Perez, F., A. Endimiani, A.J. Ray, B.K. Decker, C.J. Wallace, K.M. Hujer, D.J. Ecker, M.D. Adams, P. Toltzis, M.J. Dul, A. Windau, S. Bajaksouzian, M.R. Jacobs, R.A. Salata, and R.A. Bonomo. 2010. Carbapenem-resistant Acinetobacter baumannii and Klebsiella pneumoniae across a hospital system: impact of post-acute care facilities on dissemination. *Journal of Antimicrobial Chemotherapy* 65:1807-1818.

Perreten, V., K. Kadlec, S. Schwarz, U. Grönlund Andersson, M. Finn, C. Greko, A. Moodley, S.A. Kania, L.A. Frank, D.A. Bemis, A. Franco, M. Iurescia, A. Battisti, B. Duim, J.A. Wagenaar, E. van Duijkeren, J.S. Weese, J.R. Fitzgerald, A. Rossano, and L. Guardabassi. 2010. Clonal spread of methicillin-resistant Staphylococcus pseudintermedius in Europe and North America: an international multicentre study. *Journal of Antimicrobial Chemotherapy* 65:1145-1154.

Pitout, J.D.D., and K.B. Laupland. 2008. Extended-spectrum ?-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *The Lancet infectious diseases* 8:159-166.

Platell, J.L., R.N. Cobbold, J.R. Johnson, A. Heisig, P. Heisig, C. Clabots, M.A. Kuskowski, and D.J. Trott. 2011. Commonality among Fluoroquinolone-Resistant Sequence Type ST131 Extraintestinal Escherichia coli Isolates from Humans and Companion Animals in Australia. *Antimicrobial agents and chemotherapy* 55:3782-3787.

Poirel, L., R.A. Bonnin, and P. Nordmann. 2012. Genetic support and diversity of acquired extended-spectrum beta-lactamases in Gram-negative rods. *Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases* 12:883-893.

Pomba, C., J.D. da Fonseca, B.C. Baptista, J.D. Correia, and L. Martínez-Martínez. 2009. Detection of the Pandemic O25-ST131 Human Virulent Escherichia coli CTX-M-15-Producing Clone Harboring the qnrB2 and aac(6′)-Ib-cr Genes in a Dog. *Antimicrobial agents and chemotherapy* 53:327-328.

Radford, A.D., P.J. Noble, K.P. Coyne, R.M. Gaskell, P.H. Jones, J.G.E. Bryan, C. Setzkorn, Á. Tierney, and S. Dawson. 2011. Antibacterial prescribing patterns in small animal veterinary practice identified via SAVSNET: the small animal veterinary surveillance network. *Veterinary Record* 169:310.

Rankin, S., S. Roberts, K. O'Shea, D. Maloney, M. Lorenzo, and C.E. Benson. 2005. Panton valentine leukocidin (PVL) toxin positive MRSA strains isolated from companion animals. *Veterinary microbiology* 108:145-148.

Rantala, M., P. Huovinen, K. Hölsö, A. Lilas, and L. Kaartinen. 2004a. Survey of condition-based prescribing of antimicrobial drugs for dogs at a veterinary teaching hospital. *Veterinary Record* 155:259-262.

Rantala, M., E. Lahti, J. Kuhalampi, S. Pesonen, A.-K. Jarvinen, L. Saijonmaa-Koulumies, and T. Honkanen-Buzalski. 2004b. Antimicrobial resistance in Staphylococcus spp., Escherichia coli and Enterococcus spp. in dogs given antibiotics for chronic dermatological disorders, compared with non-treated control dogs. *Acta Veterinaria Scandinavica* 45:37 - 45.

Regula, G., K. Torriani, B. Gassner, F. Stucki, and C.R. Muntener. 2009. Prescription patterns of antimicrobials in veterinary practices in Switzerland. *The Journal of antimicrobial chemotherapy* 63:805-811.

Rice, E.W., L.A. Boczek, C.H. Johnson, and J.W. Messer. 2003. Detection of intrinsic vancomycin resistant enterococci in animal and human feces1 1 Portions of this study were presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, Dec. 2001. *Diagnostic microbiology and infectious disease* 46:155-158.

Rich, M., and L. Roberts. 2006. MRSA in companion animals. *Veterinary Record* 159:535-536.

Rogers, B.A., H.E. Sidjabat, and D.L. Paterson. 2010. Escherichia coli O25b-ST131: a pandemic, multiresistant, community-associated strain. *Journal of Antimicrobial Chemotherapy*

Rubin, J., R.D. Walker, K. Blickenstaff, S. Bodeis-Jones, and S. Zhao. 2008. Antimicrobial resistance and genetic characterization of fluoroquinolone resistance of Pseudomonas aeruginosa isolated from canine infections. *Veterinary microbiology* 131:164-172.

Rupnik, M., M.H. Wilcox, and D.N. Gerding. 2009. Clostridium difficile infection: new developments in epidemiology and pathogenesis. *Nature reviews. Microbiology* 7:526-536.

Ruscher, C., A. Lübke-Becker, T. Semmler, C.-G. Wleklinski, A. Paasch, A. Šoba, I. Stamm, P. Kopp, L.H. Wieler, and B. Walther. 2010. Widespread rapid emergence of a distinct methicillin- and multidrug-resistant Staphylococcus pseudintermedius (MRSP) genetic lineage in Europe. *Veterinary microbiology* 144:340-346.

Safdar, N., and D.G. Maki. 2002. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant Staphylococcus aureus, enterococcus, gram-negative bacilli, Clostridium difficile, and Candida. *Annals of internal medicine* 136:834-844.

Sanchez, S., M.A. McCrackin Stevenson, C.R. Hudson, M. Maier, T. Buffington, Q. Dam, and J.J. Maurer. 2002. Characterization of Multidrug-Resistant Escherichia coli Isolates Associated with Nosocomial Infections in Dogs. *Journal of clinical microbiology* 40:3586-3595.

Sasaki, T., K. Kikuchi, Y. Tanaka, N. Takahashi, S. Kamata, and K. Hiramatsu. 2007a. Methicillin-Resistant Staphylococcus pseudintermedius in a Veterinary Teaching Hospital. *Journal of clinical microbiology* 45:1118-1125.

Sasaki, T., K. Kikuchi, Y. Tanaka, N. Takahashi, S. Kamata, and K. Hiramatsu. 2007b. Methicillin-resistant Staphylococcus pseudintermedius in a veterinary teaching hospital. *Journal of clinical microbiology* 45:1118-1125.

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

Schipper, L., E. van Duijkeren, J. van Herten, S. Mesu, and F. Stembert. 2013. Formularium Gezelschapsdieren Hond en Kat.

Schwarz, S., K. Kadlec, and B. Strommenger. 2008. Methicillin-resistant Staphylococcus aureus and Staphylococcus pseudintermedius detected in the BfT-GermVet monitoring programme 2004–2006 in Germany. *Journal of Antimicrobial Chemotherapy* 61:282-285.

Scott, G.M., R. Thomson, J. Malone-Lee, and G.L. Ridgway. 1988. Cross-infection between animals and man: Possible feline transmission of Staphylococcus aureus infection in humans? *Journal of Hospital Infection* 12:29-34.

Shaheen, B.W., R. Nayak, and D.M. Boothe. 2013. Emergence of a New Delhi metallo-beta-lactamase (NDM-1)-encoding gene in clinical Escherichia coli isolates recovered from companion animals in the United States. *Antimicrobial agents and chemotherapy* 57:2902-2903.

Sidjabat, H.E., N.D. Hanson, E. Smith-Moland, J.M. Bell, J.S. Gibson, L.J. Filippich, and D.J. Trott. 2007. Identification of plasmid-mediated extended-spectrum and AmpC β-lactamases in Enterobacter spp. isolated from dogs. *Journal of medical microbiology* 56:426-434.

Sidjabat, H.E., K.M. Townsend, N.D. Hanson, J.M. Bell, H.W. Stokes, K.S. Gobius, S.M. Moss, and D.J. Trott. 2006. Identification of blaCMY-7 and associated plasmid-mediated resistance genes in multidrug-resistant Escherichia coli isolated from dogs at a veterinary teaching hospital in Australia. *Journal of Antimicrobial Chemotherapy* 57:840-848.

Simjee, S., D.G. White, P.F. McDermott, D.D. Wagner, M.J. Zervos, S.M. Donabedian, L.L. English, J.R. Hayes, and R.D. Walker. 2002. Characterization of Tn1546 in Vancomycin-Resistant Enterococcus faecium Isolated from Canine Urinary Tract Infections: Evidence of Gene Exchange between Human and Animal Enterococci. *Journal of clinical microbiology* 40:4659-4665.

Soares Magalhães, R.J., A. Loeffler, J. Lindsay, M. Rich, L. Roberts, H. Smith, D.H. Lloyd, and D.U. Pfeiffer. 2010. Risk factors for methicillin-resistant Staphylococcus aureus (MRSA) infection in dogs and cats: a case-control study. *Vet. Res.* 41:55.

Soedarmanto, I., T. Kanbar, H. Ülbegi-Mohyla, M. Hijazin, J. Alber, C. Lämmler, Ö. Akineden, R. Weiss, A. Moritz, and M. Zschöck. 2011. Genetic relatedness of methicillin-resistant Staphylococcus pseudintermedius (MRSP) isolated from a dog and the dog owner. *Research in veterinary science* 91:e25-e27.

Stegmann, R., A. Burnens, C.A. Maranta, and V. Perreten. 2010. Human infection associated with methicillin-resistant Staphylococcus pseudintermedius ST71. *The Journal of antimicrobial chemotherapy* 65:2047-2048.

Stolle, I., E. Prenger-Berninghoff, I. Stamm, S. Scheufen, E. Hassdenteufel, S. Guenther, A. Bethe, Y. Pfeifer, and C. Ewers. 2013. Emergence of OXA-48 carbapenemase-producing Escherichia coli and Klebsiella pneumoniae in dogs. *Journal of Antimicrobial Chemotherapy*

SVARM. 2010. SVARM 2009, Swedish Veterinary Antimicrobial Resistance Monitoring. In B. Bengtsson, S. Englund, C. Greko, and U. Grönlund Andersson, editors. Swedish National Veterinary Institute (SVA), Uppsala. 116.

SVF. 2009. Guidelines for the clinical use of antibiotics in the treatment of dogs and cats.

Teshager, T., L. Domínguez, M.A. Moreno, Y. Saénz, C. Torres, and S. Cardeñosa. 2000. Isolation of an SHV-12 β-Lactamase-Producing Escherichia coli Strain from a Dog with Recurrent Urinary Tract Infections. *Antimicrobial agents and chemotherapy* 44:3483-3484.
Thomson, K. 2010. Species-specific and Indication-based Use of Antimicrobials in Dogs, Cats, Cattle and Horses in Finland- Data collected using three different methods. In Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine. University of Helsinki, Helsinki, Finland. 75.
Thomson, K.H., M.H.J. Rantala, T.K. Viita-Aho, O.M. Vainio, and L.A. Kaartinen. 2009. Condition-based use of antimicrobials in cats in Finland: results from two surveys. *Journal of Feline Medicine & Surgery* 11:462-466.
Tomlin, J., M.J. Pead, D.H. Lloyd, S. Howell, F. Hartmann, H.A. Jackson, and P. Muir. 1999. Methicillin-resistant Staphylococcus aureus infections in 11 dogs. *Veterinary Record* 144:60-64.
Trott, D.J., L.J. Filippich, J.C. Bensink, M.T. Downs, S.E. McKenzie, K.M. Townsend, S.M. Moss, and J.J.-C. Chin. 2004. Canine model for investigating the impact of oral enrofloxacin on commensal coliforms and colonization with multidrug-resistant Escherichia coli. *Journal of medical microbiology* 53:439-443.
van Belkum, A., N. van den Braak, R. Thomassen, H. Verbrugh, and H. Endtz. 1996. Vancomycin-resistant enterococci in cats and dogs. *The Lancet* 348:1038-1039.
van Duijkeren, E., A.T.A. Box, M.E.O.C. Heck, W.J.B. Wannet, and A.C. Fluit. 2004. Methicillin-resistant staphylococci isolated from animals. *Veterinary microbiology* 103:91-97.
van Duijkeren, E., B. Catry, C. Greko, M.A. Moreno, M.C. Pomba, S. Pyorala, M. Ruzauskas, P. Sanders, E.J. Threlfall, J. Torren-Edo, and K. Torneke. 2011a. Review on methicillin-resistant Staphylococcus pseudintermedius. *The Journal of antimicrobial chemotherapy* 66:2705-2714.
van Duijkeren, E., B. Catry, C. Greko, M.A. Moreno, M.C. Pomba, S. Pyörälä, M. Ružauskas, P. Sanders, E.J. Threlfall, J. Torren-Edo, and K. Törneke. 2011b. Review on methicillin-resistant Staphylococcus pseudintermedius. *Journal of Antimicrobial Chemotherapy* 66:2705-2714.
van Duijkeren, E., D.J. Houwers, A. Schoormans, M.J. Broekhuizen-Stins, R. Ikawaty, A.C. Fluit, and J.A. Wagenaar. 2008. Transmission of methicillin-resistant Staphylococcus intermedius between humans and animals. *Veterinary microbiology* 128:213-215.
van Duijkeren, E., M. Kamphuis, I.C. van der Mije, L.M. Laarhoven, B. Duim, J.A. Wagenaar, and D.J. Houwers. 2011c. Transmission of methicillin-resistant Staphylococcus pseudintermedius between infected dogs and cats and contact pets, humans and the environment in households and veterinary clinics. *Veterinary microbiology* 150:338-343.
van Duijkeren, E., M. Kamphuis, I.C. van der Mije, L.M. Laarhoven, B. Duim, J.A. Wagenaar, and D.J. Houwers. 2011d. Transmission of methicillin-resistant Staphylococcus pseudintermedius between infected dogs and cats and contact pets, humans and the environment in households and veterinary clinics. *Veterinary microbiology* 150:338-343.
van Duijkeren, E., M. Moleman, M.M. Sloet van Oldruitenborgh-Oosterbaan, J. Multem, A. Troelstra, A.C. Fluit, W.J.B. van Wamel, D.J. Houwers, A.J. de Neeling, and J.A. Wagenaar. 2010. Methicillin-resistant Staphylococcus aureus in horses and horse personnel: An investigation of several outbreaks. *Veterinary microbiology* 141:96-102.
van Duijkeren, E., L. ten Horn, J. A. Wagenaar, M. de Bruijn, L. Laarhoven, K. Verstappen, W. de Weerd, N. Meessen, and B. Duim. 2011e. Suspected Horse-to-Human Transmission of MRSA ST398. *Emergining Infectious Diseases*
Vo, A.T., E. van Duijkeren, A.C. Fluit, and W. Gaastra. 2007. Characteristics of extended-spectrum cephalosporin-resistant Escherichia coli and Klebsiella pneumoniae isolates from horses. *Veterinary microbiology* 124:248-255.
Vose, D., J. Acar, F. Anthony, A. Franklin, R. Gupta, T. Nicholls, Y. Tamura, S. Thompson, E.J. Threlfall, M. van Vuuren, D.G. White, H.C. Wegener, and M.L. Costarrica. 2001. Antimicrobial resistance: risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin. *Rev Sci Tech* 20:811-827.
Wagenvoort, J.H.T., D.M.T. Burgers, T.H.C. Wagenvoort, and E. Burgers. 2003. Absence of vancomycin-resistant enterococci (VRE) in companion dogs in the conurbation of Parkstad Limburg, The Netherlands. *Journal of Antimicrobial Chemotherapy* 52:532.
Weese, J.S., H. Dick, B.M. Willey, A. McGeer, B.N. Kreiswirth, B. Innis, and D.E. Low. 2006a. Suspected transmission of methicillin-resistant Staphylococcus aureus between domestic pets and humans in veterinary clinics and in the household. *Veterinary microbiology* 115:148-155.
Weese, J.S., M. Faires, J. Rousseau, A.M.E. Bersenas, and K.A. Mathews. 2007. Cluster of methicillin-resistant Staphylococcus aureus colonization in a small animal intensive care unit. *Journal of the American Veterinary Medical Association* 231:1361-1364.

Weese, J.S., R. Finley, R.R. Reid-Smith, N. Janecko, and J. Rousseau. 2010. Evaluation of *Clostridium difficile* in dogs and the household environment *Epidemiology and infection* 138:1100–1104.
Weese, J.S., L.A. Frank, L.M. Reynolds, and D.A. Bemis. 2009. Retrospective study of methicilin-resistant and methicilin-susceptible *Staphylococus pseudintermedius* infections in dogs In ASM Methicillin-resistant Staphylococci in Animals: Veterinary and Public Health Implications A.S.o. Microbiology, editor American Society of Microbiology (ASM), London, England. 43A.
Weese, J.S., and S.L. Lefebvre. 2007. Risk factors for methicillin-resistant *Staphylococcus aureus* colonization in horses admitted to a veterinary teaching hospital. *The Canadian Veterinary Journal* 48: 921–926.
Weese, J.S., J. Rousseau, B.M. Willey, M. Archambault, A. McGeer, and D.E. Low. 2006b. Methicillin-resistant *Staphylococcus aureus* in horses at a veterinary teaching hospital: frequency, characterization, and association with clinical disease. *Journal of Veterinary Internal Medicine* 20:182-186.
Weese, J.S., H.R. Staempfli, and J.F. Prescott. 2000. Isolation of Environmental Clostridium Difficile from a Veterinary Teaching Hospital. *Journal of Veterinary Diagnostic Investigation* 12:449-452.
Weese, J.S., and E. van Duijkeren. 2010a. Methicillin-resistant Staphylococcus aureus and Staphylococcus pseudintermedius in veterinary medicine. *Veterinary microbiology* 140:418-429.
Weese, J.S., and E. van Duijkeren. 2010b. Methicillin-resistant Staphylococcus aureus and Staphylococcus pseudintermedius in veterinary medicine. *Veterinary microbiology* 140:418-429.
Werner, G., T.M. Coque, A.M. Hammerum, R. Hope, H. Hryniewicz, A. Johnson, I. Klare, K.G. Kristinsson, R. Leclercq, C.H. Lester, M. Lillie, C. Novais, B. Olsson-Liljequist, L.V. Peixe, E. Sadowy, G.S. Simonsen, J. Top, J. Vuopio-Varkila, R.J. Willems, W. Witte, and N. Woodford. 2008. Emergence and spread of vancomycin resistance among enterococci in Europe. *Eurosurveillance* 13:
Wieler, L.H., C. Ewers, S. Guenther, B. Walther, and A. Lubke-Becker. 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. *International journal of medical microbiology : IJMM* 301:635-641.
Wildermuth, B.E., C.E. Griffin, W.S. Rosenkrantz, and M.J. Boord. 2007. Susceptibility of Pseudomonas Isolates From the Ears and Skin of Dogs to Enrofloxacin, Marbofloxacin, and Ciprofloxacin. *Journal of the American Animal Hospital Association* 43:337-341.
Wolfs, T.F.W., B. Duim, S.P.M. Geelen, A. Rigter, F. Thomson-Carter, A. Fleer, and J.A. Wagenaar. 2001. Neonatal Sepsis by Campylobacter jejuni: Genetically Proven Transmission from a Household Puppy. *Clinical Infectious Diseases* 32:e97-e99.
Wright, J.G., L.A. Tengelsen, K.E. Smith, J.B. Bender, R.K. Frank, J.H. Grendon, D.H. Rice, A.M. Thiessen, C.J. Gilbertson, S. Sivapalasingam, T.J. Barrett, T.E. Besser, D.D. Hancock, and F.J. Angulo. 2005. Multidrug-resistant Salmonella Typhimurium in four animal facilities. *Emerging infectious diseases* 11:1235-1241.