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Pet animals as reservoirs of antimicrobial-resistant bacteria

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Pet animal numbers have substantially increased in modern society and attention is increasingly devoted to pet welfare. Because of these changes, antimicrobial agents are frequently used in small animal veterinary practice, often including antimicrobial preparations used in human medicine, with heavy use of broad-spectrum agents such as aminopenicillins plus clavulanic acid, cephalosporins and fluoroquinolones. Several longitudinal studies conducted at veterinary hospitals have indicated that resistance to various antimicrobial agents has emerged amongst pet animal isolates of *Staphylococcus intermedius*, *Escherichia coli* and other bacteria, including species with a potential for zoonotic transmission and resistance phenotypes of clinical interest, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and multidrug-resistant *Salmonella* Typhimurium DT104. Based on a review of the current literature, the role of pets in the dissemination of antimicrobial resistance has been given little attention when compared with that of food animals. A marked contrast is evident between the current policies on antimicrobial usage in food and companion animals. Apart from a few countries where limited data on antimicrobial usage and occurrence of resistance in bacteria from pet animals are provided, national surveillance programmes only focus on food animals. However, data on pet animals are clearly needed for guiding antimicrobial use policy in small animal veterinary practice as well as for assessing the risk of transmission of antimicrobial resistance to humans.

Keywords: dogs, cats, antimicrobial resistance

Introduction

Antimicrobial resistance is a very complex problem involving various bacterial species, resistance mechanisms, transfer mechanisms and reservoirs. Several studies have shown that antimicrobial use in food animals contributes to the selection of antimicrobial resistance and poses risks to humans because of transmission of resistant zoonotic bacteria via the food chain[1] and indirect transfer of resistance genes from animals to man.[2] However, some authors have recently questioned the hazard to human health caused by the use of antimicrobials in food animals.[3] Resistant bacteria might be acquired by humans through alternative pathways such as person-to-person transmission, environmental exposure and direct exposure to animals. In a recent study on analytical modelling of antimicrobial resistance, Barber *et al.*[4] pointed out that the role of food animals in the transmission of antimicrobial resistance has been overemphasized in the scientific literature, with a consequent underestimation of non-foodborne sources of transmission.

Cats and dogs represent potential sources of spread of antimicrobial resistance due to the extensive use of antimicrobial agents in these animals and their close contact with humans. The number of cats and dogs has substantially increased in modern society, with an estimated population of above 70 million in the EU countries.[5] The relationship between companion animals and humans has radically changed through the years, with cats and dogs being more and more in close contact with humans. While in the past dogs usually were maintained outside households, today they are often kept inside houses. Close physical contact by touching, petting and licking occurs at high frequency on the basis of the current perception of household pets as actual family members.

This article reviews the current knowledge on antimicrobial use and prevalence of antimicrobial resistance in dogs and cats. The role of these animals as reservoirs of antimicrobial resistance is discussed on the basis of available data on transmission of resistant bacteria between pets and humans as well as on exchange of resistance genes. Light is shed on the sharp contrast

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existing between the current policies on antimicrobial usage in food-producing animals and pet animals, with focus on the possible implications for human health.

Antimicrobial use in pet animal veterinary practice

Causes of antimicrobial use

Today, increased attention is devoted to small animal welfare, resulting in increased expenditure on veterinary care, and prevention and therapy of infectious diseases. As a consequence of these changes, antimicrobial agents are now frequently used in pet animals, particularly in canine medicine, including antimicrobial preparations licensed for human use and compounds of primary importance in the treatment of human infections. In 2002, the use of pharmaceutical products in companion animals and other non-food animals accounted for 36.5% of animal health sales in the European Union, with anti-infective products representing 17% of pharmaceutical sales in animals, excluding parasiticides and medicinal feed additives.[6] Compared with large animal veterinarians, colleagues working in small animal practice can count on a stronger economic basis to support laboratory analysis and antimicrobial therapy. However, this situation may result in some laxity in antimicrobial prescription, especially in difficult cases when diagnostic uncertainty, concern about risks of secondary infection, empirical selection of antibiotics and pressure by the owner can lead to inappropriate use of antimicrobial agents. Furthermore, bacterial identification and antimicrobial susceptibility testing are often not carried out for guiding antimicrobial therapy in pet animals, thus leading to inappropriate empirical treatment (e.g. cases of viral feline upper respiratory infection).

Antimicrobial classes frequently used in small animal veterinary medicine include penicillins, cephalosporins, macrolides, lincosamides, fusidic acid, tetracyclines, chloramphenicol, potentiated sulphonamides, aminoglycosides and fluoroquinolones.[7] The most frequent causes of antimicrobial treatment in dogs and cats are skin and wound infections, otitis externa, respiratory infections, and urinary tract infections (UTI). Gastrointestinal infections are also common but antimicrobial therapy is not warranted in most of these syndromes. Some canine infections (e.g. pyoderma and some forms of otitis externa) often require repeated and prolonged treatment. Recurrent pyoderma caused by *S. intermedius* is often treated with cefalexin and sometimes with continuous low-dose or regular pulse therapy.[8] Difficult cases are often treated with fluoroquinolones and can involve continuous therapy for periods as long as 7 months.[9] Fusidic acid is commonly used topically in canine eye and skin infections, and mupirocin is used as an alternative to fusidic acid in skin infections. Aminoglycosides, such as gentamicin and neomycin, are routinely used for topical therapy in canine otitis. Chronic otitis externa, which commonly involves multi-resistant *Pseudomonas aeruginosa*, is often treated topically and/or systemically with fluoroquinolones or ticarcillin.[10,11] First-line drugs and alternatives for treatment of common UTI and respiratory infections in dogs and cats are described in Table 1.

The commonest infections in cats are those affecting wounds, particularly cat bites and scratches.[12] These are sporadic events for the individual cat and good responses to treatment are normally obtained. However, they represent a substantial level of veterinary antimicrobial use in cats. Compared with dogs, cats have a higher incidence of infections in the oral cavity (periodontitis, gingivitis and acute ulcerative stomatitis), which are commonly treated with penicillin G, amoxicillin,

Table 1. First-line antimicrobials and alternatives in the treatment of common urinary tract infections (UTI) and respiratory infections in dogs and cats

Infection site	Diagnosis	First-line antimicrobials	Alternatives
Urinary tract	lower UTI cystitis	amoxicillin co-amoxiclav cefotaxime sulphonamides/trimethoprim	tetracyclines fluoroquinolones cefalexin metronidazole
	pyelonephritis	amoxicillin co-amoxiclav	fluoroquinolones sulphonamides/trimethoprim
	prostatits (often associated with UTI in male dogs)	sulphonamides/trimethoprim chloramphenicol	macrolides lincosamides fluoroquinolones
Respiratory tract	bacterial rhinitis	penicillin amoxicillin	sulphonamides/trimethoprim chloramphenicol
	tracheo-bronchitis	penicillin co-amoxiclav tetracyclines sulphonamides/trimethoprim	chloramphenicol
	pneumonia	co-amoxiclav sulphonamides/trimethoprim	β-lactam plus aminoglycoside chloramphenicol
	pyothorax purulent pleuritis	penicillin amoxicillin co-amoxiclav	lincosamides chloramphenicol sulphonamides/trimethoprim

Modified from Watson & Rosin.[7]

amoxicillin with clavulanic acid, spiramycin, clindamycin or metronidazole.[7]

Data on overall antimicrobial use

Data on overall use of veterinary antimicrobial formulations are available in various European countries but generally do not include specific figures on antimicrobial use in different species or groups of animals. An exception is the national surveillance programme on use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark (DANMAP 2002),[13] where antimicrobial use in different animal groups is inferred from pharmacy sales and use in veterinary practice. In Denmark in 2002, a total of 422 kg of antimicrobials were sold from pharmacies to pet owners with veterinary prescriptions (Table 2). Reporting of antimicrobial usage in pet animals is not required by veterinarians and this causes difficulties in the estimation of the total amount of antimicrobials used in these animals. Certain antimicrobial preparations for veterinary use (e.g. tablets and topical products) are mainly administered by veterinarians to pet animals. Based on data concerning consumption of such antimicrobial preparations, it is estimated that an additional 1500–2000 kg of antimicrobials were administered to pet animals in veterinary practice in 2002 (Vibeke Frøkjer Jensen, Danish Institute of Food and Veterinary Research, personal communication).

The total sales of veterinary antimicrobial formulations approved for use in pet animals in Sweden and Norway increased from 3% of all veterinary antimicrobial formulations in 1990 to 8% and 7% in 1998, respectively.[14] In the UK, therapeutic antimicrobials indicated for use in companion animal (dogs, cats and horses) represent approximately 6% of the total amount used in animals.[15] These figures suggest similar proportions of overall antimicrobial use accounted for by pets in different European countries. However, they are likely to be underestimates since they do not include drugs administered to pets by veterinarians and drugs that are licensed for use in human medicine or in food animals, which may be used for treatment of pet animals. Furthermore, such generalized data are not useful in evaluating trends in use of antimicrobial agents and resistance selection pressure for different antimicrobial classes. Sales figures reported as kilograms of active compound must be interpreted with caution, as they do not take into consideration the potency of the drug, the rate of absorption, the weight of the animal and the population size for each animal species. It is clear that the impact of antimicrobial use on the development of resistance can be properly assessed only by collecting data for individual antimicrobial classes and subclasses, taking into account the potency of each specific drug and the type of animal in which the drug is used.

The use of animal daily dosages (ADDs) has been recently adopted by the Danish national surveillance programme in order to enable standardization of drug dosage.[13] ADDs are defined for each therapeutic formulation as the daily dosage required for treating an animal of a certain weight and are calculated for each age group. The general principles for standardization of dosage are the same as those used to calculate defined daily doses (DDDs) in humans. Table 2 reports the overall

Table 2. Usage of antimicrobial agents in animals in Denmark measured by kg of active compound and animal daily dosages (ADDs) based on sales from pharmacies and feed mills

Animal group	Population size[a]	Standard weight (kg)[b]	Antimicrobial usage	
			kg	ADDs (1000s)
Pigs	12 732 035	weaners: 15 slaughter pigs: 50 breeders, suckling pigs: 200 age not given: 50	72 833	207 988
Cattle	1 798 118	calves: 100 heifers, steers: 300 cows, bulls: 600 age not given: 600	2046	2235
Poultry	20 579 918	all ages and species: 1 younger than 12 months: 25	405	21 025
Sheep	131 063	older than 12 months: 50 age not given: 50	20	25
Mink	ND	age not given: 1	766	40 550
Aquaculture	ND	age not given: 1	4251	ND
Other production animals[c]	ND	age not given: 1	79	4380
Horses	38 136	age not given: 500	138	9
Pet animals	1 200 000	age not given: 1	422	11 780
Species not given[d]			16 158	ND
Total			97 068	

Modified from DANMAP 2002.[13] ND, not determined.
[a]Data provided by Statistics Denmark.[93]
[b]For some species age group is not given. Thus standard weights were set as 1 kg animal and ADDs were reported as 'kg animal treated'.
[c]Including ADD for intramammary administration independent of animal weight.
[d]For use in veterinary practice (14 820 kg) or for production animals when species are not given at the pharmacies.

antimicrobial use expressed in ADDs for each group of animals in Denmark in 2002. Comparison amongst different groups indicates that the antimicrobial selective pressure exerted on pet animals (11 780 000 ADDs) is markedly lower than in pigs (207 988 000 ADDs), lower than in poultry (21 025 000 ADDs) and higher than in cattle (2 235 000 ADDs). These figures are based on sales from pharmacies and feed mills, and exclude a large amount of antimicrobials administered to pet animals in veterinary practice. Furthermore, it should be noted that the selective pressure exerted on a population, animal as well as human, depends on the amount of antimicrobials used but also on the size of the population under study. This aspect is particularly important when comparing data on antimicrobial usage between food animals and pet animals in Denmark, since the populations of poultry and pigs substantially exceed the size of the pet animal population (Table 2).

Data on use of different antimicrobial classes

Qualitative differences in the use of antimicrobials occur between different countries, even within the same geographical area. Odensvik *et al.*[14] reported the amounts (kg of active compound) of oral antibacterial drugs approved for use in dogs and cats sold by wholesalers to pharmacies in Sweden and Norway between 1990 and 1998. The most heavily sold antibacterial preparations in Sweden were β-lactams, although the relative use of these antimicrobials fell from 84% in 1990 to 63% in 1998. The use of sulphonamides, macrolides, lincosamides and fluoroquinolones increased by over 100% between 1992 and 1998. In Norway, sulphonamides/trimethoprim represented the vast majority of veterinary preparations prescribed for dogs and cats, with oscillations between 77% and 90% during the study period.[14]

According to DANMAP 2002,[13] the usage of cephalosporins in animals in Denmark increased by 27% from 302 kg in 2001 to 385 kg in 2002, mainly due to increased usage in pet animals. A large proportion of the preparations containing aminopenicillins with clavulanic acid, cephalosporins and fluoroquinolones used in veterinary practice are administered to pet animals. If pharmacy sales to pet owners are included (Table 3), the total amounts of aminopenicillins with clavulanic acid, cephalosporins

and fluoroquinolones used in pet animals in 2002 were estimated to be 133, 247 and 20 kg, respectively, which correspond to 88%, 64% and 21% of total veterinary use of these antimicrobials (Vibeke Frøkjer Jensen, Danish Institute of Food and Veterinary Research, personal communication). An increasing trend in the prescription of cephalosporins was noted in Sweden since 1997, when this class of antimicrobials was introduced for use in pets.[16] This trend was probably due to increased prescription of commercial preparations authorized for veterinary use instead of off-label prescription of products authorized for humans, but could also reflect an actual increase in the use of cephalosporins in small animal practice. A similar increase was also observed in the sales of aminopenicillins, broad-spectrum penicillins that are often commercialized in the form of tablets and therefore sold mainly for use in pet animals.[16]

These data indicate an increasing use of certain broad-spectrum antimicrobials in small animal veterinary practice and a relatively higher use than in animal production. The tendency of veterinarians to prescribe broad-spectrum antimicrobials can be explained by the fear of a possible treatment failure using first-line antimicrobials such as penicillins and sulphonamides. Treatment failure is detrimental to pet health, and discourages pet owners who must pay for additional consultations and antimicrobials while questioning the effectiveness of further treatment. Pharmaceutical companies may also have some responsibility by exerting marketing pressures on veterinarians for the use of newer drugs in cases where older drugs are still effective.[17]

Antimicrobial resistance in bacteria from dogs and cats

Trends of antimicrobial resistance in pet animal pathogens

The consequences of antimicrobial use in small animal veterinary practice do not differ from those observed in human medicine and animal production. The amounts and patterns of use determine the rate at which resistance develops and spreads in the exposed bacterial population. Various longitudinal retrospective studies in Europe and the United States have reported an increase in the prevalence of antimicrobial resistance in different

Table 3. Antimicrobials (kg of active compound) sold from pharmacies and feed mills in Denmark in 2002 by animal group

Animal group	Amin	Ceph	Fluor	Linc	Macr	Pen 1	Pen 2	Sul/tri	Tet	Others
Pigs	9502	43	42	2676	14 804	11 141	6825	5368	22 248	182
Cattle	284	3	3	17	70	485	234	214	341	47
Poultry	5	–	6	1	42	<1	281	50	22	2
Sheep	1	–	<1	<1	1	3	9	3	2	<1
Mink	167	–	1	45	104	<1	375	38	36	<1
Aquaculture	2	–	<1	–	–	1	49	2964	3	1059
Other prod. animals	9	1	<1	2	4	24	18	17	4	<1
Horses	15	<1	<1	<1	<1	17	1	101	2	<1
Pet animals	102	77	5	8	20	21	73	80	24	11
Species not given	2038	261	42	179	1157	5729	1946	3059	1737	267
Total	12 126	385	97	2928	16 203	17 421	10 026	11 894	24 420	1569

Modified from DANMAP 2002.[13] Amin, aminoglycosides; Ceph, cephalosporins; Fluor, fluoroquinolones; Linc, lincosamides; Macr, macrolides; Pen 1, β-lactamase-sensitive penicillins; Pen 2, penicillins with extended spectrum, cloxacillin and co-amoxiclav; Sul/tri, sulphonamides/trimethoprim; Tet, tetracyclines.

bacterial species isolated from pet animals. In the UK, Lloyd et al.[18] examined antimicrobial susceptibility in 2296 isolates of coagulase-positive staphylococci from canine infections (predominantly *S. intermedius*) of the skin, ears and mucosae in referral practice over the period 1980–1996. Resistance to penicillin increased from 69% to 89%, whereas oxytetracycline resistance remained constant at about 40%. A peak in the prevalence of resistance to erythromycin and lincomycin (20%), and to sulphonamides/trimethoprim (15%) was observed amongst staphylococcal isolates from 1987 to 1989, followed by a slight decrease in the following years. Normand et al.,[19] also reporting from the UK, found significant rising trends for amoxicillin, co-amoxiclav and streptomycin resistance in *Escherichia coli*, and for erythromycin resistance in *Staphylococcus* species obtained from clinical cases in a small animal hospital between 1989 and 1997. There was an equivocal rising trend for resistance of *Staphylococcus* species to cefalexin. In France, a study conducted at the National Veterinary School in Nantes showed that the proportion of multiresistant (≥3 drugs) strains of *S. intermedius* increased from 11% in the period 1986–1987 to 28% in the period 1995–1996.[20] Similarly, a significant temporal increase in resistance to penicillin, neomycin, sulphonamides, co-trimoxazole and erythromycin was reported amongst *S. intermedius* isolated from dogs in Switzerland.[21]

National monitoring programmes on antimicrobial resistance in animals generally do not provide data on companion animals. The only exceptions are the surveillance programmes in Sweden (SVARM)[16] and Norway (NORM-VET).[22] SVARM has reported data on antimicrobial resistance in canine isolates of *S. intermedius* from skin infections and *E. coli* from UTI since 1992. Such data indicate a common occurrence of *S. intermedius* isolates resistant to macrolides, lincosamides and tetracyclines (18–30%) and *E. coli* isolates resistant to ampicillin, streptomycin, tetracycline and sulphonamides/trimethoprim (11–24%).[16] In Norway,[22] canine isolates of *S. intermedius* from skin infections and otitis externa were analysed in 2002, revealing a high prevalence of resistance to fusidic acid (59%) and tetracycline (53%), which concomitantly often were associated with penicillin resistance (33%). There was a sharp increase in the levels of resistance to fusidic acid and tetracycline compared to NORM-VET 2000 (46% and 36%) and even more compared to data for the periods 1986–1987 (1% and 20%) and 1993–1994 (45% and 28%) from previous studies in Norway.[23] In both countries, high prevalences of penicillin resistance (72–86%) have been reported in the last 10 years for canine isolates of *S. intermedius*, indicating that penicillinase-sensitive penicillins are not efficient for treatment of canine pyoderma.

A study carried out in Canada on large numbers of clinical canine isolates of *S. aureus* (n = 867) and *S. intermedius* (n = 1339) indicated different trends of antimicrobial resistance depending on species, site of isolation, sex and age of the animal.[24] For example, *S. aureus* isolates were significantly more resistant to cloxacillin and erythromycin compared with *S. intermedius* isolates. Independent of their species, ear isolates were markedly more resistant to cefalothin compared with isolates from other body sites. The authors concluded that the observed variation of resistance patterns complicates the empirical selection of antimicrobial agents, emphasizing the need for bacterial culture with species identification and susceptibility testing of site-specific isolates in order to choose appropriate antimicrobial therapy.[24]

Although the authorization of fluoroquinolones for use in small animal veterinary practice is quite recent in Europe (mid 1990s), resistance to this antimicrobial class is emerging in pet animal bacteria. The licensing of fluoroquinolones for use in small animals has been associated with increasing resistance to these antimicrobials amongst *Pseudomonas* isolates from otitis externa in dogs,[11] *S. intermedius* isolates from pyoderma in dogs,[25] and *E. coli* and α-haemolytic *Streptococcus* spp. from canine UTI.[26] Lloyd et al.[25] reported a prevalence level of 0.9% fluoroquinolone resistance amongst 858 *S. intermedius* isolates from dogs examined between 1996 and 1998. A higher prevalence of fluoroquinolone resistance is observed amongst *S. intermedius* from dogs in Sweden, where constant resistance prevalences (8–12%) have been reported between 1992 and 2002.[16] Although enrofloxacin is still efficient in the treatment of canine infections caused by *S. intermedius*, cases of treatment failure have been reported for dogs with recurrent deep pyoderma.[9,27] A further increase in the prevalence of fluoroquinolone resistance is expected to occur in coming years as a consequence of the rising use of enrofloxacin and other fluoroquinolones in small animal veterinary practice. *In vitro* studies indicate that prolonged or inappropriate use (e.g. low dose or pulse-dose) might favour development of resistant strains *in vivo*, particularly when long-term treatment is required.[28]

Association between antimicrobial use and antimicrobial resistance in pet animal pathogens

Some studies indicate a possible association between antimicrobial use and emergence of antimicrobial resistance in pets. For example, the increased use of lincosamides observed in Sweden during the period 1990–1998 corresponded with a parallel increase in lincosamide resistance among staphylococcal isolates from canine pyoderma.[29] The study also showed that resistance to macrolides, lincosamides, fusidic acid, tetracycline and streptomycin was significantly more common in isolates from recurrent cases than from first-time cases. These differences were probably due to the selective pressure exerted by previous antimicrobial treatment in recurrent cases of pyoderma. Another study conducted at a veterinary teaching hospital in the USA showed an increase in enrofloxacin resistance amongst *E. coli* isolates from dogs with UTI.[30] The increase in enrofloxacin resistance observed in 1997 followed a marked increase in enrofloxacin usage at the veterinary hospital from 1334 g in 1995 to 2358 g in 1996. The increased prevalence of enrofloxacin-resistant *E. coli* in urine of dogs with UTI was not attributable to a single enrofloxacin-resistant clone but rather to acquisition of resistance in genetically unrelated strains.

Prescott et al.[17] demonstrated fluctuations in levels of resistance amongst coagulase-positive staphylococci isolated in a veterinary teaching hospital in Canada during 1984–1998 and concluded that these reflected changing uses of different classes of antimicrobials in the hospital. They also demonstrated an increase in the prevalence of multiresistant *Enterococcus* spp. associated with urinary tract infections. Nosocomial infections with multiresistant Gram-negative bacteria such as *Acinetobacter baumannii*,[31] *E. coli*[32] and *Salmonella enterica* serovars[33] have been recently recognized in hospitalized dogs, especially in intensive care units. The emergence of multiresistant nosocomial pathogens in dogs is likely to reflect the abundant use of broad-spectrum antimicrobials in intensive care units at veterinary hospitals.

Occurrence of antimicrobial-resistant human pathogenic bacteria in pets

Household pets can be reservoirs of bacterial species and resistance genes of clinical importance in humans, like methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE) and multidrug-resistant *Salmonella* Typhimurium DT104. The occurrence of MRSA in a dog was first described in 1994,[10] but more widespread occurrence was not reported until 1999, including cases in the United States,[34] in the UK,[35] and in South Korea.[36] Canine infection has been subsequently reported in Canada[37] and in the Netherlands.[38] MRSA was first described in healthy cats by Lilenbaum *et al.*[39] in a study of the staphylococcal flora of 148 cats in Brazil. In the UK, recent reports of MRSA isolation from small animals[40,41] suggest that MRSA is much more prevalent in small animal veterinary practice than has been hitherto recognized. MRSA carriage can be a hazard to owners, especially if they have increased susceptibility to infection. However, it should be noted that pet animals appear to become reservoirs of MRSA through exposure to infected humans and thus probably do not constitute the primary reservoir for MRSA but act as a small secondary reservoir.

Methicillin resistance is also recognized in *S. intermedius*, coagulase-negative staphylococci and coagulase-variable species such as *Staphylococcus schleiferi*. Lilenbaum *et al.*[39] described the occurrence of methicillin-resistant *S. intermedius* and coagulase-negative staphylococci in clinically healthy Brazilian cats. In the USA, Frank *et al.*[42] reported the isolation of methicillin-resistant *S. schleiferi* from 11 dogs with recurrent pyoderma. Although infection in man is uncommon, *S. schleiferi* is increasingly recognized as the cause of hospital-acquired infections.[43] Thus, canine infections or carriage of such organisms represent a potential hazard for people in contact with dogs.

VRE are another important cause of concern in human medicine due to the importance of vancomycin for treatment of nosocomial infections caused by multiresistant Gram-positive bacteria. In order to preserve the effectiveness of vancomycin in human medicine, the use of avoparcin as a growth promoter in animal production was banned in the EU in 1997 because it was liable to induce resistance to vancomycin (Commission Directive 97/6/EC of 30 January 1997). Recent studies in Europe have documented a relatively high occurrence (7–23%) of VRE (mainly *Enterococcus faecium*) in dogs living in contact with farm animals,[44] as well as in dogs living in urban areas.[45] A study conducted on healthy animals in Spain revealed a higher prevalence of VRE in pets (23%) compared with pigs (4%).[46] The occurrence of VRE has also been reported in New Zealand[47] and in the USA,[48] where the occurrence of VRE has not been documented in food animals. Canine VRE isolates generally contain the *vanA* resistance gene cluster and exhibit multiple resistance to other antimicrobials such as macrolides [*erm*(B) gene], tetracycline [*tet*(M) gene] and aminoglycosides [*aac(6′)-aph(2″)* genes].[45,46,48] Thus, although vancomycin is normally not used in small animal veterinary practice, VRE are likely to be co-selected by the use of such antimicrobials.

The occurrence of multiresistant *S.* Typhimurium phage type DT104 in cats has been reported in the UK,[49,50] in Germany,[51] and in the USA.[52] These strains are usually resistant to at least five antimicrobials, including ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracycline. A study on a large number (*n* = 6589) of diarrhoeic dogs in the Netherlands revealed the presence of *Salmonella* in 69 (1%) animals tested.[53] Amongst the 80 canine isolates analysed in this study, 53% were resistant to cefalexin, 37% to tetracycline, 14% to amoxicillin with clavulanic acid, 6% to sulphonamides with trimethoprim and 4% to enrofloxacin. Recently, the occurrence of *Salmonella* serovars has been demonstrated in animal-derived dog treats.[54] The study indicated that animal-derived dog treats could be a potential source of animal and human infections with *Salmonella*, including multidrug-resistant *S.* Typhimurium DT104 with the characteristic penta-resistance phenotype.

Transmission of antimicrobial-resistant bacteria between pet animals and humans

The close contact between household pets and humans offers favourable conditions for the transmission of bacteria by direct contact (petting, licking, physical injuries, etc.) or through the domestic environment (contamination of food, furnishings, etc.). Children are at greater risk than adults because of their closer physical contact with cats and dogs as well as with household environments contaminated by pets (floors, carpets, etc.). Horizontal transfer of resistance genes may occur in the opposite direction to bacterial transmission. For example, human bacteria transmitted to pet animals may acquire resistance genes from the commensal flora of pet animals and may be selected by antimicrobial treatment in these animals. Furthermore, even in the case of human-to-pet transmission, pet animals contribute to the propagation of acquired resistant bacteria by faecal shedding, therefore enhancing their spread in the human population and in the environment.

Transmission of resistant human pathogens between pet animals and humans

Most information available in the scientific literature on bacterial transmission between pets and humans relates to human pathogenic bacteria. Dogs and cats are potential sources of various zoonotic bacteria that can be transmitted via faecal–oral transmission, physical injuries (i.e. dog bites and cat scratches) or vectors (i.e. ticks).[55] Pet-associated zoonoses are usually sporadic and their frequencies are not easily determined because of the difficulty in recognizing and validating disease transmission from pets. Transmission of antimicrobial-resistant bacteria from pet animals to humans represents a particular risk when the strains harbour resistance genes of clinical relevance in human medicine. Bite wounds in humans present opportunities for the transfer of resistant organisms from cats and dogs to man and can have serious consequences unless the susceptibility of infecting organisms is determined and appropriate therapy given.[12,56]

At least 1% of annually-reported salmonellosis cases in the USA are likely to be associated with companion animals.[57] Transmission of *S.* Virchow from two household dogs to an infant was substantiated by pulsed-field gel electrophoresis (PFGE),[58] a highly discriminatory method for bacterial typing. In 1999, outbreaks of multiple-resistant *S.* Typhimurium associated with small animal veterinary facilities were reported in Idaho, Minnesota and Washington.[52] The strains causing these outbreaks exhibited the aforementioned penta-resistance phenotype typical of *S.* Typhimurium DT104. In all outbreaks, illness in animal health care workers and pet owners followed illness in

cats attending the veterinary facilities. Feline and human isolates from the outbreaks in Minnesota and Washington were indistinguishable by PFGE. Direct evidence of zoonotic transmission could not be demonstrated in the Idaho outbreak because the cats died before the onset of clinical symptoms in humans and stool specimens were not cultured from these animals. However, the 10 humans involved in this outbreak were infected with the same PFGE type and had no common exposure outside the veterinary facility where they worked.[52]

It has been estimated that approximately 6% of enteric campylobacteriosis is transmitted from pet animals.[59] Various studies, including case–control studies, indicate that pet ownership is a significant risk factor for *Campylobacter jejuni* infections in humans, particularly young children.[59–63] The same PFGE profiles have been identified in *C. jejuni* isolates from dogs, cats and humans living in different geographical regions,[64] suggesting the possible existence of clones able to adapt to different hosts. Direct evidence of transmission of *C. jejuni* between human patients and pets living in the same households has been shown based on amplified-fragment length polymorphism (AFLP)[65] and PFGE.[64] In the latter study,[64] a 2-year-old girl and her dog were found to share the same fluoroquinolone-resistant strain. Neither of them had ever been treated with fluoroquinolones, indicating that the strain was not selected by previous exposure of any of the two individuals to quinolones but that it was acquired from an external source. Even though the dog was fed a commercial diet, acquisition from a common food source was possible, since the dog was occasionally given human food scraps.

Various studies have documented transmission of MRSA or methicillin-susceptible *S. aureus* between human patients, their family members and dogs living in the same household.[66–69] However, the typing methods used in two of these studies[66,67] were not sufficiently discriminatory to draw inference on the genetic relationship of human and pet isolates. MRSA are more likely to be transmitted from humans to pets, as indicated by the frequent recovery of MRSA from pets living with human patients or medical staff. However, these animals can play an important role as reservoirs of MRSA within family households. Recurrent MRSA infection has been reported in a patient with diabetes, who had an infected wound, and his wife.[69] PFGE analysis indicated that the MRSA infecting the two owners was the same as that which could be cultured from the family dog. The human infections were eliminated and ceased to recur after successful removal of the MRSA from the dog's nares.

E. coli strains causing UTI in dogs are phylogenetically related to human extraintestinal pathogenic *E. coli* (ExPEC) and exhibit virulence genes that are characteristic of human clinical isolates.[70,71] Over 15% of environmental canine faecal deposits have been found to contain *E. coli* strains closely related to human virulent ExPEC clones.[72] Although direct evidence of transmission has not been documented yet, these data indicate that canine faeces could represent an important reservoir for the acquisition of ExPEC by humans. Dogs and cats have also been addressed as a potential source of VRE for hospitalized patients based on the strong similarity of AFLP patterns amongst human clinical isolates and pet isolates.[73] In New Zealand, a vancomycin-resistant *Enterococcus faecalis* isolate from mastitis in a dog was shown to have the same PFGE profile found in poultry and human isolates, therefore supporting the hypothesis of a clonal lineage in this country.[47] A recent study in the USA[48]

showed that a vancomycin-resistant *E. faecium* isolate from a dog with UTI infection contained a specific type of Tn*1546*-like element—the transposable element associated with *vanA*—that has only been described in human clinical VRE isolates unique to the USA, suggesting a possible exchange of this transposable element between human and canine strains.

Transmission of resistant commensal bacteria between pet animals and humans

Little is known about the possible exchange of commensal bacteria between pets and humans living in contact. The current knowledge on this subject is mainly limited to the transmission of *S. intermedius*, a commensal, but also pathogen of dogs and cats.[74] *S. intermedius* appears to be common in veterinary staff in constant contact with dogs and owners of dogs with atopic dermatitis.[75] The fact that *S. intermedius* is normally rare in humans[76,77] suggests dog-to-human transmission. Strains carried by humans generally correlate with strains recovered from their dogs.[78,79] Owners of dogs affected by deep pyoderma frequently carry the same strains occurring in their dogs and such strains can be resistant to a variety of antimicrobial agents, including penicillins, fusidic acid, macrolides, lincosamides, tetracyclines and chloramphenicol.[80] Since antimicrobial resistance in canine *S. intermedius* strains is common,[81] there is a risk that resistance genes are transferred from *S. intermedius* to human pathogenic staphylococci.

Gene transfer between bacteria from pet animals and humans

Unlike most diseases, antimicrobial resistance can be transmitted from one host to another by low bacterial numbers. In theory, even a single bacterial cell may be able to transfer resistance genes to the bacterial flora of the recipient host. Resistance gene transfer between bacteria of pet animal and human origin may take place in or on humans and pet animals, or through the environment. Resistant bacteria selected by antimicrobial use in pet animals can reach a human host and exchange their resistance genes with bacteria resident in or on the human host, or vice versa (Figure 1). Alternatively, bacteria of pet animal and human origin can meet outside their hosts, for example in the household environment or in sewage. In any case, transfer of resistance genes may involve pathogenic species as well as members of the normal flora originating from the two hosts. The location of resistance genes on plasmids and other mobile elements enables a wide distribution, which often is not even limited by species or genus. The wider a resistance gene is disseminated among bacteria from humans, animals, plants or environmental sources, the larger are the options for bacteria from humans to acquire this resistance gene.

Members of most classes of antimicrobials, such as tetracyclines, macrolides, lincosamides, chloramphenicol, aminoglycosides, penicillins and cephalosporins, have been used for long periods in both human and veterinary medicine, and the same resistance genes have been identified in bacteria from humans and pet animals. Although the occurrence of the same resistance gene in bacteria from different sources suggests the transfer of the resistance gene, in particular if the gene is associated with a mobile genetic element, it is often difficult, if not impossible, to
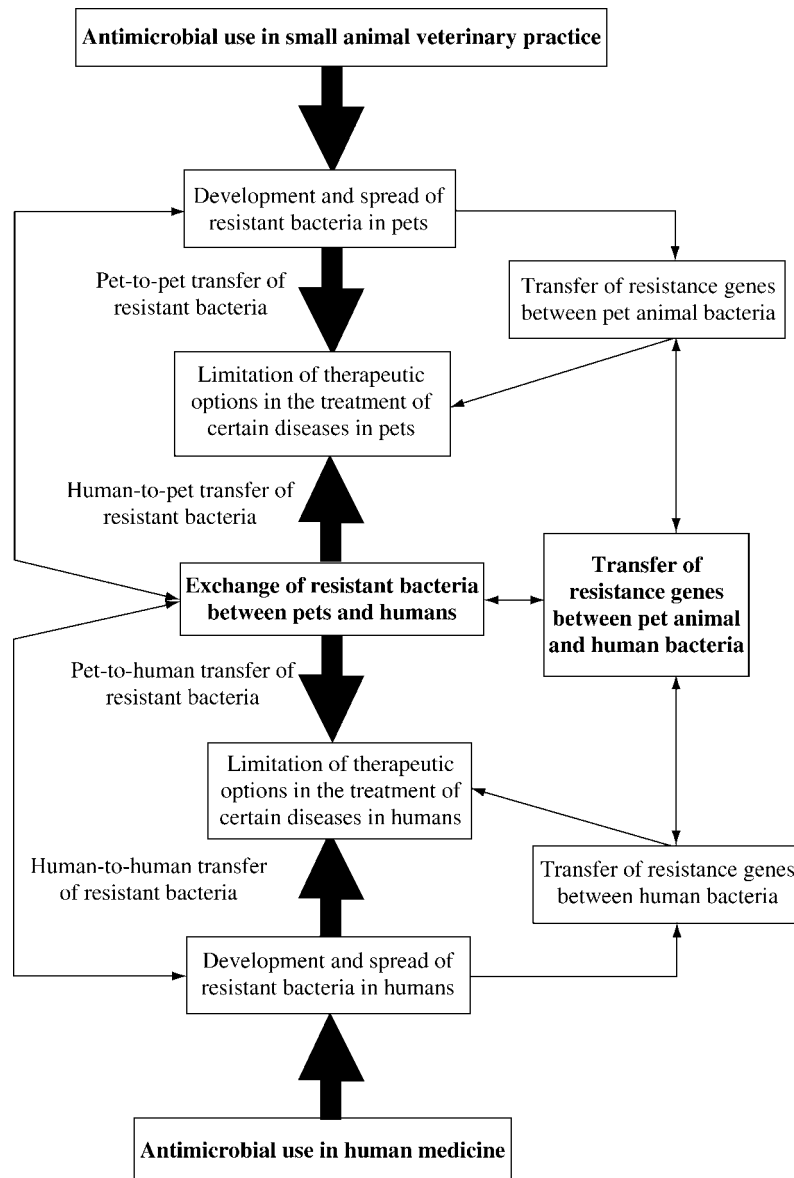
Figure 1. Schematic representation of the consequences of antimicrobial use in small animal veterinary practice and human medicine on exchange of resistant bacteria and transfer of resistance genes between pet animals and humans.

determine where the resistance gene has developed first and in which direction(s) transfer has taken place since then. Pet-to-man transfer of antimicrobial resistance genes is even more difficult to prove than transmission of resistant bacteria from pets to humans. While in the latter case molecular typing of the strains in question will provide valuable information to confirm or exclude the close relationship between the resistant strains isolated from pet animal and human hosts, the detection of the same resistance gene in bacteria from both sources can be considered as a hint, but not as evidence for the transfer of this gene from a specific donor source.

For example, the sulphonamide resistance genes *sul1* and *sul2*, the streptomycin resistance genes *strA*, *strB* and *aadA2*, and the tetracycline resistance genes *tet*(A) and *tet*(B) have been shown to occur in *E. coli* strains from UTI in dogs and cats.[82] However, all these genes are associated with mobile genetic elements such as transposons, integrons or plasmids. Therefore, it is not surprising that the same resistance genes can also be found in *E. coli* strains from humans and other animals,[82,83] as well as in other enteric bacteria such as *Salmonella* Typhimurium.[51] The genes *sul2*, *strA*, *strB* and *tet*(B) have even been identified in distantly related bacteria such as *Pasteurella multocida* and other members of the family *Pasteurellaceae*,[84] indicating that such genes are not only present in bacteria of the urinary and intestinal tract, but also in those of the respiratory tract.

The genetic basis of antimicrobial resistance in *S. intermedius* is the most extensively studied amongst bacteria from pet animals. Small plasmids mediating resistance to tetracyclines via *tet*(K), macrolides and lincosamides via *erm*(C) and chloramphenicol via cat_{pC221} have been detected in a few canine *S. intermedius* isolates.[85] These plasmids closely resemble the *tet*(K)-, *erm*(C)- or cat_{pC221}-carrying plasmids previously described in other staphylococci of human or animal origin.[81,86] However, the vast majority of the *S. intermedius* strains appear

328

Review

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