Antimicrobial susceptibility trends in small animals

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The determination of the number of pets worldwide is very difficult, many countries do not have dog licences and in countries that require a licence, this figure does not represent the entire population of pets in that country. In 2016-2017, in the United States (US), 105 million households were reported to have dogs, with multi dog ownership increasing. There were 59 million reported cat owners. The top four pets in the European Union (EU) in 2017 included: cats, dogs ornamental birds and small mammals (respectively 74.4m, 66.4m, 35.4m and 22m). Pets are becoming more integrated into human lives, many now living indoors, sharing sleeping space with owners and owners becoming more affectionate towards their pets, this can allow for cross contamination of infectious organisms including: bacteria, viruses, parasites and fungi. Antimicrobial resistance (ARM) has been declared a global threat to public health and to jeopardise the significant health care gains to society in the past decades. With reported research on genetic similarities in AMR susceptibility profiles between organisms isolated from humans and household pets, this is causing concern. With the majority of veterinary care privately funded and when antibiotics are cheaper than diagnostics many animal owners are reluctant for veterinary personnel to engage in diagnostic testing for microorganism identification and antibiotic susceptibility tests and instead seek a prescription antibiotic.

The most prescribed antibiotics in small animal practice fall under the WHO classification of critically (CI) and highly important (HI) antibiotics and can include: ampicillin (CI), amoxicillin-clavulanic acid (CI), cephalexin (HI), clindamycin (HI), enrofloxacin (CI) and marbofloxacin (CI), framycetin (CI). The top diseases which are encountered by veterinarians in small animals include ear and urinary tract infections (UTI). As the number of antibiotics becoming obsolete due to resistance exceeding the number of new therapies being approved, emphasis needs to be continually enforced with worldwide agreement on: reduced use of antibiotics, tackling substandard and falsified antimicrobial products, providing incentives to the biotech industry to develop vaccines, phage therapies and new drugs. Veterinarians can also contribute to the worldwide effort to address ARM.

Keywords: Companion pets, Antimicrobial susceptibility, Small animals

1. Introduction

Small animals also called companion animals can include dogs, cats, pet rabbits, a small rodent, birds, homing pigeons aquarium fish and horses. In addition novel agriculture animal's e.g. small pigs can now be included. The determination of the number of pets worldwide is very difficult, many countries do not have dog licences and in countries that require a licence, this figure does not represent the entire population of pets in that country. In 2016-2017, in the United States (US), 105 million households were reported to have dogs, with multi dog ownership increasing, there were 59 million reported cat owners [1]. The top four pets in the European Union (EU) in 2017 included: cats, dogs, ornamental birds and small mammals (respectively 74.4m, 66.4m, 35.4m and 22m) [2]. China has recently emerged as third in the world for dog ownership with 27.4m dogs or 7% or urban household owing a dog, cat ownership amounted to 2% (58.1m cats) and is the second in global cat ownership. The pet industry is rapidly outpacing the US market [3].

The European Union has provided 40 years of animal welfare with directives and regulations from the first legislation on protection of animals in slaughterhouses in 1974 to the landmark inclusion of animals as sentient beings in the Treaty of Amsterdam in 1999. Its newest regulation abbreviated to the 'Animal Health Law' 2016/42 9 [4], is in line with the "one health" policy approach to safeguard animal health and its link to human health. Many argue that this does not go far enough as regards the welfare of dogs and cats which can still be moved without restriction around Europe and unregistered and illegal breeding houses lack sufficient controls. In the EU member states, there is strong legislating on the licencing of veterinary medicines and control of their distribution with antimicrobials administration to animals, must be prescribed by a veterinarian in accordance with European Commission directive 2001/82/EC, '*Community code relating to veterinary medicinal products'* amended in 2004 by Directive 2004/28/EC [5]. In addition, all antibiotic products carry label/package leaflet warnings, relating to the responsible use of antibiotics. There are multiple situations for limiting antimicrobial usage under a variety of voluntary, regulatory and legal policy frameworks going back to the first feed additive directive 70/524 in 1970, that was amended in 1997 [6]. As of 1 January 2006, all antimicrobial growth promoters were phased out in the EU [7].

In the US, veterinary drugs are restricted by federal law, and can only be prescribed on the order of a licensed veterinarian under the Food, Drug, and Cosmetic Act. Section 503 [(f)(1)(A) [8]. Veterinary feed drugs comes under section 504 of the same act. The law requires that the drug sponsor label such drugs with the statement: "*Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian*'. The control of drugs in the US come under different jurisdiction's from the department of health and human series, department of justice and the office of national drug control policy. In non-developed countries drugs are easily obtained without control measures in place.

The major aims of these strategies and legislative regulations are to encourage veterinarians to prescribe prudently and responsibly and furthermore to reduce antimicrobial use. Decisions made by veterinarians in treating animals reflect an ethical requirement to improve and maintain animal health.

1.1 Important Antimicrobial agents

The World Health Organisation (WHO) has classified antimicrobials into different classes depending on their important to human medicine (**Table 1**). Three group of antimicrobials in the Critically Important Antimicrobial (CIA) grouping are used in both animals and human medicine, they are: erythromycin, ampicillin and colistin. Some of the CIA drugs have prioritization criteria (P1, P2, and P3) and are considered the highest priority CIA's. The P1 drugs are for treating bacterial diseases for which the antimicrobial class is the sole or one of few alternatives to treat serious infections in humans. P2 drugs used in high frequency may favour selection of resistance in serious infections or in care settings. The P3 drugs when used to treat infections in people for which their evidence of transmission of resistance bacteria or resistance genes from non-humans [9].

The carryover between drug use in humans and humans is important, as it is estimate that more than 6 out of every 10 known infectious diseases and 3 out of every 4 new or emerging infectious diseases are spread from animals to humans [10]. The method of contacting such infections is by: direct contact through bodily fluids (saliva, blood, urine, mucous, faeces) from touching or petting. Indirect contact is from surfaces or objects contaminated by the animal e.g. soil, plants, pet food and pet water dishes. Other methods include vector borne e.g. bites from mosquitos, ticks and fleas and food borne diseases from eating contaminated food.

Table 1 World health Organisation list of critically important antimicrobials [9]

Aminoglycosides	Gentamycin
Ansamycins	Rifampicin
Carbapenems and other penems	Meropenem
Cephalosporins (3rd, 4th & 5th generation)	Ceftriaxone, cefepime, ceftaroline
Glycopeptides	Vancomycin
Glycylcyclines	Tigecycline
Lipopeptides	Dapomycin
Macrolides & ketolides	Erythromycin*, telithromycin
Monobactams	Aztreonam
Oxazolidinones	Linezolid
Penicillins (natural, aminopenicillins, and antipseudomonal)	Ampicillin*
Phosphonic acid derivatives	Fosfomycin
Polymyxins	Colistin*
Quinolones	Ciprofloxacin
Drugs used solely to treat tuberculosis or other mycobacterial diseases	Isoniazid

- Drugs used in both human and animals

The importance of the emerging antimicrobial resistance globally in animals, humans and the environment was highlighted in the G20 leader's Summit meeting in Hamburg, Germany, in 2017 and again reiterated in the Buenos Aires, Argentina Summit meeting in July 2018 [11], which emphasised combatting antimicrobial resistance (AMR) in a 'One Health' approach. One Health (formerly called One Medicine), focus of combating health measures in humans and animals by encouraging cooperation between physicians, veterinarians, other professionals on a global platform [12,13]. The ARM industry alliance has produced a report and activities to engage industry to target the ARM challenges [14].

Antibiotic stewardship was initially established to focus on human antibiotic use [15], to reduce and change the way antimicrobial are used. Their inappropriate use in humans and much of antibiotic use in animals is unnecessary, with more kilograms of antibiotics sold in the US for food-producing animals than for people [16]. The commitment to always use antibiotics appropriately and safely—only when they are needed to treat disease, and to choose the right antibiotics and to administer them in the right way in every case—is known as antibiotic stewardship. Changing people's behaviours is not easy. Four factors influencing antimicrobial prescribing behaviours by Dutch companion animal veterinarians was found to be (i) veterinarian-related factors (i.e. experience and habits), (ii) patient-related (i.e. owner- and pet-related factors i.e. aggressive animas and pet housing), (iii) treatment-related factors (i.e. alternative treatment options and antimicrobial-related factors) and (iv) contextual factors (i.e. professional interactions) [17]. A Delphi study in the UK [18], identified similar behavioural influences.

1.2 Zoonosis

Zoonoses is the term given to diseases that can spread between people and animals through close contact with the animals. An estimated 60% of know infectious human diseases have their source in animals [19]. Research or reports of companion animal associated zoonosis is not well represented in the literature. A significant number of known diseases transmitted from small animals, such as dogs and cats to affect humans are zoonotic, the main bacterial pathogens include Campylobacter spp., and Salmonella spp., infections, Leptospira spp., and Bartonella spp. [20]. Transmission routes such as dog bites and cat scratch disease (CSD), particularly bites to the face and hands can become infected and cats can cause deep puncture wounds that can carry serious pathogens in the mouth and claws. *Bartonella henselae* (Bh) is the etiologic agent in most cases of CSD [21].

There are many virus that have zoonotic potential and are of economic importance [22], with many more being identified each year in wild animals e.g. bats and rodents [23]. The EU Callisto project prioritised companion animal transmissible diseases for policy intervention in Europe [24, 25]. Five viral zoonotic agents of particular concern were identified, rabies and bluetongue virus were of concern in both dogs and cats and Crimean –Congo haemorrhage fever virus in dogs [24, 26]. The prioritised parasitic zoonosis diseases in dogs and cats, included Toxocara spp., Giardia spp., and *Leishmanis infantum* [27].

2. Antibiotic susceptibility testing methods

Traditional antibiotic sensitivity methodology was by a disk diffusion method, where paper disks with concentration of select antibiotics were embedded. The disks were applied to agar medium generally Muller Hinton or Iso sensitest agar. The methodologies were developed in the US by the Clinical and Laboratory Standards Institute (https://clsi.org/), for human infections. Most countries developed their own methodologies and breakpoints for antibiotic sensitivity determination [28]. Minimal inhibitors concentrations (MIC's) had to be determined for each organism and for each antibiotic, many years of work was carried and is still being developed. The EU has combined many of its member states methodologies into one system under the European Union committee on antimicrobial susceptibility testing EUCAST (www.eucast.ie), established in 1997. It is jointly organized by ESCMID (European society of clinical microbiology and infectious diseases), ECDC (European centre for disease prevention and control- www/ecdc.europa.eu) and the European national breakpoint committees. ESCMID have a study group for veterinary microbiology.

Susceptibility testing methodologies and breakpoints for veterinary isolate have only recently been developed. CLSI has been continually developing standard methodologies for the current recommended methods for disk diffusion susceptibility testing and the reference methods for determining MIC's of aerobic bacteria by broth macrodilution, broth microdilution, and agar dilution for veterinary use. The choice of antibiotics selected to test is based on the disease presenting. The interpretative standards or breakpoints have been established by CLSI and are different for each drug and bacterial species. The most recent update for performance standards include the CLSI-VET01 5th edition June 2018 [29] and the supplementary tables in VET08, 4th edition June 2018 [30].

The identification of microbial isolates has also advanced with the use of laser technologies and mass spectroscopy (MS). bioMérieus has advanced systems with the VITEK® MS, an automated mass spectrometry microbial identification system that uses Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) technology and IDEXX systems. The IDEXX antibiotic sensitivity testing methodology follows the MIC's, a quantitative method of susceptibility testing. The IDEXX microbiology result shows the identity of the organism and the sensitive pattern or antibiogram. The IDEXX The microbiological guide to interpreting minimum inhibitory concentrations (MIC), the IDEXX system in availed on line [31]. Other commercial systems include the Sensititre® Automated Reading and Incubation System 2x System (ARIS) https://www.thermofisher.com/order/catalog/product/V) and Bruker MALDI-TOF, which has acquired Merlin technologies to add AMR testing to its MALDI Biotyper ID platform (https://www.bruker.com).

3. Discussion

In a small study of ARM in dogs, (unpublished data), bacterial isolates have included *Enterococcus faecalis* isolated with resistance to tetracycline (HI) and doxycycline (HI), both highly important WHO classified antibiotics and with intermediate resistance to enrofloxacin and marbofloxacin both CI antibiotics. *Staphylococcus pseudintermedius* x5 canine patient isolates, with only one with intermediate resistance to gentamycin (CI). Two separate canine patients had *Pseudomonas aeruginosa* isolates with one isolate with intermediate resistance to enrofloxacin (CI). This early indication of AMR in canines needs to be monitored.

Enterococcus spp., are opportunistic nosocomial pathogens that do not cause illness in healthy humans or animals. However, they are isolated from urinary tract and central nervous systems that can lead to endocarditis and bacteremia. Canine ampicillin-resistant *E. faecium* was reported in 2008 [32]. In a more recent study of dogs (n=84) and cats (n =16) in Japan, resistance to erythromycin (44.2%) and oxytetracycline (44.2%), lincomycin (41.6%), gentamicin (31.2%) and kanamycin (31.2%) was observed [33].

S. pseudintermedius (SP) is most commonly associated with skin and soft tissue infections in humans but colonised 90% of health dogs, and is treated with topical or systemic antibiotics. Companion dogs have been associated with its transmission and recognized as a potential zoonosis of canine origin [34]. The scare of methicillin resistant staphylococcus (MRSA) outbreaks and infections and MRSP infections have not been realised as a major problem to date [35], but this can change.

In veterinary medicine, *P. aeruginosa* is associated with otitis and urinary tract infections in dogs. It is a serious pathogen in humans in particular in suffers of cystic fibrosis and is naturally resistant to most antibiotics [36]. It is rarely documented in veterinary studies, but in a French study resistant phenotypes were more frequent and multidrug resistance *P. aeruginosa* seemed to emerge in those suffering from otitis. The major resistance found in a study of 46 dogs, were to ciprofloxacin (29/46), gentamycin 26/46) and fosfomycin (22/46), [37], worryingly all WHO critical important antimicrobials (table 1).

The prescribing habits of veterinarians have been demonstrated in a number of studies and their actions do have an impact on the control of antimicrobial use. In a study in conjunction with SAVSNET (small animal veterinary surveillance network), in England and Wales [38], reported that 75% of antimicrobials prescribed were from the β-lactams group of antimicrobials, with clavulanic acid potentiated amoxicillin the most prescribed for dogs and cats (35% and 49% respectively), next were the lincosamides class of antibiotics (9%), this class includes lincomycin, clindamycin and pirlimycin, followed by the fluoroquinolones and quinolones (6%). In a study on dogs presenting with diarrhoea to the University of Liverpool small animal teaching hospital [39], showed 71% (*n*= 263) of canine patients were given antibacterial agents with amoxicillin-clavulanate, amoxicillin the principle agents prescribed and metronidazole a protozoal agent. In a more recent UK study clavulanic acid potentiated amoxicillin was the most frequently prescribed antimicrobial agent in dogs (28.6%), whereas cefovecin, a third generation cephalosporin, was the most frequently prescribed antimicrobial agent in cats (36.2%). Prescription of topical antimicrobial agents was more frequent in dogs (7.4%) than cats (3.2%), whilst prescription of systemic antimicrobial agents was more frequent in cats (14.8%) than dogs [40].

4. Conclusion

Antibiotic resistance is emerging and with increased monitoring and diagnostic in companion animals being undertaken data is now been reported more frequently so the scale of the problem has emerged. The one health approach to collaborations by participants in the fight against ARM might work. The frequency of pet travel and lack of control measures in many countries will increase ARM. Pharmaceutical active ingredients are currently excluded from EU environmental legislation and worldwide this situation need serious attention. The antibiotic industry waste pollution in water is a reservoir for antimicrobial resistant microorganisms.

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