Knowledge, Attitudes and Influencers of Pet-Owners Surrounding Antimicrobials and Antimicrobial Stewardship in North America

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Madeleine R. Stein

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Examiners' Names	Examiner's Signatures
Dr. J Trenton McClure, Supervisor	______________________________
Dr. Adam Ogilvie, Chair	______________________________
Dr. Etienne Cote	______________________________
Dr. Charlotte Pye	______________________________
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Abstract

The primary aim of this research project was to establish the current knowledge, attitudes and influencers (KAI) of North American pet-owners with respect to antimicrobial stewardship (AMS) and resistance (AMR). A secondary aim was to utilise a novel survey technique to identify what aspects of antimicrobial drug prescriptions pet-owners view as important for their animal. The project was divided into two parts, which are described in the two chapters below.

Chapter 2 explores the KAIs of North American dog-owners. Three populations were surveyed via an online questionnaire: dog-owners in the United States, dog-owners in Canada, and dog-owners recruited via educational social media (ESM). A novel study methodology (conjoint analysis) determined to what extent specific features (cost, method of administration, and importance in human medicine) influenced dog-owner decision-making when selecting between two antimicrobials. We determined that cost had the largest influence on a dog-owner's choice between two (otherwise similar) antimicrobials, accounting for 47% of the decision-making preference. Method of administration accounted for 31%, and drug importance in human medicine had the smallest influence (22%). All groups preferred low-cost medications that were administered once by injection. Canadian and US participants were more likely to prefer drugs that were "very important" in human medicine whereas ESM participants preferred drugs that were "not important."

In the descriptive (KAI) analyses, dog-owners were asked a series of closed-ended Likert questions. The majority (86%) of participants considered AMR to be important. In contrast, only 29% of dog-owners reported that antimicrobial use (AMU) in pets posed a risk to humans. This study determined that the dog-owners surveyed prioritise cost over all other features when their pets are prescribed an antimicrobial, despite considering AMR important.

Chapter 3 describes cat-owner understanding and priorities when their pet is prescribed an antimicrobial drug. Cat-owners were recruited and surveyed in the same manner as dog owners in chapter 2. Conjoint analysis was used to calculate what proportion each of the three features (cost, dosing frequency, and importance in human medicine) of a prescription influenced cat-owner preferences when choosing between antimicrobials for their cat. Method of administration (38%) and cost (37%) had a similar weight in owner decision-making. Drug importance in human medicine had the smallest impact on the decision-making process (25%). The most desirable drugs were low-cost, single injection medications that were “very important” in human medicine for the US and Canadian groups. Conjoint analysis for the ESM group was not available. Analysis of cat-owners’ KAIs revealed that 86% reported AMR to be important in human medicine. However, only 28% stated that AMU in pets may be a risk to humans. This study demonstrates that North American cat-owners are equally concerned by cost and ease of drug administration. Cat-owners appear to have low levels of understanding of AMR in pets and view it as lower priority when their animal is prescribed an antimicrobial medication.

Our work indicates knowledge of AMR in human and veterinary medicine is limited. Education and inclusion of pet-owners is likely to be an important component of future AMS efforts.

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List of Abbreviations

AGP	Antimicrobial growth promoter
AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
AMU	Antimicrobial use
CDC	Centers for Disease Control and Prevention
CIA	Critically important antimicrobial
ESM	Educational social media
HAI	Healthcare-associated infection
KAIs	Knowledge, attitudes, and influencers
KAPs	Knowledge, attitudes, and practices
LMICs	Low- and middle-income countries
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSP	Methicillin-resistant *Staphylococcus pseudintermedius*
UK	United Kingdom
USA	United States
WHO	World Health Organisation

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Table 3.4. Summary of the number and proportion of participants in a survey of knowledge, attitudes and influencers of cat owners in North America around antimicrobials and antimicrobial stewardship who indicated that one for four factors that are taken into consideration when their cat is given an antimicrobial is "very important" or "important" to them.

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1.0 Introduction

1.1 Antimicrobial resistance

Antimicrobial resistance (AMR) is defined as the ability of pathogenic organisms to avoid, destroy, or inactivate therapeutic drugs through innate mechanisms, random mutation, or gene acquisition from other organisms (U.S. Centers for Disease Control and Prevention 2020). While this term, AMR, is appropriate for use when referring to multiple microbes (e.g., fungi, viruses, protozoa), it is commonly used when referring to resistant bacteria.

In the US in 2019, there were over 3 million resistant bacterial or fungal infections reported, and over 38,000 deaths attributed to AMR in the human population (U.S. Centers for Disease Control and Prevention 2019). Similarly, many other countries have reported increasing rates of AMR (Organisation for Economic Cooperation and Development 2018). The Interagency Coordination Group (IACG) estimates that by 2050 there could be up to 10 million deaths per year worldwide due to AMR infections if no action is taken to try and reduce occurrence globally (Interagency Coordination Group on Antimicrobial Resistance 2019). Similar data surrounding AMR in animals, including pets, is not as readily available, but it is likely that there is a comparative impact on animal health and welfare. As a consequence of rising rates of AMR there has been an increasing global effort to develop new antimicrobial drugs, and preserve the efficacy of those currently available through reduction of AMR (Dyar *et al.* 2017).

1.1.1 Development of resistance in bacterial species

Bacteria are a large domain of diverse species that are adapted to live in many ecological niches (Hibbing *et al.* 2010), and possess unique structural features that allow antimicrobial drugs to target bacterial cells without causing any damage to the host organism (Saga & Yamaguchi 2009). Bacteria are able to reproduce both sexually and asexually, which allows AMR genes to develop through random mutation, and then be transferred between individuals both in the same and different species (Levy & Bonnie 2004). The ability of bacteria to develop and transfer resistance presents a challenge to treatment that has resulted in a global healthcare crisis (Ventola 2015).

1.1.1.1 Intrinsic resistance

Due to the differences in bacterial genotypes, some species have an intrinsic resistance to certain antimicrobials, which predates the use of these drugs in medicine (Prescott *et al.* 2002). The most common example of intrinsic bacterial resistance is related to the structural difference between Gram-negative and Gram-positive bacteria (Cox & Wright 2013). Gram-negative bacteria have an outer membrane surrounding their cell wall (Salton & Kim 1996), which is impermeable to many classes of therapeutic agents (Exner *et al.* 2017). This gives Gram-negative species an innate (i.e. intrinsic) resistance to many drugs that are effective against Gram-positive bacteria, which lack this additional protective layer (Cox & Wright 2013; Exner *et al.* 2017). Another example of intrinsic resistance is the presence of bacterial efflux pumps, which are thought to have initially developed to remove toxic by-products produced by host species. These pumps have the additional benefit of being able to reduce intracellular concentrations of antimicrobials below effective levels (Cox & Wright 2013). Along with the physical structural differences described above, many bacterial species possess intrinsic resistance genes that can be expressed in the presence of an antimicrobial agent (Cox & Wright 2013).

1.1.1.2 Acquired resistance

Bacteria that do not have intrinsic genetic mechanisms that make them resistant to certain therapeutic agents may be able to acquire resistance (Saga & Yamaguchi 2009). This can be acquired through random mutation, where errors during replication result in a resistance gene developing by chance (MacLean & San Millan 2019). Bacteria reproduce asexually rapidly, and a single cell can double as frequently as once every 20 minutes (Allen & Waclaw 2019). As an antimicrobial is introduced to a bacterial population, there is a specific selection pressure which may allow the resistant bacterial population to thrive over the susceptible population. Selection pressure, together with the bacterium's rapid ability to multiply (i.e., doubling), can allow for resistant bacteria to quickly become the dominant population in the individual being treated with antimicrobial drugs (Davies & Davies 2010).

Bacteria are also able to reproduce sexually, known as conjugation, and can transmit genetic material between bacteria, including between different bacterial species (Davies & Davies 2010; Watanabe 1963). This is most commonly through transfer of small mobile DNA strands called plasmids (Norman *et al.* 2009), though several other mechanisms are possible, including transfer of chromosomal DNA (Levy & Bonnie 2004). These mutations can occur sequentially and many plasmids have been shown to convey resistance to multiple unrelated antimicrobial drugs (Levy & Bonnie 2004; Watanabe 1963).

As well as sexual reproduction, there are two other, less efficient ways, in which bacteria can acquire new DNA that may confer AMR (McManus 1997). Transduction is a relatively rare event that occurs when a bacterium is infected with a virus, called a bacteriophage (McManus 1997; Tenover 2006). Bacteriophages insert their DNA into the bacterial chromosome so that their genetic material can be replicated and new bacteriophages can be formed (Olson & Horswill 2014). As these new particles are formed, a copy of the bacteriophage DNA is packed into the viral capsule (Olson & Horswill 2014). Occasionally bacterial chromosomal or plasmid DNA is also unintentionally packed, and this is then incorporated into the DNA of the next bacterium that is infected by the bacteriophage (McManus 1997; Olson & Horswill 2014; Tenover 2006). Bacteria are also able to acquire new DNA through transformation, where they can uptake DNA in the external environment through their cell wall and cell membrane and then incorporate it in their own genetic material (Chen & Dubnau 2004). This DNA can come from a variety of sources, but in the case of transformation of genes that confer AMR, it is genetic material from other bacteria that have recently been lysed (McManus 1997). Transduction and transformation are less common methods of AMR, but exemplify the many strategies bacteria use to adapt to (and survive) external insults in the form of antimicrobial drugs (Tenover 2006).

1.1.2 Drivers of antimicrobial resistance

Bacterial species with AMR properties were detected soon after the first antimicrobials were discovered and went into general use (Saga & Yamaguchi 2009). As new antimicrobial drugs have been developed, more resistance mechanisms have emerged (Saga & Yamaguchi 2009). Development of AMR by bacteria is a normal consequence of antimicrobial use (AMU); however, it is estimated that up to 50% of AMU in human medicine is unnecessary (Fleming-Dutra *et al.* 2016; Wise *et al.* 1998). In these cases of unnecessary AMU, antimicrobials are being given for self-limiting or non-bacterial diseases, or they are being prescribed at doses that are too low or for treatment durations that are unnecessarily long (Hecker *et al.* 2003). It is estimated that unnecessary AMU is even higher in veterinary medicine (Weese *et al.* 2015). Unnecessary AMU exposes more bacteria to antimicrobials and drives development and transmission of resistance genes (Saga & Yamaguchi 2009; Weese *et al.* 2015). Low or sub-therapeutic doses of antimicrobials increase the risk of AMR further, as infections do not resolve and resistant bacteria survive to recolonise the patient (Pouwels *et al.* 2019).

The emergence of resistant bacterial pathogens in human medicine such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) has been directly linked to overuse of antimicrobials (Cetinkaya *et al.* 2000;

Grundmann *et al.* 2006). Many of these infections are healthcare-associated (HAI), acquired in hospital rather than within the community (Beović 2006; Cetinkaya *et al.* 2000), and the incidence of all resistant infections has been noted to decrease when AMU within a hospital is reduced (Bergman *et al.* 2004). Infections caused by AMR bacteria result in prolonged treatments and poorer outcomes for patients, including increased mortality, as well as increased costs to the hospital and on a national scale (Beović 2006).

In veterinary medicine, food-production animal AMU has historically been perceived to be the greatest driver of AMR, as many antimicrobials may be dispensed without veterinary prescriptions and added to feed in subtherapeutic doses to promote growth (Wegener *et al.* 1999). Despite bans on the use of antimicrobial growth promoters (AGPs) in most countries, antimicrobials are still being used legally for both treatment and prevention, and AGP use is still allowed in many low- and middle-income countries (LMICs) (Schar *et al.* 2018). Concerns about AMR related to use in animal food production were raised as early as 1969 (Swann & Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine 1969), and there have been multiple studies demonstrating a link between AGPs and increased isolation of resistant bacteria in livestock (BENNO *et al.* 1988; Wegener *et al.* 1999, 1998). This is a concern for all fields of healthcare (One Health) as resistant bacteria are thought to be transmitted from food animals to humans through contamination of the environment, or from contamination of meat or crops in the food chain (Dorado-García *et al.* 2016; One Health

Initiative Task Force 2008; Tang *et al.* 2017; Wegener *et al.* 1999). Links between increased resistant bacteria in livestock leading to an increase in the human population are tentative; however, there is speculation of a correlation (Tang *et al.* 2017).

Similar to production animals, there is a growing public health concern for companion animal AMR and a subsequent impact on human health (Pomba *et al.* 2017). Many companion animals are colonised with zoonotic bacteria and the same, or similar, antimicrobials are used in dogs and cats as are used in human medicine (Pomba *et al.* 2017). Companion animals and their owners are in close contact, and share living spaces, meaning that risk of transmission of bacteria between animals and human is high (Dickson *et al.* 2019). There have been several publications that suggest direct transmission of AMR infectious agents between pets and their owners (Walther *et al.* 2012; Wright *et al.* 2005).

1.1.3 Resistant infections in human and companion animal veterinary medicine

Bacterial resistance to one of the first antimicrobial drugs to be commercially available, penicillin, was detected prior to its widespread use (Abraham & Chain 1988). Within two decades of commercial release, penicillin resistance was present in over 80% of infections caused by some common bacterial species (Lobanovska & Pilla 2017). A common resistance mechanism of bacteria to penicillin is the production of beta-lactamase enzymes, which inactivate penicillins by destroying the beta-lactam ring that inhibits bacterial cell wall synthesis (Shaikh *et al.* 2015). New antimicrobials, such as methicillin, that are similar to penicillin in structure and function, but resistant to beta-lactamase, have been produced (Chambers 1997; Lobanovska & Pilla 2017). However, resistance to these new drugs developed rapidly (Chambers 1997). Instead of inactivating the antimicrobial drug itself, new resistance mechanisms allow bacteria to continue synthesising a cell wall, despite the presence of inhibitory beta-lactam rings (Chambers 1997). There is evidence that the genes that code for methicillin resistance were acquired from an external source several years prior to the introduction of methicillin, and that earlier penicillins were drivers of the prevalence of this genotype (Harkins *et al.* 2017).

Within 20 years of methicillin being developed, MRSA was a major source of HAIs, and today remains of critical importance in both hospital and community settings (Weese & van Duijkeren 2010). *Staphylococcus* species are prone to developing AMR due to their ability to mutate rapidly, but there has been an increase in AMR in many other pathogenic bacteria in human medicine, including several species in the family Enterobacteriaceae, such as *Escherichia coli* and *Enterococcus* species (Bassetti *et al.* 2016).

AMR bacterial species are emerging in companion animal practice, most notably methicillin resistant *Staphylococcus pseudintermedius* (MRSP) (van Duijkeren *et al.* 2011). Like *Staphylococcus aureus* in humans, *S. pseudintermedius* is a commensal bacterium of dogs that commonly causes opportunistic infections (Ruscher *et al.* 2010). MRSP was first identified in 1999 (Gortel *et al.* 1999), and has become a common source of AMR infections in companion animal practice in Europe, North America, and Asia (Ruscher *et al.* 2010; Weese & van Duijkeren 2010). There is now evidence of MRSP carriage within the canine community that is not associated with previous antimicrobial treatments (Kjellman *et al.* 2015).

There is increasing prevalence in AMR *E. coli*, particularly in samples isolated from dog urinary tract infections. In 14 European countries, 11-68% of *E. coli* cultured from urine samples collected in 2012-2013 were AMR to one or more antimicrobials, with southern European countries having a higher prevalence of *E. coli* resistant to all antimicrobial drugs tested compared to northern countries (Marques *et al.* 2016). In South Africa, between 2007-2012, 98% of canine urinary *E. coli* isolates in the veterinary teaching hospital were multi-drug resistant, meaning they were resistant to at least one drug in three or more antimicrobial classes (Qekwana *et al.* 2018).

In veterinary practice, AMR has animal welfare and financial implications for pets and their owners, as these infections often require more costly antimicrobials and longer treatment durations, as well as increasing the risk of poor outcome (Prescott *et al.* 2002; Prescott & Boerlin 2016). Further, many bacterial species are potential zoonotic pathogens, and many of the same antimicrobials are used in people and animals (Pomba *et al.* 2017). The CDC currently classifies 5 AMR pathogens as “urgent threats” and 11 as “significant threats” for human health in the US, with several more that are considered concerning or to be watched (U.S. Centers for Disease Control and Prevention 2019).

Many of these bacterial pathogens that are urgent or serious threats can either infect or are commensal organisms in companion animal species (Pomba *et al.* 2017).

There have been several reports of companion animals carrying MRSA or developing MRSA infections, most likely associated with contact with humans with MRSA infections or colonisation (Morris *et al.* 2012; Walther *et al.* 2012). While there is no direct evidence of transmission, it is reported that companion animals may be an infrequent source of MRSA infections in humans (Sing *et al.* 2008; Weese & van Duijkeren 2010). MRSP colonisation or infection of humans is more rare, but transient colonisation has been reported in veterinary personnel and some pet owners (Van Hoovels *et al.* 2006; Walther *et al.* 2012), along with cases of MRSP infections that have originated from an unknown source (Starlander *et al.* 2014; Van Hoovels *et al.* 2006). For several bacterial species, such as certain strains of *E. coli* and *Salmonella*, there is evidence of direct transmission between humans and animals. Pet-ownership increases this risk of shared infections due to the close physical contact and common environments pets and their owners share (Pomba *et al.* 2017). Good hygiene, infection control practices, and avoidance of practices that increase risk of bacterial infection, such as the feeding of raw food diets, is needed to help mitigate these risks (Behravesh *et al.* 2010; Dickson *et al.* 2019; Hoelzer *et al.* 2011; Leonard *et al.* 2011; van Bree *et al.* 2018; Walther *et al.* 2012).

1.2 Antimicrobial stewardship

By 1996, new classes of antimicrobials were becoming difficult and less financially viable to develop, meaning that there was a need to preserve the drugs that were currently available (Owens 2008; Ventola 2015). At the same time, it was identified that inefficient antimicrobial treatment of infections using overly complex medication regimes was resulting in increased healthcare costs and negative patient outcomes such as prolonged hospitalisation (Briceland *et al.* 1988). The term antimicrobial stewardship (AMS) was coined in 1996 and was intended as a way to optimise AMU to prevent, reduce and control AMR (McGowan & Gerding 1996). Stewardship practices emphasise a reduction in use of antimicrobials where they are unnecessary, and ensure that when antimicrobials are being prescribed they are being used effectively (Dyar *et al.* 2017).

Several human healthcare bodies have produced recommendations to help reduce AMU for human (Shlaes *et al.* 1997) and veterinary medicine (World Health Organization 1997). One year after AMS was defined, updated recommendations on a local and global scale were produced by a variety of sectors (World Health Organization 2017). These recommendations ranged from global initiatives to guidelines for the treatment of individual patients.

1.2.1 Drug classification by importance

One of the most important initiatives on a global scale, both in human and veterinary medicine, has been the classification of antimicrobial drugs by importance. It has been recognised that resistance to certain classes of antimicrobial drugs has a greater impact on public health than resistance to other antimicrobials, and that use of these drugs should be reserved for when there is no alternative (World Health Organization 2005). These concerns of AMR were initially raised surrounding the use of antimicrobials in food-producing animals due to the concern this may result in increased AMR infections in the human population (World Health Organization 2018).

In 2005 the WHO first produced a list of important antimicrobials according to two criteria: "Criterion 1) Sole therapy or one of few alternatives to treat serious human disease, Criterion 2) Antibacterial used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases caused by organisms that may acquire resistance genes from non-human sources." Any antimicrobials that meet both criteria are classified as "critically important," those that meet one are "highly important," and those that meet neither are "important" (World Health Organization 2005). Since 2005 this list has been regularly revised, with the 6th edition being produced in 2018 (Table 1.1).

Drugs that are considered "critically important antimicrobials" (CIAs) are now further categorised according to three prioritisation (P) factors: "P1: Used to treat a large number of people with infections for which limited antimicrobials are available, P2: Used with high frequency in human medicine or in certain high risk groups, P3: Used to treat human infections for which an extensive evidence exists on the transmission of resistant-bacteria or genes from non-human sources." CIAs that have all three prioritisation factors are considered "highest importance" (World Health Organization 2018).

Drug Classification		Antimicrobial Drugs
Important	Not used in humans	Aminocoumarins, arsenical, bicyclomycin, orthosomycins, phosphoglycolipids, ionophores (including polyesthers), quinoxalines
	Used in humans	Aminocyclitols, cyclic polypeptides, nitrofuran derivatives, nitroimidazoles, pleuromutilins
Highly Important		Amphenicols, cephalosporins (1^{st} and 2^{nd} generation), lincosamides, penicillins (amidinopenicillins, anti-staphylococcal, narrow spectrum), pseudomonic acids, riminofenazines, steroid antibacterials, streptogramins, sulphonamides, dihydrofolate reductase inhibitors and combinations, sulfones, tetracyclines
Critically Important	High Priority	Aminoglycosides, ansamycins, carbapenems and other penems, glycylcyclines, lipopeptides, monobactams, oxazolidinones, penicillins (antipseudomonal, aminopenicillins with and without beta-lactamase inhibitors), phosphonic acid derivatives, drugs solely used to treat tuberculosis or other mycobacterial diseases
	Highest Priority	Cephalosporins (3^{rd}, 4^{th}, and 5^{th} generation), glycopeptides, macrolides and ketolides, polymyxins, quinolones

Table 1.1. Drug classification and prioritisation according to the World Health Organisation (World Health Organization 2018).

Antimicrobial classifications are designed to aid stewardship efforts by identifying which drugs are highest priority and need to be monitored closely (World Health Organization 2018). These classifications are also intended to assist with the development of treatment guidelines and recommendations for limiting or restricting AMU (World Health Organization 2018). Some other bodies, such as the World

Organisation for Animal Health (OIE) and Health Canada, have produced their own versions of antimicrobial guidelines to make them more applicable to different areas of healthcare or geographical regions (Health Canada 2009; World Organisation for Animal Health 2015).

Local drug classifications are especially important in veterinary medicine where the majority of licensed products, including many "first line" treatments are considered to be critically important by human guidelines (Weese *et al.* 2015). The Health Canada guidelines (Table 1.2), for example, have a lower classification than the WHO for drugs such as macrolides, aminoglycosides, and tetracyclines, which are all commonly used in veterinary medicine. In contrast other drugs, such as penicillins, carbapenems, and nitroimidazoles have higher classifications.

Drug Classification	Antimicrobial Drugs
Category IV: Low Importance	Flavophospholipols, ionophores
Category III: Medium Importance	Aminocyclitols, aminoglycosides (topical agents), bacitracins, fosfomycin, nitrofurans, phenicols, sulphonamides, tetracyclines, trimethoprim
Category II: High Importance	Aminoglycosides (except topical agents), cephalosporins (1st and 2nd generation), fusidic acid, lincosamides, macrolides, penicillins, quinolones (except fluoroquinolones), streptogramins, trimethoprim/sulfamethoxazole

Category I: Very High Importance	Carbapenems, cephalosporins (3rd and 4th generation), fluoroquinolones, glycopeptides, glycylcyclines, ketolides, lipopeptides, monobactams, nitroimidazoles, oxazolidinones, penicillins with beta-lactamase inhibitors, polymyxins, therapeutic agents for tuberculosis

Table 1.2. Drug classification and prioritisation according to the Health Canada Veterinary Drugs Directorate (Health Canada 2009)

The differences between guidelines highlight a lack of consensus in recommendations, as they are often made with limited data. These limitations are recognised by the authors of several of these guidelines and publications. However, the general aim of these resources is to encourage mindful use of antimicrobials (i.e. stewardship), and they are not intended as a prescriptive list (Medicines Agency 2018; World Health Organization 2017)

1.2.2 Prescription guidelines

One of the keystones of AMS in human and veterinary medicine is the use of antimicrobial prescription guidelines to try and reduce unnecessary AMU and promote judicious use of CIAs. The use of antimicrobial prescription guidelines predates the term antimicrobial stewardship, as these were initially developed in human medicine to reduce the costs associated with excessive AMU (Briceland *et al.* 1988). In human medicine, it was demonstrated that these guidelines were effective at reducing costs, and also resulted in improved patient outcomes such as reduced hospitalisation time (Briceland *et* *al.* 1988). Since these initial antimicrobial prescription guidelines were developed there has been a shift in attitude towards antimicrobials, mainly the recognition of a need for AMS to prevent the emergence of resistant pathogens, and to preserve CIAs for scenarios when there are no or limited alternative drugs (Fishman 2012). As a consequence, prescription guidelines now have a broader purpose than cost reduction, and initiatives such as the WHO classification of antimicrobials have aided the redevelopment of guidelines to focus on AMS (MacDougall & Polk 2005).

Prescription guidelines, consisting of a broad set of recommendations that are applicable to a large community, can be produced on a national or regional scale (Slekovec *et al.* 2012). These usually consist of recommendations for "first line" or empirical antimicrobial therapy for common infections, and may include recommendations for diagnostic work-up (National Centre for Disease Control 2016; National Institute for Health and Care Excellence 2020; Norwegian Directorate of Health 2013; Public Health Ontario 2016). Guidelines can also be developed on a smaller scale (e.g. for an individual hospital) or adapted from the national guidelines to be more applicable to the local setting (Gross & Pujat 2001; van Kasteren *et al.* 2003). Smaller scale guidelines take into account what drugs are available locally, as well as the AMR patterns observed in the common infectious agents in the community (Dellit *et al.* 2007). Within a specific hospital the guideline adherence can be improved with restriction of certain antimicrobials, monitoring of hospital antimicrobial use, and regular, personalised feedback on individual clinician antimicrobial prescribing habits (Paskovaty *et al.* 2005).

Unfortunately, the infrastructure to implement this level of feedback and individual support is lacking in many community medicine settings.

Large scale treatment guidelines are frequently developed for use in veterinary medicine. In companion animal practice there is a range in the type of resources available. Some national professional associations such as the Canadian Veterinary Medical Association (CVMA), and several large scale veterinary organisations such as the British Small Animal Veterinary Association (BSAVA), the Federation of European Companion Animal Veterinary Association (FECAVA) have produced their own AMU and AMS guidelines (American Veterinary Medical Association 2020; British Small Animal Veterinary Association 2019; Canadian Veterinary Medical Association 2008; Federation of European Companion Animal Veterinary Associations 2018). These guidelines are usually developed through the collaboration of veterinarians from different specialties (and general practice) and cover a variety of systems (e.g., dermatology, ophthalmology, orthopaedics). The information contained in these guidelines varies from strict recommendations for drug choice, dosing, and treatment duration, to a general overview of what constitutes empirical therapy and which diagnostics should be considered. In addition to these generalised guidelines, the International Society for Companion Animal Infectious Diseases (ISCAID) has produced detailed consensus statements that focus on specific diseases or systems. These are produced with the collaboration of a smaller group of specialists and contain an in-depth overview of the disease, along with diagnostic and treatment recommendations (Hillier *et al.* 2014; Lappin *et al.* 2017; Marks *et al.* 2011; Weese *et al.* 2019, 2015).

1.3 Antimicrobial stewardship (AMS) in human medicine

Since AMS has become a global priority there has been an effort in human medicine to develop hospital AMS programs, as in-patient care is where patients are most likely to develop HAIs (Beović 2006). These AMS programs rely on the coordinated efforts of many hospital teams, including clinicians, hospital infection control, and the pharmacy (Barlam *et al.* 2016; Dellit *et al.* 2007; Paskovaty *et al.* 2005). These AMS programs and associated collective interventions have been successful, and further methods to improve AMU in hospitals are being developed and studied (Davey *et al.* 2017; MacDougall & Polk 2005). There have been recommendations by large scale health organisations for every hospital to have an AMS program (Fishman 2012). A new focus in human medicine is ensuring that this recommendation is followed wherever possible (World Health Organization 2017).

A similar dedication to AMS in community medicine (i.e., general practice) is lacking, and research is needed to determine areas of improvement globally. In many countries the majority of antimicrobial prescriptions come from general practitioners (Costelloe *et al.* 2010; Goossens *et al.* 2005; Mccaig & Hughes 1995), and a large number of cultured infections with AMR bacteria come from general practice outpatients (Costelloe *et al.* 2010). Despite this, there has been less focus on AMS in community medicine, and many of the interventions in this setting have been shown to be unsuccessful (Arnold & Straus 2005a; Barnett & Linder 2014). Generalised AMS initiatives, such as large scale treatment guidelines, are commonly used in general practice and provide a useful framework for practitioners; however, adherence can be poor (Gerber *et al.* 2014; Pakyz *et al.* 2014; Wathne *et al.* 2019). As in hospital programs, successful AMS outcomes in general practise are achieved through targeted education of prescribers and personalised feedback on prescribing habits (Gerber *et al.* 2014). More focus is needed on outpatient/community care to help optimise AMS efforts in community practice, and identify how hospital stewardship programs can be adapted to this setting (Jeffs *et al.* 2020).

Since 1996, interpretation of the term "stewardship" has continued to develop. A more recent definition, produced by the Infectious Diseases Society of America, describes AMS as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration" (Fishman 2012). Here the responsibility for AMS is primarily placed on the drug prescriber, but there has been a recent move to expand stewardship efforts to include the wider community (Dyar *et al.* 2017; Mendelson *et al.* 2017). AMS programs have been demonstrated to be most successful when they are targeted at both doctors and patients (Arnold & Straus 2005a; Lee *et al.* 2015), and there is recognition that there is a need to better educate the general public about AMR and AMS (Spellberg *et al.* 2008). Education efforts have been two-fold, with a combination of national AMR awareness campaigns ("Antibiotic Awareness Week Canada" 2019; "World Antibiotic Awareness Week" 2019; Huttner *et al.* 2019), and one-on-one conversations with physicians (Cals *et al.* 2013, 2009; Francis *et al.* 2009; Mangione-Smith *et al.* 2015).

1.4 Antimicrobial Stewardship in Veterinary Medicine

Some of the initial large scale AMS efforts were focussed on veterinary medicine, particularly production animal medicine, as this was viewed as an important source of resistant infections in the human population (Tang *et al.* 2017). Many of the same antimicrobial classes are used in both human and veterinary medicine, and there was concern for the level of veterinary use. Antimicrobial therapies have been used in production animals in large quantities and often at subtherapeutic and sub-optimal dosing regimens (Van Boeckel *et al.* 2015). This practice raised concerns that humans were at risk of developing AMR zoonotic infections either by directly working with these animals, or indirectly further down the food chain through contamination of food products (Tang *et al.* 2017). Concerns have also been raised about the contribution of companion animal medicine to AMR. This concern initially came from within the veterinary community itself (Prescott *et al.* 2002; Weese 2006).

There is now greater recognition of the contribution that AMU in companion animal medicine may have to the human population. Several global and national strategies to reduce AMR have included recommendations that veterinary hospitals develop AMS programs similar to human hospitals (Prescott & Boerlin 2016; World Health Organization 2017). This increasing move to a One Health approach to AMS has resulted in many national veterinary bodies producing policy statements or guidelines for judicious AMU. Currently AMS programs in veterinary medicine remain rare, and an effort to bring veterinary medicine in line with AMS in human medicine is needed (Hardefeldt 2018; Weese *et al.* 2015).

1.4.1 Veterinary legislation

Specific therapeutic recommendations in veterinary medicine are primarily driven by a concern that veterinary antimicrobial use will contribute to AMR in the human population (Pomba *et al.* 2017; Tang *et al.* 2017). As a consequence, some governments have placed legal restrictions on veterinary AMU in an attempt to preserve antimicrobials for human medicine. The majority of restrictions have been placed on products used in food producing animals, to reduce or eliminate the use of antimicrobial growth promoters (AGPs).

Legislation has been introduced slowly, with the first country to institute restrictions being Sweden in 1986. This occurred nearly 20 years after the concern for the risk of AMR in food animals was first raised (Wierup 2001). The WHO recommended, in 1994, and again in 1997, that all antimicrobials that were used in human medicine, or would cause cross-resistance in antimicrobials used in human medicine, should not be used as AGPs (World Health Organization 1997). The European Union gradually reduced the number of drugs that were allowed to be used as AGPs before a complete ban in 2006 (European Commission 2005). North America was much slower to follow the WHO recommendations, and medically important antimicrobials were only banned as AGPs in the US in 2017 (AccessScience 2017), and in Canada in 2018 (Canadian Food Inspection Agency 2018). While there has been a total ban on AGPs in Europe and North America, many low- and middle-income countries have no restrictions on AMU for growth promotion (Kakkar *et al.* 2020). Where legislation surrounding AGPs has been put in place, most countries have successfully demonstrated a reduction in AMU, as well as an observed decrease in AMR bacteria in livestock (Bengtsson & Wierup 2006; Tang *et al.* 2017). Some studies have demonstrated a reduction in AMR bacterial infections in the human population after this legislation was introduced, though these studies have mostly focussed on farm workers in direct contact with food-producing animals (Tang *et al.* 2017).

Companion animal veterinary practice has not been given the same priority for AMU as food animals, but there has been recognition that use of CIAs in pets requires regulation (Prescott *et al.* 2002). These are usually antimicrobials that are classified as "highest priority" by the WHO such as fluoroquinolones and 3rd and 4th generation cephalosporins. Some European countries have produced restrictions that prevent use of these drugs unless specific criteria are met, such as mandatory culture and susceptibility testing prior to use (Hopman *et al.* 2018). Where these regulations have been put in place there has been a decrease in the amount (and duration) of these drugs being prescribed (European Medicines Agency 2017; Hopman *et al.* 2018). The effect of these changes on AMR is still unclear, and there are concerns for animal welfare impact of these restrictions (Weese *et al.* 2015).

1.4.2 Current antimicrobial use in veterinary medicine

An important feature of AMS is surveillance of current antimicrobial use practices (Kahn 2017). Surveillance raises awareness, highlights current practises and identifies areas where there is a need for AMS improvement, along with monitoring the effects of AMS programs (Owens 2008). Many countries measure AMU yearly by reporting AMU in kilograms, categorized by species (Van Boeckel *et al.* 2014). This allows for overall trends to be tracked, but does not give any specific information about which antimicrobials are being dispensed and for what purpose (Redding *et al.* 2019). Other ways to report antimicrobial consumption include defined daily dose (DDD) where the average therapeutic dose in human adults is calculated and the number of defined daily doses of a drug is measured in a population (e.g. 20 DDDs per 1000 inhabitant days). Another measure is to utilise population correction unit (PCU) which is the mg/kg of a drug used in a production animal based on the average weight of each species at various life stages (Public Health Agency of Canada 2017; Veterinary Medicines Directorate 2016; World Health Organization 2020). These are useful measurements for quantifying AMU with a population, but still do not give specific information about why antimicrobials are being prescribed. A more detailed method of surveillance is looking at individual prescriptions; however, this is labour intensive and can be difficult to implement on a large scale

(Redding *et al.* 2019). A few AMU surveillance methods have been tested in companion animal practice, including using medical records, insurance data, and questionnaires (Barbarossa *et al.* 2017; Hardefeldt *et al.* 2018c; Schmitt *et al.* 2019).

Large scale AMU surveillance using medical records has largely come from the UK and Australia, and demonstrates that AMU in veterinary practice is high and, more concerningly, that CIAs are still frequently used (Buckland *et al.* 2016; Hardefeldt *et al.* 2018c; Radford *et al.* 2011; Singleton *et al.* 2018). Studies from the UK estimate antimicrobial prescription events range from 18.8% to 35.1% of consultations for dogs, and between 17.5% to 48.5% of consultations for cats (Hughes *et al.* 2012; Radford *et al.* 2011; Singleton *et al.* 2018). This varies by region, and in one location antimicrobials were prescribed in 73% of cat consultations (Radford *et al.* 2011). Similar prescription proportions have been identified in Australia, with total prescription proportions of 14.5% of dog and 10.8% of cat consultations (Hur *et al.* 2020). In another study, in a two year period 54% of insured dogs and 48% of insured cats that had a claim received an antimicrobial prescription (Hardefeldt *et al.* 2018c). Across all British and Australian surveillance studies, up to 34% of antimicrobial prescriptions were drugs of highest importance according to the WHO, with cats being approximately 5 times more likely to receive one of these drugs (Buckland *et al.* 2016; Hardefeldt *et al.* 2018c). Establishing this information provides a baseline level of AMU and helps guide targets for improvement.

As well as determining how often antimicrobials are prescribed, it is important to note if they are being prescribed appropriately, and in accordance with guidelines. In several conditions, such as acute haemorrhagic gastroenteritis, feline lower urinary tract disease, and canine infectious respiratory disease complex, antimicrobials are not always indicated, even if a bacterial pathogen is suspected to be part of the aetiology (Lappin *et al.* 2017; Marks *et al.* 2011; Weese *et al.* 2019). Despite this, surveillance data demonstrate that antimicrobials are often prescribed for these conditions, and in some scenarios are being used prophylactically (Barbarossa *et al.* 2017; Gómez-Poveda & Moreno 2018; Hardefeldt *et al.* 2018c; Jones *et al.* 2014; Lutz *et al.* 2020; Murphy *et al.* 2012; Schmitt *et al.* 2019). This inappropriate AMU is occurring despite easily accessible data that demonstrates that AMU in these scenarios is ineffective, and often inappropriate, which highlights the need for education targeting prescribers.

For several common disease processes, such as urinary tract or skin infections, culture and susceptibility is recommended to guide treatment choice (Hillier *et al.* 2014; Weese *et al.* 2019). Multiple surveys of veterinarians; however, show that compliance with this recommendation is low (De Briyne *et al.* 2013; Van Cleven *et al.* 2018). In general practices in Spain and Canada, only approximately 5% of all antimicrobial prescriptions were associated with culture and susceptibility testing (Gómez-Poveda & Moreno 2018; Murphy *et al.* 2012). Similar results were found in veterinary teaching hospitals, with fewer than 5% of prescriptions in an Italian hospital being associated with culture and susceptibility, and only 17% in a US hospital being associated with a confirmed diagnosis of bacterial infection (Escher *et al.* 2011; Wayne *et al.* 2011). In addition, there is often empirical use of CIAs such as fluoroquinolones or 3rd generation cephalosporins without culture and susceptibility testing to justify their use (Barbarossa *et al.* 2017; Murphy *et al.* 2012). When surveyed, a large proportion of European companion animal veterinarians (51.1%) only performed a culture and susceptibility test if the initial treatment failed, and compliance with guidelines was poor (De Briyne *et al.* 2013). More research is needed to determine how best to encourage utilisation of culture and susceptibility testing, and improve adherence to prescription guidelines.

1.5 Barriers to antimicrobial stewardship in human medicine

Antimicrobial stewardship programs in hospitals and the community have become increasingly sophisticated as they have grown to include a multitude of specialists (Barlam *et al.* 2016; MacDougall & Polk 2005). However, appropriate antimicrobial prescribing still largely relies on the individual physician treating the patient (Wester *et al.* 2002). Many hospital programs include interventions that will limit which antimicrobials can be prescribed, and may even require authorisation from a pharmacist before a drug will be dispensed (Drew *et al.* 2009). For these to be truly successful, it has been demonstrated that there needs to be education for the prescribers (Lee *et al.* 2015; Schaffner *et al.* 1983).

Education on AMU and appropriate prescribing is often lacking during medical school and post-graduate training (Laguio-Vila & Lesho 2020; Pulcini & Gyssens 2013).

Programs that include small group teaching have shown to be more effective than those that rely on printed materials (Schaffner *et al.* 1983). Many doctors also feel that their personal contribution to the problem of AMR is minimal, which reduces adherence to AMS practices in various medical professions (Golding *et al.* 2019). The use of prospective audit, where a specialist reviews prescriptions in high risk cases, makes treatment suggestions and gives feedback to the prescriber, has resulted in significant reductions in inappropriate AMU. However, this practice of prospective audit is usually limited to a hospital setting where the staff required to allow for this are easily accessible (Arnold & Straus 2005b; Dellit *et al.* 2007; Pakyz *et al.* 2014). Prospective audit also provides the opportunity to give one-on-one education, as well as highlighting where prescription habits might be improved (Arnold & Straus 2005a; Dellit *et al.* 2007; Gerber *et al.* 2014). While improvements are being made, a universal shift in the attitudes of physicians regarding AMS is required.

A variety of social factors can have an impact on AMU and adherence to AMS guidelines (Cars *et al.* 2001; van Kasteren *et al.* 2003). Many physicians perceive that patients expect to be given antimicrobials, especially in general practice or paediatric medicine (Butler *et al.* 1998; Mangione-Smith *et al.* 1999; Weiss *et al.* 2004). To help reduce pressure on prescribers from patients, as well as ensure that patients are complying with prescription instructions, there has been an effort to educate the general public about AMR (Huttner *et al.* 2010). This has largely been accomplished through national awareness campaigns, which have had mixed success. While there has been evidence that prescribing of antimicrobials has been reduced in some countries after these campaigns, the improvements have been small (Bauraind *et al.* 2004; Bernier *et al.* 2014; Lambert *et al.* 2007; McNulty *et al.* 2010). For example, when patients have been surveyed about their knowledge of AMR after these campaigns there is little change and understanding of the problem remains superficial (McNulty *et al.* 2010). In contrast, expectation of receiving antimicrobials is generally reduced if physicians are able to take the time to discuss their therapy rationale with patients or their caregivers (Cals *et al.* 2009; Mangione-Smith *et al.* 2015). Practically, there is often limited time to ensure these conversations occur in a brief consultation and other educational alternatives that may prove to be more effective (and efficient) include interactive campaigns, leaflets, and repeated messages. It is apparent that a change in public perception is required to assist with global stewardship efforts (Huttner *et al.* 2019, 2010; McNulty *et al.* 2010; Mortazhejri *et al.* 2020).

AMS efforts in high-income countries have significantly increased in the past three decades and are beginning to be successful. These programs require access to infrastructure and resources that allow effective interventions to be put in place, which is lacking in many low- and middle-income countries (LMICs) (Bebell & Muiru 2014). To complicate matters LMICs often have a high prevalence of infectious diseases, reduced sanitation and infection control standards, and antimicrobials are often available to purchase without a prescription (Kakkar *et al.* 2020; Laxminarayan *et al.* 2013). In many LMICs there are comparatively few AMS programs, even in the hospital setting. Good

AMS practices in hospitals in LMICs are hindered by a variety of factors including lack of communication between services, a reluctance by clinicians to perform diagnostic testing, and a fear of treatment failure (Gebretekle *et al.* 2018). However, when AMS programs are able to be implemented in these hospitals, it often only requires small changes to the existing structure to result in large improvements in AMU (Brink *et al.* 2016; Singh *et al.* 2018).

A commitment to AMS starts on a national level, with regulations such as those that prevent antimicrobials from being dispensed over-the-counter, and financial provisions to aid development of AMS programs (Kakkar *et al.* 2020; Laxminarayan *et al.* 2013). To reduce AMR on a global scale an effort to improve AMU in all countries is required, especially those where AMU is continuing to increase (Hamers & van Doorn 2018). Development of achievable AMS programs in LMICs to help improve efforts even where resources may be limited should be prioritised (World Health Organization 2019).

1.6 Barriers to antimicrobial stewardship in veterinary medicine

Despite the variety of AMS resources available, current AMU surveillance indicates that compliance with AMS recommendations in veterinary medicine is poor (De Briyne *et al.* 2013; Van Cleven *et al.* 2018). As in human medicine, studies have been conducted to identify what is contributing to inappropriate AMU in veterinary medicine, with a hope to gain insights into how to better prevent it (De Briyne *et al.* 2013; Golding *et al.* 2019; Hardefeldt *et al.* 2018a; Mateus *et al.* 2014; Smith *et al.* 2018). Barriers to

AMS in veterinary medicine, as in human medicine, have been demonstrated to be complex and multifactorial (Mateus *et al.* 2014; Smith *et al.* 2018) and AMU appears dependent on the veterinarian, practice location, and season (Hardefeldt *et al.* 2018a; Hopman *et al.* 2019a; Mateus *et al.* 2014).

In human medicine there has been successful implementation of AMS programs in many large hospitals (Davey *et al.* 2017; J L Hulscher *et al.* 2010; Nathwani *et al.* 2019). While some veterinary hospitals have the resources to follow human models, this level of AMS program is rare in clinical practice or in veterinary teaching hospitals. When a multidisciplinary approach has been employed in veterinary practice it has successfully led to a significant reduction of total AMU, specifically 1^{st} and 2^{nd} line drugs, with a slight but insignificant decrease in 3^{rd} line AMU (Hopman *et al.* 2019b). Use of practice guidelines has also been effective in reducing overall AMU, but has resulted in an increase in the use of 3^{rd} line antimicrobials (Van Cleven *et al.* 2018; Weese 2006). The majority of veterinary practices face similar barriers to human general practice, as they are small, and lack the local infrastructure to allow development of hospital-style interventions (Hardefeldt 2018; Hardefeldt *et al.* 2018a). Research on how to approach successful AMS in companion animal practice is limited and large-scale studies are required. A multifaceted approach to AMS appears possible in small clinics but needs to be implemented by a larger institution that can then assist within the local area (Hopman *et al.* 2019b).

1.6.1 Veterinarian factors

One of the biggest drivers for inappropriate prescribing habits in companion animal medicine is that training for veterinarians on AMS is lacking or insufficient. Australian veterinary students in one study did not feel their curriculum adequately equipped them for antimicrobial prescribing in practice (Hardefeldt *et al.* 2018b), and the same concern has been raised for veterinary students in the US (Ekakoro & Okafor 2019). Lack of education is listed as a barrier to stewardship by veterinarians after graduation, and in one study nearly all strongly supported more continuing education materials on AMS (Hardefeldt *et al.* 2018a). There has been an increase in the production of education materials to aid with veterinary AMS efforts, but many veterinarians remain unaware of the resources available to them (De Briyne *et al.* 2013; Ekakoro & Okafor 2019; Hardefeldt *et al.* 2018a; Mateus *et al.* 2014). These education materials are targeted at veterinarians and owners to assist in getting the entire veterinary team involved in the reduction of AMU (American Veterinary Medical Association 2020; The College of Veterinarians of Ontario 2020). Some veterinary regulatory bodies have even begun to set minimum annual requirements for continuing education on AMR (Prince Edward Island Veterinary Medical Association 2020). Surveys of veterinarians across Europe have found that veterinarians who report routinely using AMU guidelines, and are engaging in AMS continuing education, prescribe more appropriately in clinical scenarios (Jessen *et al.* 2017; Van Cleven *et al.* 2018). Better dissemination of these resources, and more time dedicated to AMS education both before and after graduation will likely result in improved prescribing practices.

Unfortunately there are also many veterinarians who are aware of AMS guidelines, but choose not to use them (Hardefeldt *et al.* 2018b; Van Cleven *et al.* 2018). This can be because they are mistrustful of the information provided (Hardefeldt *et al.* 2018a), think that it is unnecessary or impractical in a clinic setting, or feel that they do not have time to learn from these resources (Mateus *et al.* 2014). Compliance with guidelines at the individual level improves if they are implemented at a clinic level (Hopman *et al.* 2019b; Sarrazin *et al.* 2017; Weese 2006). In human medicine compliance with guidelines is improved if doctors receive feedback on their performance, and there is a level of accountability within their practice (Gerber *et al.* 2014). Veterinarians may also benefit from these types of personalised interventions.

Many veterinarians report perceiving “pressure to prescribe antibiotics” from pet-owners, which results in them prescribing these drugs at times when they are unnecessary (Hardefeldt *et al.* 2018a; Mateus *et al.* 2014; Smith *et al.* 2018). This was commonly reported by veterinarians working in general practice in the UK and Australia (Hardefeldt *et al.* 2017; Mateus *et al.* 2014; Smith *et al.* 2018), but not by veterinarians in central Europe (De Briyne *et al.* 2013), or clinicians in one teaching hospital (Ekakoro & Okafor 2019). This is often a perceived pressure and is not one that is explicitly stated by the pet-owner (Smith *et al.* 2018). Surveys of clients, on the other hand, demonstrate that most trust their veterinarians’ opinion and would not push for antimicrobials if they were told they were not indicated (Redding & Cole 2019; Stallwood *et al.* 2019). In some cases, owners have stated that they believe veterinarians overprescribe antimicrobials (Smith *et al.* 2018), and do not offer diagnostics such as culture and susceptibility testing, or adequately communicate their rationale for an antimicrobial prescription (Stallwood *et al.* 2019). This disconnect indicates a need for improved veterinarian-client communication to ensure that both the client and veterinarian are satisfied with the treatment decisions being made, and that good AMS practices are still being followed (Smith *et al.* 2018).

1.6.2 Pet-owner factors

As with human medicine, stewardship in veterinary medicine is dependent on more than just the prescriber. Studies exploring the attitudes of pet-owners are limited and those that have been performed involved a small number of owners, which may not be generalisable to other groups.

Pet-owners often report feeling that their animals are members of their family, and that they have a responsibility for their health and well-being (Dickson *et al.* 2019). As a consequence they feel pressure to advocate for them, and are more likely to push for antimicrobials “just in case” for their pets than they might for themselves if they were unwell (Dickson *et al.* 2019). A study of 25 US pet-owners found that, in a scenario where antimicrobials may not be effective, most (n=21) would still like them to be prescribed (Redding & Cole 2019). The majority of owners (n=21) would accept their veterinarian’s decision if they chose not to prescribe antimicrobials, while the remaining four participants would still push for them because they would not want their pet to potentially suffer (Redding & Cole 2019).

In a larger study of cat-owners in the UK approximately half (n=405/822) went in to their consultation expecting that antimicrobials would be prescribed, but nearly all (n=792/827) stated that they would follow their veterinarian's recommendations (Stallwood *et al.* 2019). An expectation that antimicrobials would be prescribed was also found by Smith et. al in 2018, similarly most owners also reported trusting their veterinarian's decision if they were to deem them unnecessary (Smith *et al.* 2018). As the majority of these surveys utilise hypothetical scenarios, it is difficult to assess how many pet-owners may choose to push for antimicrobials if their animal was actually ill. It is also difficult to assess the magnitude of the Hawthorne effect, where study participants modify their behaviour or answers to questions because they are being observed and will respond to what they believe the researcher wants or considers correct (McCambridge *et al.* 2014).

In many locations, cost further complicates AMS in veterinary medicine as most pet-owners need to pay for their pets' veterinary services and medication, as opposed to being covered under an insurance program. This often poses a challenge when diagnostic testing such as culture and susceptibility are indicated. Companion animal and farm animal veterinarians in Europe, North America, and Australia all report that owner financial constraint is a barrier to best antimicrobial and veterinary practices (De Briyne *et al.* 2013; Fowler *et al.* 2016; Golding *et al.* 2019; Hardefeldt *et al.* 2018c). Information from pet-owners on this topic is conflicting. In one UK study 65.8% of cat-owners (n=778) said they would be willing to pay for diagnostic testing to ensure that their cat received the most appropriate antibiotic (Stallwood *et al.* 2019). However, only 7 of 25 US pet-owners in another study would provide unconditional support for culture and susceptibility testing. Of the remaining 18 participants, cost was a barrier to testing for 5, and the remainder gave conditional support, preferring to first trial therapy depending on the severity of the infection (Redding & Cole 2019). Financial barriers in veterinary medicine are likely to be difficult to overcome, but owners are often willing to spend more money on their pets if it will improve the outcome for their animal, or if it is explained that this may reduce costs in the long term (Dickson *et al.* 2019; Redding & Cole 2019; Smith *et al.* 2018).

Much like other sections of the population, pet-owners seem to have a strong level of awareness that AMR is a problem in human medicine (Stallwood *et al.* 2019). As with studies of human patients, this knowledge of AMR is superficial (Gualano *et al.* 2015; Redding & Cole 2019; Smith *et al.* 2018; Stallwood *et al.* 2019). Most participants in three studies of pet-owners were aware of the concept of AMR, and had some understanding of factors that might contribute to the development of a resistant infection (Redding & Cole 2019; Smith *et al.* 2018; Stallwood *et al.* 2019). In one UK study, 84% of cat-owners agreed with the statement “antibiotics are effective against bacteria” and 83% agreed with the statement “bacteria can become resistant to antibiotics used in cats” (Stallwood *et al.* 2019). This seems to demonstrate a high level of understanding of AMR in this particular population, but it is unclear how much of this is due to the use of Likert-type questions to assess a complex topic, such as knowledge. In two other studies where owners were interviewed using broad, open ended questions, the level of understanding was much lower (Redding & Cole 2019; Smith *et al.* 2018). In one study, only 25% of the owners stated that antimicrobials were used for bacteria, and a common theme was the belief that it was the person taking the drug that became resistant to the antimicrobial not the bacteria infecting them (Redding & Cole 2019). When asked about AMR in their pets, few owners in any group surveyed were aware that this was a problem, and those that knew there is a risk of interspecies transmission mostly referred to farm animals rather than their own pets (Redding & Cole 2019; Smith *et al.* 2018; Stallwood *et al.* 2019). It is reported that AMR is low on the list of priorities for many pet owners, and is unlikely to have an influence on their decision making when it comes to their pets (Smith *et al.* 2018).

Education of pet-owners about AMR in their animals may improve AMS in veterinary medicine. Most owners trust their veterinarian's decision, and would accept being told that antimicrobials were not indicated in their pet (Redding & Cole 2019; Smith *et al.* 2018). A better understanding of the mechanisms of resistance, and the potential zoonotic risks of AMR, may also help improve pet-owner compliance (Redding & Cole 2019).

1.7 Assessment of knowledge, attitudes, and practices

Surveys are an important tool in many fields of research as they allow collection of data such as knowledge, attitudes, and practices (KAPs), which are difficult to determine by other means (Bennett *et al.* 2011). In human healthcare over the past 50 years there has been recognition that survey-based research is valuable for improving services (Sitzia & Wood 1998). Patient satisfaction is now considered to be an important measure of the quality of care that is provided to them, and there has been a widespread effort to elicit patient feedback to guide improvements to care (Ford *et al.* 1997; Sitzia & Wood 1998). This is primarily accomplished through surveys (Ford *et al.* 1997).

Along with patients, surveys of physicians have also been proven to be valuable. Surveys can be used to assess clinician practices, and identify areas for education or improvement that might improve adherence to hospital or practice policies such as AMS guidelines (Colbert & Professor 2013). Current research in veterinary medicine is also adapting survey methodology for research involving pet-owners, farmers, and veterinarians (Dean 2015; Gunn *et al.* 2008; Mwacalimba *et al.* 2020).

1.7.1 Survey methods

As there has been recognition that patient and physician attitudes and practices are an important part of improving healthcare, there has been an increase in survey-based medical research (Colbert & Professor 2013). Many different survey methods can be employed, ranging from online questionnaires to in-person interviews, depending on the type of information that needs to be gathered (Mccoll *et al.* 2001). Qualitative assessment, such as focus groups and in-person or telephone interviews, allow for a broad range of information or ideas to be gathered. However, these types of assessments do not necessarily allow inferences to be made about the prevalence of these opinions or practices within the larger population (Marsland *et al.* 2000). Quantitative assessment, such as online questionnaires, is often a secondary survey method that can be used on large participant populations to identify what proportion will respond a certain way to a question, but the amount of new data gathered by this method can be limited (Marsland *et al.* 2000). As well as basic survey questions where the participants are asked a direct question and they give either an open or closed response, there is increasing use of techniques like discrete choice experiments (e.g., conjoint analysis) where participants provide subconscious information based on the decisions they make (Ryan & Farrar 2000).

1.7.2 Conjoint analysis

Conjoint analysis is a marketing tool that has gained popularity as a survey method in human and veterinary medical research (Bridges *et al.* 2011; Louviere & Woodworth 1983; Luce & Tukey 1964). Choice-based conjoint analysis relies on hierarchical Bayes analysis to generate numerical values that quantify participant preferences for different attributes of a product or scenario (Lenk *et al.* 1996). Survey participants are provided with a series of choices with two or more options for the product or scenario being studied. In marketing these products will vary on attributes such as colour, cost, or material (Louviere 1988; Stebler *et al.* 2016). For every choice-based conjoint model there are several attributes (features) being studied, each of which has different levels (e.g., within the colour feature, there are levels red, blue, or green). As participants make choices between the options provided, they provide information on which attributes are most valuable to them.

A numerical value, commonly referred to as the utility value, is calculated based on the choices a participant makes, which allows direct quantification of individual preferences. A positive utility value indicates that the participant prefers this level of a feature over the others (e.g. red), and so is more likely to select a particular product that contains that level. A negative value indicates the opposite. The greater the distance from zero, the greater the influence this level has on a participant's preference or aversion towards a particular product. The difference between the levels with the highest and lowest utility scores for each feature (preference score) gives an indication as to how important that feature is. These numerical values allow comparison and quantification of participant preferences for various aspects of a product or scenario that provides useful information to help guide improvements both in its original intended use in marketing, and increasingly in healthcare.

1.8 Aims of this study

Drivers of antimicrobial resistance in companion animal medicine are complex, and to date there have been few studies performed to fully explore these in North

America (Ekakoro & Okafor 2019; Fowler *et al.* 2016; Redding & Cole 2019). Surveys of pet-owners have been on a small scale and none have included Canadian owners. To develop antimicrobial stewardship efforts in Canada that are suited to local needs, target areas for awareness and education in both veterinarian and pet-owner populations need to be identified. This research project had two aims: first, to quantify the influence of cost, ease of administration and an antimicrobial drug's importance in human medicine on companion animal owner selection of antimicrobials for their pet (Chapters 2 and 3 dog-owners and cat-owners, respectively); second, to explore the influence of demographics (i.e. age, gender, household income, level of education) on pet-owner understanding of antimicrobial resistance in human and veterinary medicine and their perception of its importance (Chapters 2 and 3).

1.9 References

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2.0 Knowledge, attitudes and influencers of North American dog-owners surrounding antimicrobials and antimicrobial stewardship [1]

Abstract

The objectives of this study were to quantify the individual influences of antimicrobial cost, method of administration, and drug importance in human medicine on dog-owner preferences, and determine knowledge, attitudes, and influencers of dog-owners surrounding antimicrobials and antimicrobial stewardship. Data were collected through an online survey targeting three dog-owner participant groups. These consisted of individuals residing in: 1) Canada, 2) United States, and 3) any country recruited through an educational social media site. US and Canadian participants were financially compensated. Conjoint analysis was used to quantify the influence of antimicrobial cost, method of administration and drug importance in human medicine. Descriptive and analytical statistics were used for data evaluation. A total of 809 surveys were completed. Antimicrobial cost accounted for 47% of dog-owner preferences, followed by method of administration (31%) and drug importance in human medicine (22%). All groups preferred lower-cost drugs that were administered once by injection. Participants were more likely to prefer drugs considered “very important” in human medicine, except for the social media participants, who preferred drugs that were “not at all important.” Most respondents (86%) reported antimicrobial resistance as important in human medicine and 29% believed antimicrobial use in pets posed a risk for antimicrobial resistance in humans. Participants recruited through social media, and those in the highest education

category, were significantly more likely to report antimicrobial use in pets as a risk to people. Cost was the most important factor for dog-owner antimicrobial preferences and there is a need to educate pet-owners on antimicrobial stewardship.

[1] Stein, M R; Evason, M D; Stull, J W; Mcclure, J T; Weese, J S; Knowledge, attitudes and influencers of North American dog-owners surrounding antimicrobials and antimicrobial stewardship. Journal of Small Animal Practice (2021)

2.1 Introduction

Antimicrobial resistance (AMR) is an emerging global health crisis that is likely to change the face of human and veterinary medicine over the coming decades (O'Neill 2016). Resistant bacteria have been identified in multiple animal species, including companion animals (Awosile *et al.* 2018; Cummings *et al.* 2015; Marques *et al.* 2018), and there are multiple reports of direct transmission of resistant pathogens between humans and animals (Meyer *et al.* 2012; Rogers *et al.* 2011; Wright *et al.* 2005).

In light of AMR concerns, there has been increasing focus on, and the subsequent creation of, antimicrobial stewardship (AMS) programs to reduce and improve antimicrobial use (AMU) (Barlam *et al.* 2016; Dellit *et al.* 2007; Pouwels *et al.* 2019). Stewardship programs aim to optimise AMU, by maintaining maximal clinical benefits while minimising adverse effects, including resistance. There are various components to AMS programs, and they address a range of individuals, including end users (or animal owners). However, despite the rise of AMS programs in human health and in veterinary production animal medicine, there have been comparatively few documented attempts at implementing these programs in companion animal practice (Hopman *et al.* 2019b; Hubbuch *et al.* 2020; Prescott & Boerlin 2016).

In human paediatric medicine, parental expectation historically has been the most significant driver of unnecessary antimicrobial prescription among paediatricians, e.g. AMU for suspected viral disease (Mangione-Smith *et al.* 1999). Parental pressure on paediatricians to prescribe antimicrobials is reduced when non-antimicrobial symptomatic treatment is recommended (Mangione-Smith *et al.* 2015) and contingency plans for worsening patient clinical signs are communicated (Mangione-Smith *et al.* 2001). Similarly, veterinarians widely report that they feel pressured by animal owners to prescribe antimicrobials, even when they are not indicated (Currie *et al.* 2018; Hardefeldt *et al.* 2018a; Smith *et al.* 2018). Further, there is evidence that communication with animal owners about diagnostic and treatment rationales and contingency plans could be improved upon by veterinarians (Coe *et al.* 2009; Stallwood *et al.* 2019). This may reduce pressure and expectations for AMU by animal-owners, similar to findings in paediatric medicine.

In human medicine, AMS programs have been most successful when education and awareness is directed at physicians, patients, and the general public, vs. a single group, e.g. physicians alone (Formoso *et al.* 2011; Huttner *et al.* 2019; Lee *et al.* 2015). To identify targets for education, a number of studies have been performed to identify the baseline level of understanding of AMR by human patients (Gualano *et al.* 2015). Investigation of companion animal owner antimicrobial resistance and stewardship knowledge has been comparatively limited. Two studies from the United Kingdom have indicated that pet-owners have a good understanding of what antimicrobials do and awareness of the threat of AMR in humans (Smith *et al.* 2018; Stallwood *et al.* 2019). However, when pet-owners were asked specifically about their pets, owner antimicrobial knowledge was reduced and most were not aware AMR concerns also exist in veterinary medicine, or that their pets had the ability to carry zoonotic AMR infections (Smith *et al.* 2018; Stallwood *et al.* 2019). A smaller study carried out in North America found a similar lack of awareness on these topics in pet-owners, along with a poorer grasp than UK pet-owners of how antimicrobials work and how resistance develops (Redding & Cole 2019).

There has been recognition in the past few decades that understanding patient or owner preferences results in improved patient outcomes (Brennan & Strombom 1998; Pantaleon 2019). As a consequence marketing-tools such as conjoint analysis have been increasingly adapted for use in medical and veterinary research (Bridges *et al.* 2011; Louviere & Woodworth 1983; Luce & Tukey 1964). In choice-based conjoint analysis, survey takers are given a series of questions where they are made to choose their preferred option between two or more products with different attributes. In medical research this has been successfully adapted for a variety of different scenarios, such as infectious disease outbreaks (Stebler *et al.* 2016) and treatment outcomes for patients with depression (Zimmermann *et al.* 2013). By choosing between options, participants provide information on what is important to them and hierarchical Bayesian analysis is used to quantify choices by calculating a numerical score (Lenk *et al.* 1996).

Available data on pet-owner knowledge, attitudes and influencers (KAIs) regarding antimicrobial use and resistance in North America are limited. This study aimed to address this knowledge gap through a survey of a primarily North American dog-owning population. The objectives of this study were to: 1) quantify the influence of cost, ease of administration and drug importance in human medicine on dog-owner selection of antimicrobials, and 2) Explore associations between demographics (i.e. respondent age, gender, household income, level of education) on owner understanding of antimicrobial resistance in human and veterinary medicine and their perception of its importance. We hypothesised that 1) dog-owners would identify cost as the most important attribute in a drug, 2) dog-owners would have a limited knowledge of antimicrobial resistance and stewardship in a veterinary setting.

2.2 Materials and Methods

2.2.1 Survey design

This study used a prospective, survey-based design intended to gather information from a sample of the North American dog-owning population. Data were collected via means of a questionnaire administered through an online platform (Qualtrics®) between May and September 2019. The questionnaire was developed by one of the principal investigators and pilot-tested on 5 pet-owners prior to its administration. All questions were closed ended to facilitate quantitative data collection. The questionnaire consisted of three parts: demographic information, choice-based conjoint questions, and KAI questions. It was estimated to take 10-15 minutes to complete, and all responses were anonymous. A copy of the complete dog-owner survey is included in Appendix I.

Conjoint questions were used to individually quantify the influence of three features: cost, method of administration and importance of antimicrobials in human medicine, on dog-owner antimicrobial preferences. Features and levels for each feature are presented in Table 2.1. In this study, participants were presented with a mock scenario in which their dog had been diagnosed with a urinary tract infection, and an antimicrobial was being prescribed. Each individual participant was presented with a different set of 10 randomly generated conjoint questions, out of nearly 1.7 million possible combinations of the 10 levels in the three features of this project. Each question consisted of a choice between two antimicrobial options (each with different levels for each of the three features), and participants were asked to select their preferred option, assuming all antimicrobial options were equally effective.

2.2.2 Study population

Convenience samples from three groups of participants were recruited: dog-owners residing in Canada, dog-owners in the United States (US), and dog-owners recruited through an educational social media (ESM) platform. All participants were required to be 18 years or older, and to have owned or looked after a dog in the past year. Canadian and US participants were recruited via the proprietary platform (Qualtrics®) using a panel of paid survey takers. Survey takers were compensated in the form of points towards a rewards scheme of their choice. ESM participants were recruited in addition to the US and Canadian groups through advertising on a veterinary infectious diseases blog (http://www.wormsandgermsblog.com) to provide a group with contrasting demographics and potential difference in baseline knowledge of AMR. No incentive was offered to the ESM group for participation. A minimum sample size of 150 participants per group was recommended by the Qualtrics® proprietary platform for small choice-based conjoint projects with this study's number of features and levels. A sample size of 300 per group was selected in order to increase statistical power and allow for comparisons between groups, as this was twice the number recommended by the Qualtrics® proprietary platform for a project of this size.

2.2.3 Statistical analysis

All statistical analyses were performed using commercial software (Minitab® Statistical Software; State College, PA). Anderson-Darling normality tests were performed on all continuous variables (utility value and preference score), and data were visually assessed for symmetry, normality and presence of outliers. Non-normally distributed data were expressed as a median with 1st and 3rd quartiles. Percentage preference share was calculated by dividing the mean preference score for a feature by the sum of the mean preference scores for all 3 features.

Utility values were calculated by the online survey platform (Qualtrics®). A utility value for each level of each feature was calculated for every individual using Bayes hierarchical analysis after all 10 choices were made. A positive value indicated a participant was more likely to select a product (antimicrobial) if that level of a feature (e.g. $25) was included in the package, and a negative value indicated they were less likely to select a product. The greater distance from zero in either direction, the greater the measured effect on a participant's choice to select or reject a product. To assess the overall utility of a feature, the difference between the highest and lowest utility value for every individual was calculated to generate a preference score. A larger difference (or larger preference score) was considered to be reflective of a higher utility, as it indicated that feature had a greater influence on consumer selection, either negatively or positively. The preference scores for each individual participant were calculated as the difference between the utility values of the highest and lowest levels for each feature in the conjoint analysis.

To facilitate data analysis, responses to multiple choice or Likert-type KAI questions with 5 possible answers were recoded into 2 or 3 answer choices where possible. Responses to the matrix question "*If you need to treat your dog with an antibiotic, how important do you consider the following factors: number of times a day it must be given, cost, importance of the drug for treatment of infections in people, and whether or not you need to give your dog a pill"* were dichotomised into two categories of roughly equal sample size based on the median values. Proportions and corresponding 95% confidence intervals were calculated using the exact method for the number of respondents who selected "very important" or "important" (as opposed to "somewhat important", "not important at all" or "no preference") for each of the four antimicrobial factors. Responses to the questions "*What is your highest level of education?*" and "*Do* *you think antibiotic use in pets poses a risk to people?*" were each combined into three categories of approximately similar size.

Pearson's chi-square test was used to investigate associations between respondent demographics and KAIs surrounding AMR in human and companion animal medicine, and between respondent demographics and recruitment groups. Comparisons between participant age and approximate household income and response to the question *"How important do you think antibiotic resistance is in human* medicine?" did not meet the assumptions for Pearson's chi-square test and a Fisher's exact test could not be performed due to computational challenges. To allow comparison age and income were collapsed into two categories of equal size (<36 and ≥36, and ≤$50,000 and >$50,000) for this question only. The Kruskal Wallis test was used to evaluate the effect of level of education on participant utility value for the level "*not important*" of the feature "importance of the drug for treating people." All other data were analysed descriptively. Prior to analysis, *P*-values < 0.05 were selected as the threshold for statistical significance per scientific convention. Where multiple comparisons were made between groups and within groups for variables of interest a Bonferroni correction was used to reduce the chance of a type I error. When assessing differences between the demographic make-up of the three participant groups, a *P*-value < 0.0125 was considered statistically significant. For the associations between demographic groups and responses to the questions: *"How important do you think antibiotic resistance is in human* medicine?" and "*Do you think antibiotic use in pets poses a risk to humans?*" a *P*-value < 0.01 was considered statistically significant.

2.3 Results

A total of 910 responses were received (Canadian participants, n=315; US participants, n=315; participants recruited through ESM, n=280). Thirty-nine responses from the ESM group, and 17 from the Canadian group were discarded due to incomplete conjoint sections. A further 45 from the ESM group were discarded because they failed to respond to, or responded "no" to the question "*Do you currently own or care for a dog*?" This resulted in a total of 809 (89%) responses sufficiently complete to be included in the final analysis consisting of 298 from the Canada group, 315 from the US and 196 from ESM. Of the 809 included in the analysis 798 (99%) had no missing data. The final ESM group consisted of 168 participants from Canada, 25 from the US, and one participant each from Australia, Brazil, and Thailand.

2.3.1 Demographic data:

Full demographic data were summarised (Table 2.2). Differences were observed between the three recruitment groups (Table 2.2). The ESM group had a higher proportion of female participants (95%) compared to the US (50%) and Canadian (53%) groups (P<0.001). There was also an overall higher level of education (94% community college or higher) in the ESM group compared to the US (62%) and Canadian (61%) groups (P<0.001). There were some differences in the distribution of ages between the groups, with more older participants in the Canadian group, compared to the US and ESM, and more participants in the 18-25 category (27%) compared to the Canadian (14%) and ESM (15%) groups ($P<0.001$). The US group also had a greater proportion (38%) of participants with a household income <$50,000 compared to the Canadian (24%) and ESM (26%) groups.

2.3.2 Choice-based Conjoint Analysis

The most important feature for all three participant groups was cost (Table 2.3), with a median preference score of 5.92 (range: 3.90-9.06) and a total preference share of 47% (range 44%-51%). Within cost, the highest positive median utility value (2.83) was for the lowest cost value ($25) and the lowest utility value was for the highest cost ($120; -3.07). The second most important feature for all three study groups was method of administration, with a median preference score of 3.61 (range 2.81-5.12) and a total preference share of 31% (range: 29%-32%). The administration level with the highest median utility value was "injected once by your veterinarian" (2.11) and the lowest was "oral pill three times a day for 5 days" (-1.97). The least important feature for all 3 recruitment groups was the importance of a drug for treating infections in people with a median preference score of 2.33 (range: 1.76-2.93) and a total preference share of 22% (range 18%-25%). For the US and Canadian groups, the highest utility value was for the antimicrobial drug being "very important" for human medicine (0.756 and 1.32, respectively) and the lowest was "not important" (-0.844 and -1.36, respectively).

Conversely, the highest utility value for the ESM group was “not important” (0.626) and the lowest was “very important” (-0.459).

Participants’ utility value for the level “not important” of the feature “importance of the drug for treating people” differed by level of education. A Kruskal Wallis was performed, where all utility values are placed in ascending order and assigned a rank. The mean rank of the utility values for each category of education is then calculated. Participants with a high school level education had the lowest mean rank of (361.0), followed by a mean rank of 405.2 for community college, and 431.6 for university level education (P=0.002).

2.3.3 Knowledge, Attitudes, and Influencers (KAIs)

Participant responses to KAI questions were consistent with the conjoint analysis results. Participants were asked to rate the importance of four levels (“number of times a day a pill must be given,” “cost,” “the importance of the drug for treating infections in people,” and “whether or not you need to give your dog a pill”) as method of administration was separated into “number of times a day a pill must be given” and “whether or not you need to give your dog a pill.” The majority of respondents reported all four levels to be of high importance (Table 2.4). The level with the largest proportion of respondents indicating that they considered it to be of high importance was cost (73%; 95% CI: 69%, 77%), which was true for all three recruitment groups. The level with the lowest proportion of participants indicating that it was of high importance to them was “the importance of the drug for treating infections in people,” (52%; 95% CI: 49%, 56%) which appeared to be higher in the US and Canadian groups (58% and 55%, respectively) than the ESM group (39%). Subjective assessment of the ESM group showed that the level with the lowest proportion of participants indicating it was of high importance to them (25%) was whether or not the owners had to administer a pill.

2.3.4 Knowledge of antimicrobial resistance

When asked how important they thought AMR was in human medicine over half of participants (57%) indicated they thought it was very important. This was true for all three recruitment groups, though there was a difference between groups, with a larger proportion of the ESM (78%) group selecting very important compared to 49% of Canadian and 52% of US participants ($P<0.001$). Participant responses to KAI questions are fully summarised in Tables 2.5 – 2.7. When asked "*Do you think antibiotic use in pets poses a risk to humans?*," only 29% of participants thought that it definitely or probably did. A difference was found between the proportion of respondents in each participant group that responded yes to this question ($P<0.001$). In the ESM group this was the majority of participants (52%), which is in contrast to the US (23%) and Canadian groups (20%), where this was the smallest proportion.

A Pearson's chi-squared test demonstrated an association between participant response to the question "*Do you think antibiotic use in pets poses a risk to humans?"* and level of education, with a higher proportion of participants who responded yes (57%) having a university level education compared to those who answered might or might not (39%) or no (39%) ($P<0.001$). There was also an association between age and participant opinion of the risk of AMU in pets ($P<0.001$). More participants in the 26-35 age bracket (33%)

responded yes compared to those who responded might or might not (22%) or no (22%), and participants over the age of 51 were more likely to respond no.

2.4 Discussion

Our study demonstrated that the North American dog-owners surveyed considered cost to be the most important factor in antibiotic selection for their pet. In the choice-based conjoint analysis this was the feature with the largest median preference score, accounting for nearly half of the decision making when participants chose between drugs in the conjoint scenarios. Cost was also the factor for which the greatest proportion of respondents indicated it was of high importance when directly queried (73%).

Despite evidence that pet ownership is increasing in North America (Volk *et al.* 2014), veterinary visits are decreasing (Volk *et al.* 2011). While data on the reason(s) behind this decrease in veterinary visits by pet-owners is limited, a large portion of this is suspected to be attributed to the rising costs of veterinary care (Access to Veterinary Care Coalition 2018; American Veterinary Medical Association 2017; Volk *et al.* 2014). Veterinarians themselves widely report that owner financial constraint is an important consideration in their day-to-day practice, and influences diagnostic testing performed and treatments prescribed (De Briyne *et al.* 2013; Hardefeldt *et al.* 2018a). Our results highlight that medication costs are of significant importance to the majority of dog-owners in our study when their pet is being prescribed an antimicrobial. It is likely that this cost consideration-importance is extended to other aspects of veterinary care, such as diagnostics (e.g. bacterial culture and susceptibility testing) and may be a contributing factor to the lack of compliance with existing AMS guidelines that is observed in companion animal practice (De Briyne *et al.* 2013). It is important to note that the US and Canadian groups had a financial incentive for their participation, so this may bias our results. Our ESM participants, despite being offered no incentive, had the largest median utility value for cost so recruitment method does not seem to have a significant effect. Alternatively, our results may indicate that cost is only of comparatively high importance, and that considerations such as method of administration and the importance of a drug in human medicine are low priority for most owners. However, for all four levels assessed in the KAI questions, over 50% of owners indicated these levels ("number of times a day a pill must be given," "cost," "the importance of the drug for treating infections in people," and "whether or not you need to give your dog a pill") to be of high importance to them, and as the KAI responses and conjoint data had high levels of agreement, it is likely that our conjoint analysis demonstrated a combined effect of cost being of high importance to most owners together with a lower prioritisation of other considerations, particularly drug importance in human medicine.

Our choice-based conjoint analysis revealed that the importance of a drug for treating infections in people was the lowest priority for pet-owners, as compared to cost and ease of administration of antimicrobials. Despite being lowest priority, just over half of our participants stated that the importance of the drug as an important factor when their dog was given an antibiotic. A consistent theme from studies looking into perception of AMR, including in the pet-owning population, is that many perceive it to be a distant problem, one that either does not need to be worried about now, or does not influence or impact them directly (Golding *et al.* 2019; Hardefeldt *et al.* 2018b; Hughes *et al.* 2012; Redding & Cole 2019). It was interesting that the US and Canadian study groups would rather have a drug that is “very important” in human medicine, rather than one that is “not important,” while the opposite was true for the ESM participants. This may indicate a lack of clarity in the question format; however, another study of pet-owner KAIs found that no owners were concerned by the idea that their pets received the same drugs as humans, and several were even comforted by that fact (Redding & Cole 2019). The US and Canadian participants in this study may value a drug considered important in human medicine because they perceive it to be a more effective treatment for their dog. In contrast, the ESM participants, who have sought educational material through a blog site, were more likely to prefer a drug that was “not important” in human medicine because of a greater awareness of AMR.

When asked about AMR in human medicine, the majority of participants in our study indicated that they considered this to be “very important” or “important,” which is in agreement with all other studies surveying pet-owners (Redding & Cole 2019; Smith et al. 2018; Stallwood et al. 2019). Larger studies that have focussed solely on human medicine have also found that the general public are largely aware of AMR in the human population (Gualano et al. 2015); however, the level of understanding is fairly superficial, and public perception of the level of threat AMR poses is variable (Gualano et al. 2015;

Hawkings et al. 2007; Micallef et al. 2017; Stallwood et al. 2019). This finding in human medicine of a superficial understanding may explain the apparent disconnect between the non-ESM groups' conjoint results and survey responses, which indicated that non-ESM participants valued drugs that were important in human medicine.

Only 29% of participants in this study recognised the risks AMU in companion animals potentially poses to humans, which is similar to the findings of other veterinary studies of pet-owners (Smith et al. 2018; Stallwood et al. 2019). When data have been collected via subject interviews, several human and veterinary studies indicate that participants do not understand the general mechanism of AMR (Hawkings et al. 2007; Micallef et al. 2017; Redding & Cole 2019; Smith et al. 2018). Many believe it is the person taking the drug, rather than the bacteria, that becomes resistant to the antimicrobial (Hawkings et al. 2007; Redding & Cole 2019). In light of this, it is not surprising that animal owners may not understand that AMR bacteria can be transmitted between pets and humans. Our results support that the majority of dogs-owners do not understand how the AMU in their pets may impact human health, and indicate that this should be a target for veterinarian-client AMS education.

Significant differences were found in the responses between our three participant groups, as well as in their demographic make-up. This is most likely due to the difference in recruitment methods between the ESM group compared to the US and Canadian, as the ESM group are interacting with veterinary literature on this topic in at least some form, though there are some potential confounding variables. The ESM group had the highest level of understanding of AMR, both in human and veterinary medicine. Of the participants that believed AMU in companion animals posed a risk to humans, nearly half were from the ESM group. The ESM group had a higher proportion of female participants, had a higher average household income, and a higher education level, than the other groups. Of these demographic characteristics, only a higher education level was associated with both an increased likelihood of perceiving AMR as a problem in human medicine and AMU in pets being a potential risk of AMR to humans. Participants with a higher education level were also more likely to prefer drugs that were "not important" for treating infections in people. Thus, education level was likely an important confounder in our study and in-part responsible for why our ESM group varied in certain areas from our other recruitment groups.

Choice-based conjoint analysis was selected as the assessment method in this study due to its success in other studies conducted in the medical field, as well as the ability to directly quantify participant preferences for certain aspects of a medication (Bridges et al. 2011; Ryan & Farrar 2000; Stebler et al. 2016). A major limitation of this study was inability to determine the motivations behind participant selections, which could have been identified by a more qualitative tool such as subject interviews. It is also important to note that the scenario with which the participants were presented was hypothetical, and their motivations and preferences may change when they are making decisions about their sick pet in a real-life setting. While this study of dog-owners is one of the largest surveys of pet-owners to date, this sample size is still limited compared to the total dog-owning population of North America and caution should be observed when applying these findings to the population at large. In addition, the ESM group was not limited to North America, but given that less than 2% (n=3) of this study group originated from outside the US and Canada, this is unlikely to have influenced the results. Other study limitations include that participants were not asked if they had a background in a medical field, as has been done in previous pet-owner studies (Stallwood et al. 2019), which may have resulted in non-representative sample population, especially from the ESM group. Other studies only had a low proportion of participants with a veterinary background; however, despite using veterinary clinics to gather pet-owner data (Stallwood et al. 2019).

It is clear that cost is the main driving factor for the majority of North American dog-owners surveyed in this study when it comes to selecting an antimicrobial. To fully evaluate how cost impacts other pet-owner decisions related to antimicrobial selection, (e.g. willingness to perform diagnostics), questionnaires specifically addressing these areas ideally would be performed. This study also identified some interesting differences between our ESM group and the US and Canadian groups, relating both to their drug preferences in the conjoint analysis and their responses to the KAI questions. Knowledge of AMR in human medicine is high, but the potential role AMU in companion animals has on AMR is not well recognised by the majority of dog owners in this survey. This highlights the need for education of dog-owners as part of ongoing antimicrobial stewardship programs in companion animals. It also serves as an important demonstration of how recruitment methods, particularly the use of social media, and study population can alter survey responses and the conclusions of a study. Further studies are required to explore what forms owners' perceptions and identify effective communication methods between veterinarians and their client(s). These studies, together with development of client-specific education resources, are needed to increase antimicrobial stewardship in companion animals.

Table 2.1 Summary of the features and levels included in the conjoint analysis section of a survey of the knowledge, attitudes, and influencers of North-American pet owners surrounding antimicrobials and antimicrobial stewardship.

Feature	Level
Cost	$25 USD/$30 CAD
	$60 USD/$75 CAD
	$120 USD/$150 CAD
How the antimicrobial is given	Injected once by your veterinarian
	Oral (pill or liquid) once a day for 5 days
	Oral (pill or liquid) twice a day for 5 days
	Oral (pill or liquid) three times a day for 5 days
Importance of the drug for treating infections in people	Very important
	Somewhat important
	Not important

Table 2.2 Summary of participant demographics (number and proportion) for the total study population and the three recruitment groups of a survey of the knowledge, attitudes, and influencers of North-American pet owners surrounding antimicrobials and antimicrobial stewardship. *P*-values are reported for Pearson's chi-square tests performed to examine the different demographic distributions of the three participant groups.

	Canada	US	Educational Social Media	Total
	Gender			
Male	139 (47%)	156 (50%)	8 (4.1%)	**303 (38%)**
Female	158 (53%)	158 (50%)	187 (95.9%)	**503 (62%)**
Total	**297**	**314**	**195**	**806**
				P<0.001

	Age			
18-25 years old	41 (14%)	86 (27%)	29 (15%)	**156 (19%)**
26-35 years old	63 (21%)	78 (25%)	62 (32%)	**203 (25%)**
36-50 years old	81 (27%)	83 (26%)	51 (26%)	**215 (27%)**
51-65 years old	77 (26%)	51 (16%)	41 (21%)	**169 (21%)**
>65 years old	34 (11%)	17 (5.4%)	12 (6.2%)	**63 (7.8%)**
Total	**296**	**315**	**195**	**806**
				P<0.001
	Approximate Household Income			
< $50,000	70 (24%)	119 (38%)	50 (26%)	**239 (30%)**
$51,000 - $100,000	143 (48%)	115 (37%)	75 (38%)	**333 (41%)**
$101,000 - $200,000	61 (21%)	41 (13%)	44 (22%)	**146 (18%)**
> $200,000	9 (3.0%)	11 (3.5%)	8 (4.1%)	**28 (3.5%)**
Prefer not to answer	15 (5.0%)	29 (9.2%)	19 (9.7%)	**63 (7.8%)**
Total	**298**	**315**	**196**	**809**
				P<0.001
	Highest Level of Education			
High School	87 (29%)	119 (38%)	11 (5.6%)	**217 (27%)**
Community College	95 (32%)	59 (19%)	82 (42%)	**236 (29%)**
University degree	116 (39%)	137 (44%)	103 (53%)	**356 (44%)**
Total	**298**	**315**	**196**	**809**
				P<0.001

† *P*-values indicate differences among the three participant groups
‡ Percentages in each column may not add up to 100 due to rounding

Table 2.3 Summary of conjoint analysis in a survey of the knowledge, attitudes, and influencers of North-American pet owners surrounding antimicrobials and antimicrobial stewardship, including median utility value for all levels and the total preference score (with 1st and 3rd quartiles) for the three features. Data provided by recruitment group and overall.

	Canada		US		Educational Social Media		Total	
	Total Preference Score ‡ (Q1,Q3)	Median Utility Value †	Total Preference Score (Q1,Q3)	Median Utility Value	Total Preference Score (Q1,Q3)	Median Utility Value	Total Preference Score (Q1,Q3)	Median Utility Value
Method of administration	**3.54** (2.27, 5.43)		**2.81** (1.73, 4.20)		**5.12** (3.52, 7.36)		**3.61** (2.29, 5.27)	
Injected once by your veterinarian		1.55		1.41		2.11		**1.56**
Oral (pill or liquid) once a day for 5 days		0.753		0.409		1.12		**0.660**
Oral (pill or liquid) twice a day for 5 days		-0.373		-0.305		-0.177		**-0.306**
Oral (pill or liquid) three times a day for 5 days		-1.97		-1.47		-2.87		**-1.88**
Cost	**6.47** (3.03, 9.47)		**3.90** (1.75, 6.45)		**9.06** (6.12, 12.4)		**5.92** (2.83, 8.77)	
$25 USD/$30 CAD		3.09		1.86		4.32		**2.83**
$60 USD/$75 CAD		0.250		0.186		0.441		**0.245**
$120 USD/$150 CAD		-3.34		-2.02		-4.77		**-3.07**
Importance in human medicine	**2.93** (1.46, 4.96)		**1.76** (0.807, 3.15)		**2.59** (1.46, 4.74)		**2.33** (1.07, 4.30)	
Very important		1.32		0.756		-0.459		**0.718**
Somewhat important		0.0602		0.0752		-0.139		**0.0593**
Not important		-1.36		-0.844		0.626		**-0.802**

† Positive or negative numerical value indicating participant's preference for each level of each feature after all 10 conjoint questions were completed.
‡ Difference between highest and lowest level for each feature.

Table 2.4. The number and proportion of participants who selected "very important" or "important" when asked how important a specific factor was when their dog was given an antimicrobial in a survey of the knowledge, attitudes, and influencers of North-American pet owners surrounding antimicrobials and antimicrobial stewardship.

	Canada	*US*	*Educational Social Media*	*Total*	
	Number of participants (Percentage %)	Number of participants (Percentage %)	Number of participants (Percentage %)	Number of participants (Percentage %)	95% CI
Number of times a day a pill must be given	N=199 (67%)	N=212 (67%)	N=107 (55%)	**N=518 (64.2%)**	**(60.8%, 67.5%)**
Cost	N=222 (75%)	N=237 (75%)	N=125 (64%)	**N=584 (72.5%)**	**(69.3%, 75.6%)**
The importance of the drug for treating infections in people	N=163 (55%)	N=181 (58%)	N=77 (39%)	**N=421 (52.2%)**	**(48.9%, 55.7%)**
Whether or not you need to give your dog a pill	N=174 (60%)	N=198 (63%)	N=49 (25%)	**N=421 (52.4%)**	**(48.9%, 55.9%)**

Table 2.5 Summary of participant responses to the questions *"How important do you think antibiotic resistance is in human medicine?"* and *"Do you think antibiotic use in pets poses a risk to people?"* in a survey of the knowledge, attitudes, and influencers of North-American pet owners surrounding antimicrobials and antimicrobial stewardship

	Canada	US	Educational Social Media	Total
	Importance of Antibiotic Resistance in Humans			
Very Important	146 (49%)	165 (52%)	152 (78%)	**463 (57%)**
Important	104 (35%)	89 (28%)	38 (19%)	**231 (29%)**
Slightly Important	25 (8.4%)	37 (12%)	2 (1.0%)	**64 (7.9%)**
Don't Know	22 (7.4%)	16 (5.1%)	3 (1.5%)	**41 (5.1%)**
Not Important at All	1 (0.3%)	8 (2.5%)	1 (0.5%)	**10 (1.2%)**
Total	**298**	**315**	**196**	**809**
	Risk of Antibiotic Use in Pets to Humans			
Yes	59 (20%)	73 (23%)	100 (51%)	**232 (29%)**
Might or Might Not	119 (40%)	117 (37%)	48 (25%)	**284 (35%)**
No	120 (40%)	125 (40%)	48 (25%)	**293 (36%)**
Total	**298**	**315**	**196**	**809**

† Percentages in each column may not add up to 100 due to rounding

Table 2.6 Summary of participant response to the question "*How important do you think antibiotic resistance is in human medicine?"* in a survey of the knowledge, attitudes, and influencers of North-American pet owners surrounding antimicrobials and antimicrobial stewardship. Displayed by demographic group. *P*-values are reported for Pearson's chi-square tests performed to examine the differences in responses across demographic groups.

	Very important	Important	Slightly important	Don't know	Not at all important	Total
	Gender					
Female	309 (67%)	132 (57%)	33 (52%)	23 (58%)	6 (60%)	**503 (62%)**
Male	153 (33%)	98 (43%)	31 (48%)	17 (43%)	4 (40%)	**303 (38%)**
Total	**462**	**230**	**64**	**40**	**10**	**806**
						P=0.040
	Age					
18-25 years	81 (18%)	48 (21%)	18 (28%)	9 (22%)	0 (0%)	**156 (19%)**
26-35 years	112 (24%)	65 (28%)	18 (28%)	7 (17%)	1 (10%)	**203 (25%)**
36-50 years	125 (27%)	61 (27%)	13 (20%)	13 (32%)	3 (30%)	**215 (27%)**
51-65 years	101 (22%)	39 (17%)	13 (20%)	12 (29%)	4 (40%)	**169 (21%)**
>65 years old	42 (9.1%)	17 (7.4%)	2 (3.1%)	0 (0%)	2 (20%)	**63 (7.8%)**
Total	**461**	**230**	**64**	**41**	**10**	**806**
						P=0.016[§]
	Approximate Household Income					
< $50,000	141(31%)	58 (25%)	25 (39%)	12 (29%)	3 (30%)	**239 (30%)**
$51,000 - $100,000	174 (38%)	112 (49%)	25 (39%)	16 (39%)	6 (60%)	**333 (41%)**
$101,000 - $200,000	94 (20%)	37 (16%)	9 (14%)	5 (12%)	1 (10%)	**146 (18%)**
> $200,000	20 (4.3%)	6 (2.6%)	1 (1.6%)	1 (2.4%)	0 (0%)	**28 (3.5%)**
Prefer not to answer	34 (7.3%)	18 (7.8%)	4 (6.3%)	7 (17%)	0 (0%)	**63 (7.8%)**
Total	**463**	**231**	**64**	**41**	**10**	**809**
						P=0.147[§]
	Highest Level of Education					
High School	105 (23%)	65 (28%)	25 (39%)	17 (42%)	5 (50%)	**217 (27%)**
Community College	151 (33%)	59 (26%)	13 (20%)	10 (24%)	3 (30%)	**236 (29%)**

University degree	207 (45%)	107 (46%)	26 (41%)	14 (34%)	2 (20%)	**356 (44%)**
Total	**463**	**231**	**64**	**41**	**10**	**809**
						***P*=0.012**
	Participant Group					
Canada	146 (32%)	104 (45%)	25 (39%)	22 (54%)	1 (10%)	**298 (37%)**
US	165 (36%)	89 (39%	37 (58%)	16 (39%)	8 (80%)	**315 (39%)**
Educational Social Media	152 (33%)	38 (17%)	2 (3.1%)	3 (7.3%)	1 (10%)	**196 (24%)**
Total	**463**	**231**	**64**	**41**	**10**	**809**
						***P*<0.001**

† *P*-values significant at P<0.01
‡ Percentages in each column may not add up to 100 due to rounding
§ Statistical analyses for these data were performed using dichotomised variables as described in the Materials and Methods.

Table 2.7 Summary of participant response to the question *"Do you think antibiotic use in pets poses a risk to people?"* in a survey of the knowledge, attitudes, and influencers of North-American pet owners surrounding antimicrobials and antimicrobial stewardship. Displayed by demographic group. *P*-values are reported for Pearson's chi-square tests performed to examine the differences in responses across demographic groups.

	Yes	Might or might not	No	Total
	Gender			
Female	155 (67.1%)	170 (59.9%)	178 (61.2%)	**503 (62.4%)**
Male	76 (32.9%)	114 (40.1%)	113 (38.8%)	**303 (37.6%)**
Total	**231**	**284**	**291**	**806**
				***P*=0.208**

	Age			
18-25 years old	44 (19%)	64 (23%)	48 (16%)	**239 (30%)**
26-35 years old	76 (33%)	63 (22%)	64 (22%)	**333 (41%)**
36-50 years old	70 (30%)	75 (26%)	70 (24%)	**146 (18%)**
51-65 years old	31 (13%)	59 (21%)	79 (27%)	**28 (3.5%)**
>65 years old	9 (3.9%)	23 (6.1%)	31 (11%)	**63 (7.8%)**
Total	**230**	**284**	**292**	**806**
				P<0.001
	Approximate Household Income			
< $50,000	63 (27%)	78 (28%)	98 (33%)	**239 (30%)**
$51,000 - $100,000	93 (40%)	119 (42%)	121 (41%)	**333 (41%)**
$101,000 - $200,000	47 (20%)	47 (17%)	52 (18%)	**146 (18%)**
> $200,000	14 (6.0%)	8 (2.8%)	6 (2.0%)	**28 (3.5%)**
Prefer not to answer	15 (6.5%)	32 (11%)	16 (5.5%)	**63 (7.8%)**
Total	**232**	**284**	**293**	**809**
				P=0.031
	Highest Level of Education			
High School	42 (18%)	86 (30%)	89 (30%)	**217 (27%)**
Community College	59 (25%)	86 (30%)	91 (31%)	**236 (29%)**
University degree	131 (56%)	112 (39%)	113 (39%)	**356 (44%)**
Total	**232**	**284**	**293**	**809**
				P<0.001
	Participant Group			
Canada	59 (25%)	119 (42%)	120 (41%)	**298 (37%)**
US	73 (31%)	117 (41%)	125 (43%)	**315 (39%)**
Educational Social Media	100 (43%)	48 (17%)	48 (16%)	**196 (24%)**
Total	**232**	**284**	**293**	**809**
				P<0.001

† *P*-values significant at *P*<0.01
‡ Percentages in each column may not add up to 100 due to rounding

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3.0 Knowledge, attitudes and influencers of cat owners in North America around antimicrobials and antimicrobial stewardship

Abstract

The objectives of this study were to determine antimicrobial prescribing preferences of North-American cat-owners, and to establish cat-owner knowledge, attitudes and influencers around antimicrobial resistance (AMR) and stewardship. An online questionnaire was used for data collection in order to survey three cat-owner groups: US cat-owners, Canadian cat-owners, and cat-owners engaging with educational social media. Participants were queried on AMR, and their preferences for their own cat when prescribed an antimicrobial, with respect to, cost, method of drug administration, and importance of a drug for treating infections in people. Responses were evaluated through conjoint analysis and Likert-type questions. Data were analysed using descriptive and analytic statistics. A total of 813 complete responses were included in the final analysis. Cost (37%) and method of administration (38%) were of equal preference. The importance of a drug for treating infections in people was of lower priority, with the majority of US and Canadian cat-owners reporting preference of an antimicrobial that was "very important." A low proportion of participants indicated that they thought antimicrobial use in pets posed a risk to humans (28%). However, a higher number of participants with a university education (40%, $P<0.001$) and from the educational social media group (51%, $P<0.001$) responded that they believed antimicrobial use in pets was a concern for people. Cat-owners appeared to prioritise cost and method of administration

equally in their preference for an antimicrobial prescribed for their pet. Few cat-owners reported concern arounds human risk due to antimicrobial use in pets.

3.1 Introduction

Antimicrobial stewardship (AMS) in companion animal practice is gaining attention worldwide, as concern for the potential transfer of antimicrobial resistant (AMR) pathogens between pets and their owners is increasingly recognised (Pomba *et al.* 2017). Similarly, there is concern for the negative impact on animal welfare due to increasing incidence of AMR infections in animals (World Organisation for Animal Health 2015). As AMS has gained traction in the human and veterinary medical fields, there has been a shift from focussing on the responsibility (and education) of the antimicrobial prescribers (i.e. doctors and veterinarians) to a more holistic approach to AMS that involves education of patients and pet-owners (Dyar *et al.* 2017).

Limited research has been performed exploring pet-owner knowledge, attitudes and influencers (KAIs) towards AMR infections in their animals. Unfortunately, pet-owners are frequently perceived by veterinarians to be a significant barrier to AMS efforts (De Briyne *et al.* 2013). The primary hurdle stated by veterinarians to their AMS efforts is owner financial constraint. A common example financial constraint in veterinary practice is cost of performing adequate testing such as culture and susceptibility testing prior to antimicrobial prescription (De Briyne *et al.* 2013; Mateus *et al.* 2014). However, previous surveys of owners have provided conflicting evidence on their willingness to spend money toward veterinary care. The study of dog-owners described in Chapter two of this thesis found that cost was the most important influencing factor when owners were given a choice between two different antimicrobials (Stein *et al.* 2021). Another study reported that owners would prefer to trial empirical therapy prior to performing culture and susceptibility testing, with many respondents listing cost as the primary motivation behind this decision (Redding & Cole 2019). In contrast, other studies report that owners would prefer to spend money on diagnostics to ensure their animal gets the most appropriate drug, but feel that they are not given this option by their veterinarian (Stallwood *et al.* 2019).

Further research is needed to determine the extent of financial concern by cat-owners regarding veterinary care. One US study of cat-owners found that 66% of owners would pay for diagnostic testing (Stallwood *et al.* 2019). This finding must be considered in the context of surveys that suggest cats are less likely to be taken to the veterinarian than dogs, are less likely to have preventive care, and have less money spent on them (American Veterinary Medical Association 2017). Despite the Stallwood study findings, the data generated by the AVMA may indicate that financial concern may be more of a barrier in feline than canine practice.

For cat-owners there is the additional complication, concern and practical challenge surrounding administering medications to cats once they are prescribed. Compliance with treatment regimens are concerns in both human and veterinary medicine (Wareham *et al.* 2019), and there is an indication that dog-owners would prefer not to administer oral medications (Chapter 2). Cats typically are perceived to be even more resistant to oral medications administration than dogs are, and are frequently prescribed long-acting injectable medications to alleviate this challenge (Buckland *et al.* 2016; Burke *et al.* 2017; Chapman 2018; Hardefeldt *et al.* 2020; Mateus *et al.* 2011). These single-injection antimicrobials are viewed as critically important in human medicine, and often are prescribed when a lower tier antimicrobial is more clinically indicated in cats, frequently with little to no justification in the medical record (Burke *et al.* 2017; Hardefeldt *et al.* 2020). Further surveys of cat-owners are required to determine the extent method of administration (i.e., oral or injectable) influences their preferences on antimicrobial prescription for their cat.

The few studies on companion and agricultural animal-owners' awareness and understanding of AMR in animals have demonstrated that AMR awareness and understanding of AMR in animals is limited and often a low priority (Golding *et al.* 2019; Redding & Cole 2019; Smith *et al.* 2018; Stein *et al.* 2021). Similarly it is recognised that the general public have superficial understanding of AMR in human medicine, and that AMS programmes that include patient education are more successful (Lee *et al.* 2015). It follows that education of pet-owners in companion animal medicine should be included in veterinary AMS programs. To date, studies performed in pet-owners have been on a small scale using qualitative techniques such as in person interviews (Redding & Cole 2019; Smith *et al.* 2018). Some large scale surveys have been performed to allow quantitative data collection (Stallwood *et al.* 2019; Stein *et al.* 2021), but further research using different subsets of the population are warranted to expand the current understanding of pet-owner KAIs surrounding antimicrobial prescription in their own pets and within veterinary medicine as a whole.

A previous study produced by our research team in North American dog-owners explored KAIs and used choice-based conjoint analysis (Stein *et al.* 2021). This technique allows direct numerical quantification of owner preferences by presenting owners with a series of mock scenarios. This cat-owner study aims to complement that canine study, using the same techniques in cat-owners. The objectives of this study were to: 1) quantify the influence of cost, ease of administration and drug importance in human medicine on a cat-owner's preference of antimicrobials, and 2) explore associations between demographics on owners' understanding of antimicrobial resistance in human and veterinary medicine and their perception of its importance. We hypothesised that 1) cat-owners will identify cost and method of administration as the most important attributes in a drug and 2) cat-owners would have a limited knowledge of antimicrobial resistance and stewardship in a veterinary setting.

3.2 Materials and Methods

3.2.1 Data collection

Data were collected as described in Chapter 2. Two participant groups (USA and Canadian cat-owners) were recruited using an online survey platform (Qualtrics®). A third group of cat-owners was recruited via a veterinary educational social media (ESM) site (www.wormsandgermsblog.com). This was a prospective study using an online questionnaire targeted at Canadian and American cat-owners. Participants were not asked if they had previously participated in the dog-owner survey. Survey data were initially collected between September 2019 and March 2020, but due to a technical error during initial collection, the Canadian data were discarded and a new data set was collected using a different study population in July 2020. The survey used was modified from a canine version of the survey found in Chapter 2, adjusting species and altering medication costs to be more reflective of feline prescriptions in the conjoint questions. In addition to conjoint style questions, owners were asked a series of multiple-choice questions consisting of basic demographic information, KAIs surrounding antimicrobial prescription in their own cat, and questions about AMR in human and veterinary medicine. A copy of the complete survey is included in Appendix II.

The conjoint analysis consisted of a scenario in which participants were asked to pick which of two equally effective antimicrobials they would prefer if their cat had a urinary tract infection. A summary of the features and potential levels are presented in Table 3.1. These were presented in a series of 10 random combinations of two antimicrobials, unique to each participant, with participants selecting their preferred option.

3.2.2 Statistical analysis

Commercially available software (Minitab® Statistical Software; State College, PA) was used for all statistical analysis. All continuous variables (i.e. conjoint data) were assessed for normality using Anderson-Darling normality tests. The majority of variables were found to be non-normally distributed and consequently all continuous data were expressed as medians and upper and lower quartiles. The data for the feature "importance of a drug for treating people" were found to be normally distributed, so parametric tests were performed on these data where appropriate.

Categorical data were analysed as described in Chapter 2. Multiple-choice questions with 5 possible responses were recoded into two or three possible responses to address small sample sizes. In such cases, the data were divided into two or three groups of roughly equal size, depending on the median and if the data was ordinal or nominal. Age, household income, and importance of AMR in human medicine were retained in their original categories.

Pearson's chi-square tests were used to identify associations between categorical variables. Investigation into the association between age and household income, and response to the question "*How important do you think antibiotic resistance is in human medicine?*" was not possible due to the computational power required for the size of these comparisons. For these comparisons only age and household income were dichotomised to allow Pearson's chi-square testing. A one-way ANOVA was performed on level of education and participant utility value for the level 'not important' of the feature "importance of a drug for treating people."

A Bonferroni adjustment to correct for multiple comparisons and reduce likelihood of type 1 error was performed. Comparisons between the demographic makeup of the three participant groups were considered significant at *P*<0.0125, and differences between participant demographics and response to the questions "*How important do you think antibiotic resistance is in human medicine?"* and "*Do you think antibiotic use in pets poses a risk to humans?"* were considered significant at *P*<0.01. All other tests were considered statistically significant at *P*<0.05.

3.3 Results

A total of 818 surveys were completed (Canadian participants, n=315; US participants, n=315; participants recruited through ESM, n=188). Five responses were removed from the ESM group due to a failure to respond to, or response of "no" to the question "*Do you currently own or care for a cat*?" The remaining 813 responses (99%) were included in the final analysis (Canada, n=315; US, n=315; ESM, n=183). Due to a technical error, ESM conjoint questions were not available, consequently only Canadian and US conjoint data were analysed.

3.3.1 Demographic data

Demographic data of all participants are summarised in Table 3.2. The ESM group had a higher proportion of female participants (96%) compared to the US (69%) and Canadian (60%) groups (*P*<0.001). The ESM group also had a higher proportion of participants with an income >$200,000 (9.8%) compared to the US (2.5%) and Canadian (2.9%) and a higher proportion of participants with a university level education (63%) compared to the US (38%) and Canadian (42%) groups (*P*<0.001). The Canadian group had a higher proportion of participants in the older age categories, compared to the US and ESM groups, whereas the US group had a higher proportion of participants in the 18-25 age group (12%) compared to the Canadian (3.2%) and ESM (9.3%) groups (*P*<0.001).

3.3.2 Choice-based Conjoint Analysis

Both the US and Canadian participant groups considered cost and method of administration to be of similar importance (Table 3.3). The median utility score for cost was 4.13, with the $25 level having the highest utility value (1.97) and $80 having the lowest (-2.19). The median utility score for method of administration was 3.86. The level with the highest utility value was “injected once by your veterinarian” (1.94) and the level with the lowest utility value (-1.78) was “oral (pill or liquid) three times a day for 5 days.” The percentage preference share for cost and method of administration were 37% and 38%, respectively.

The feature with the lowest median utility score was importance of the drug for treating infections in people (2.58), with the “very important” level having the highest utility value (1.20) and the level having the lowest utility value was “not important” (-1.24). The overall preference share was 25%. Participant education and utility value for “not important” were not statistically associated (*P*=0.088).

3.3.3 Knowledge, Attitudes, and Influencers (KAIs)

Participants were asked to rate importance of four levels (“number of times a day a pill must be given,” “cost,” “the importance of the drug for treating infections in people,” and “whether or not you need to give your cat a pill”) when their cat was prescribed an antimicrobial. Results are fully summarised in Table 3.4. The results were largely consistent with the conjoint analysis, as cost (69%; 95% CI: 65%, 72%) and number of times a day a pill is administered (76%; 95% CI: 73%, 79%) were viewed of high importance by the greatest number of participants. For the Canadian and US groups, the proportion of participants who indicated cost was important was very similar to the proportion who indicated that the number of times a day a pill must be given was important to them. However, the ESM group appeared to have a strong preference for pill number with 84% of ESM participants indicating it was “important” or “very important” to them, compared to only 51% who thought cost was important. For all three groups the importance of the drug for treating infections in people had the lowest proportion of participants who considered it to be of high importance.

3.3.4 Knowledge of antimicrobial resistance

The majority of participants (63%) indicated that they considered AMR in human medicine to be very important. The ESM group had the highest proportion of participants (86%) that selected “very important” when asked about AMR in human medicine, compared to the US and Canadian groups each with 56% of participants ($P<0.001$). A full summary of participant responses to the KAI questions is reported in Tables 3.5 -3.7.

Less than one third (28%) of participants indicated that they thought antimicrobial use in pets posed a risk to humans, whereas 39% thought that there was no risk. Of the participants in the ESM groups half (51%) responded “probably” or “definitely yes" when asked "*Do you think antibiotic use in pets poses a risk to humans?*," compared to less than a quarter of the US (24%) and Canadian (19%) groups. Response to the question "*Do you think antibiotic use in pets poses a risk to humans?"* significantly varied across the participant groups (P<0.001). Associations were found between participant age (P<0.001), household income (P<0.001), and level of education (P<0.001) and whether a participant thought it was likely that antimicrobial use in pets posed a risk to humans (age: P<0.001; income: P<0.003; education; P<0.001). In general, participants who were younger, reported a higher household income, or a higher level of education were more likely to indicate that they thought antimicrobial use in pets posed a risk to humans.

3.4 Discussion

This study on North-American cat owners indicated that cost and ease of administration of antimicrobials prescribed to their cat shared equal importance, and outweighed antimicrobial importance in human medicine.

It is widely believed, but only anecdotally documented, that cats are more resistant to administration of oral medications than dogs are (Chapman 2018). A similar designed study (Chapter 2 of this thesis) involving a similarly recruited group of dog-owners found that, while method of administration was important to owners, cost had the greatest influence on dog-owner antimicrobial preferences (Stein *et al.* 2021). This is in contrast to the findings of this study, where method of administration was found to have equal importance with medications that are injected once only as the most desirable. Several recent surveillance studies performed to assess antimicrobial prescription in companion animal practice have found that cats are more likely than dogs to be prescribed a long-acting injectable antimicrobial, which supports our findings that cat owners may be reluctant to administer oral medications to their pet (Buckland *et al.* 2016; Hardefeldt *et al.* 2020; Mateus *et al.* 2011; Murphy *et al.* 2012; Radford *et al.* 2011). More research is needed to establish the extent to which cat-owners influence the use of long-acting injectable antimicrobials, and determine whether it is veterinarians themselves who encourage the use of this route of administration.

Reluctance by cat-owners to administer oral medication has a potentially significant impact on AMS. For example, one long-acting injectable antimicrobial in veterinary practice, cefovecin (Burke *et al.* 2017), is a third-generation cephalosporin that is considered to be a highest priority critically important antimicrobial in human medicine (World Health Organization 2018). Critically important antimicrobials should be reserved for patients where no alternative treatment exist, but there is evidence that cefovecin is frequently prescribed in veterinary medicine with no such justification (Burke *et al.* 2017; Hardefeldt *et al.* 2020). Our data indicate that a single long-acting injectable antimicrobial was preferred by a large proportion of our study participants. Further effort may be needed to develop long-acting medications for cats that are considered to be lower tier antimicrobials, and so a more appropriate first line treatment.

In addition to a marked preference for a single long-acting antimicrobial injection, our conjoint analysis data indicated that there was a reduced preference for three times daily dosing of oral medication as compared to once or twice daily dosing. In the KAI section of our analyses a greater proportion of owners valued the number of times a pill must be given compared to any other feature. While there are few antimicrobials that require thrice daily dosing, this lowered preference for oral medication administration highlights an additional challenge in feline medicine. This preference warrants consideration by veterinarians when cats are prescribed an antimicrobial drug, and likely impacts owner compliance. Studies performed in dogs indicate that many dog-owners are not compliant with either the number of doses given or the intervals between doses, and that compliance decreases the more doses a day that are prescribed (Adams *et al.* 2005; Barter *et al.* 1996; Boda *et al.* 2011). Similar findings have been noted in human medicine (Claxton *et al.* 2001; Eisen 1990). Given the perception that cats are more difficult to medicate than dogs, and a similar aversion to increased daily dosing was found for dogs (Stein *et al.* 2021), it is reasonable to assume that similar or reduced levels of compliance may occur with increased dosing frequency in cats.

Incomplete antimicrobial courses or breaks in antimicrobial coverage due to prolonged periods between doses increase risk of treatment failure, and subsequently raise the occurrence of AMR (Kardas *et al.* 2005). While, to date, no studies have been performed in cats, extrapolations can be made from the canine literature. Dog-owner compliance has been shown to increase when clients perceive veterinarians spend sufficient time with them during a consultation, they have an understanding of the disease they are treating, or the dosing regimen is adapted to suit the owner's lifestyle (Adams *et al.* 2005; Boda *et al.* 2011; Grave & Tanem 1999). Our study demonstrates that cat-owners are reluctant to administer oral medications, especially with an increased dosing frequency. Further data is needed to examine cat-owner compliance with oral treatment regimens, and to identify areas in which this may be improved.

Similar to findings in dog owners and other studies exploring the knowledge of pet-owners (Smith *et al.* 2018; Stallwood *et al.* 2019; Stein *et al.* 2021), there was a low understanding of AMR in a veterinary setting among the participants of this study. This was particularly apparent with cat-owner knowledge of AMR risk and transmission between people and animals. Just over a quarter of the total study participants stated that they considered antimicrobial use in pets as "definitely" or "probably" posing a risk to humans. The risk of transmission between pets and other members of the household is not definitively proven. However, there is evidence of carriage of methicillin resistant *Staphylococcus pseudintermedius* (MRSP), a common commensal in dogs, in both pet-owners and veterinary staff, and there are many zoonotic species that could reasonably develop AMR (Pomba *et al.* 2017; van Duijkeren *et al.* 2011; Wright *et al.* 2005). A lack of concern for the human risk of companion animal AMU for participants in this study is combined with the results of the conjoint analysis where the majority of participants would prefer a drug that was "very important" in human medicine. These questions did not directly address a risk of AMR transmission, instead referring to a general risk to humans. It may be that participants did not make an association between AMU in pets and AMR in people, and were considering other risks. However, a lack of understanding of AMR transmission risk even between two people in the same household has been demonstrated in human studies (Bakhit *et al.* 2019), and it is likely that cat-owners in this study have a similar gap in knowledge. These findings demonstrate that increased education of pet-owners surrounding the connection between human and animal AMR, and the potential zoonotic risks of these diseases is needed.

In Chapter 2 the results from both KAI questions were similar, except for a preference for drugs that were “not important” in human medicine from the ESM group (Stein *et al.* 2021). Similar to the dogs-owners study Chapter 2, a much greater proportion of the cat-owners EMS group (51%), thought that AMU in pets posed a risk to humans, compared to the US (24%) and Canadian groups (19%). Unfortunately, conjoint analysis for the feline ESM group was not available for analysis. However, based on the similarities between the canine and feline ESM responses to non-conjoint questions, it is likely that conjoint responses would be similar. This study supports our findings in Chapter 2 that suggest that pet-owners who engage with veterinary educational material have improved understanding of AMR. Further studies are needed to determine the optimal way to disseminate AMR information to pet-owners to aid further companion animal AMS efforts.

In addition to participant group, significant associations were found between several other demographic characteristics and KAIs on AMU in pets. The most notable of these was level of education, with a higher proportion of participants with a university level education indicating that AMU in pets was a risk to people. This was also the case in Chapter 2 (Stein *et al.* 2021). However, unlike the dog-owners, there was no significant association between level of education and the utility value for drugs that are “not important” in treating infections in people. This is most likely due to the lack of conjoint data for the cat-owner ESM group, as both the canine and feline ESM groups had a higher proportion of participants with a university education. However, the level “not important” was selected arbitrarily in Chapter 2, and it was chosen to be consistent is this study. It may be that an association could be demonstrated between participant level of education and the level “very important.” Education is an important confounding variable in both these studies as it was difficult to ascertain if the increased understanding of veterinary AMR in the ESM group was due to an increased education level, or because this is a group that is already engaging with educational materials from the ESM site.

The primary limitation of this study is the lack of conjoint data for the ESM group. While previous data from Chapter 2 combined with the results from non-conjoint questions allows us to make inferences about what results may have been found, direct statistical comparisons to the other two recruitment groups cannot be made. It is also important to consider that the conjoint scenarios are hypothetical and may not accurately reflect the decisions that a cat-owner may make when facing the emotional stressors of a sick pet. The nature of the survey, which was designed to be quantitative as opposed to qualitative, also prohibits us from making conclusions about the motivations behind the participants' answers, especially for the conjoint analysis. The sample size of this survey is comparatively large when other pet-owner studies are considered, but it still a small fraction of the total North American cat-owning population. While different recruitment methods were utilised to gather a representative sample, caution must be exercised when extrapolating these data to the general cat-owning public in North America.

This study suggests that cost is an important driving factor for antimicrobial selection for the majority of feline owners, and prioritisation of antimicrobial stewardship is low. Our work also serves to highlight the differences between cat- and dog-owner preferences with respect to antimicrobials for their pets. In cat-owners, method of administration is an important consideration that, in contrast to dog-owners, is of equal priority to cost. Adequate veterinary consultation time should be dedicated to collaboration and education to ensure that dosing regimens are optimal for the individual cat, owner lifestyle and the disease process being treated.

As in our canine work, cat owner knowledge of AMR in veterinary medicine was limited. There was indication of improved knowledge of AMR in the ESM group, compared to the remaining study population, indicating that focused veterinary education materials may improve this knowledge base. Further research is needed on methods of communication to veterinary clients specific to AMS, and additional efforts towards establishment of baseline knowledge of AMR and AMS within the veterinary community. This study, combined with the dog-owner study provides practical considerations for companion animal veterinarians when prescribing antimicrobials to aid compliance, and is a One Health “call to action” towards AMR and AMS education of pet-owners.

Table 3.1. The features and levels of the conjoint section in a survey to assess knowledge, attitudes and influencers of cat owners in North America around antimicrobials and antimicrobial stewardship summarised.

Feature	Level
Cost	$25 USD/CAD
	$45 USD/$50 CAD
	$80 USD/$90 CAD
How the antimicrobial is given	Injected ONCE by your veterinarian
	Oral (pill or liquid) once a day for 5 days
	Oral (pill or liquid) twice a day for 5 days
	Oral (pill or liquid) three times a day for 5 days
Importance of the drug for treating infections in people	Very important
	Somewhat important
	Not important

Table 3.2. Participant demographics (number and proportion) from a survey to assess knowledge, attitudes and influencers of cat owners in North America around antimicrobials and antimicrobial stewardship summarised by total population and study group. The *p* values demonstrate differences in demographic distributions between the participant groups, as calculated by Pearson's chi-square tests.

	Canada	US	Educational Social Media	Total
	Gender			
Male	125 (40%)	97 (31%)	8 (4.4%)	**230 (28%)**
Female	190 (60%)	216 (69%)	175 (95.6%)	**581 (72%)**
Total	**315**	**313**	**183**	**811**
				P<0.001
	Age			
18-25 years old	10 (3.2%)	39 (12%)	17 (9.3%)	**66 (8.1%)**
26-35 years old	57 (18%)	69 (22%)	52 (28%)	**178 (22%)**
36-50 years old	85 (27%)	108 (34%)	46 (25%)	**239 (29%)**
51-65 years old	111 (35%)	73 (23%)	57 (31%)	**241 (30%)**
> 65 years old	52 (17%)	26 (8.3%)	11 (6.0%)	**89 (11%)**
Total	**315**	**315**	**183**	**813**
				P<0.001
	Approximate Household Income			
< $50,000	120 (39%)	132 (42%)	58 (32%)	**310 (38%)**
$51,000 - $100,000	122 (39%)	100 (32%)	60 (33%)	**282 (35%)**
$101,000 - $200,000	54 (17%)	57 (18%)	31 (17%)	**142 (18%)**
> $200,000	9 (2.9%)	8 (2.5%)	18 (9.8%)	**35 (4.3%)**
Prefer not to answer	10 (3.2%)	18 (5.7%)	16 (8.7%)	**44 (5.4%)**
Total	**315**	**315**	**183**	**813**
				P<0.001
	Highest Level of Education			
High School	79 (25%)	108 (34%)	12 (6.6%)	**199 (25%)**
Community College	105 (33%)	87 (28%)	55 (30%)	**247 (30%)**
University Degree	131 (42%)	120 (38%)	116 (63%)	**367 (45%)**
Total	**315**	**315**	**183**	**813**
				P<0.001

† *P*-values indicate differences among the 3 participant groups

Table 3.3. Results of conjoint analysis in a survey to assess knowledge, attitudes and influencers of cat owners in North America around antimicrobials and antimicrobial stewardship summarised. Median utility value for all levels and the total preference score (with 1st and 3rd quartiles) for the three features are reported by recruitment group and total study population.

	Canada		US		Total	
	Total Preference Score ‡ (Q1,Q3)	Median Utility Value †	Total Preference Score (Q1,Q3)	Median Utility Value	Total Preference Score (Q1,Q3)	Median Utility Value
Method of administration	**3.85** (1.80, 6.95)		**3.87** (2.33, 6.18)		**3.86** (2.16, 6.51)	
Injected once by your veterinarian		1.85		2.04		**1.94**
Oral (pill or liquid) once a day for 5 days		0.315		0.400		**0.326**
Oral (pill or liquid) twice a day for 5 days		-0.435		-0.554		**-0.495**
Oral (pill or liquid) three times a day for 5 days		-1.85		-1.69		**-1.78**
Cost	**4.34** (2.22, 6.26)		**3.94** (2.00, 6.41)		**4.13** (2.08, 6.33)	
$25 USD/CAD		2.05		1.89		**1.97**
$45 USD/$50 CAD		0.247		0.168		**0.214**
$80 USD/$90 CAD		-2.26		-2.06		**-2.19**
Importance in human medicine	**2.81** (1.31, 4.90)		**2.40** (1.23, 3.58)		**2.58** (1.30, 4.00)	
Very important		1.23		1.19		**1.20**
Somewhat important		0.173		-0.00476		**0.0863**
Not important		-1.40		-1.17		**-1.24**

† Positive or negative numerical value indicating participant's preference for each level of each feature after all 10 conjoint questions were completed.
‡ Difference between highest and lowest level for each feature.

Table 3.4. Summary of the number and proportion of participants in a survey of knowledge, attitudes and influencers of cat owners in North America around antimicrobials and antimicrobial stewardship who indicated that one for four factors that are taken into consideration when their cat is given an antimicrobial is "very important" or "important" to them.

	Canada	US	Educational Social Media	Total	
	Number of participants (Percentage %)	**Number of participants (Percentage %)**	**Number of participants (Percentage %)**	**Number of participants (Percentage %)**	**95% CI**
Number of times a day a pill must be given	N=238 (76%)	N=222 (71%)	N=155 (85%)	**N=615 (76%)**	**(73%, 79%)**
Cost	N=241 (76%)	N=224 (71%)	N=93 (51%)	**N=558 (69%)**	**(65%, 72%)**
The importance of the drug for treating infections in people	N=198 (63%)	N=163 (52%)	N=70 (38%)	**N=431 (53%)**	**(50%, 57%)**
Whether or not you need to give your cat a pill	N=228 (72%)	N=198 (63%)	N=88 (48%)	**N=514 (63%)**	**(60%, 67%)**

Table 3.5. Participant responses to the questions *"How important do you think antibiotic resistance is in human medicine?"* and *"Do you think antibiotic use in pets poses a risk to people?"* in a survey to assess knowledge, attitudes and influencers of cat owners in North America around antimicrobials and antimicrobial stewardship summarised.

	Canada	US	Social Media	Total
	Importance of Antibiotic Resistance in Humans			
Very Important	175 (56%)	177 (56%)	158 (86%)	**510 (63%)**
Important	93 (30%)	79 (25%)	17 (9.3%)	**189 (23%)**
Slightly Important	25 (7.9%)	42 (13%)	5 (2.7%)	**72 (8.9%)**
Don't Know	17 (5.4%)	12 (3.8%)	2 (1.1%)	**31 (3.8%)**
Not Important at All	5 (1.6%)	5 (1.6%)	1 (0.6%)	**11 (1.4%)**
Total	**315**	**315**	**183**	**813**
	Risk of Antibiotic Use in Pets to Humans			
Yes	59 (19%)	75 (24%)	93 (51%)	**227 (28%)**
Might or Might Not	103 (33%)	117 (37%)	46 (25%)	**266 (33%)**
No	153 (49%)	123 (39%)	48 (24%)	**320 (39%)**
Total	**298**	**315**	**183**	**813**

Table 3.6. Participant response to the question *"How important do you think antibiotic resistance is in human medicine?"* from a survey to assess knowledge, attitudes and influencers of cat owners in North America around antimicrobials and antimicrobial stewardship summarised by demographic group. The *P*-values demonstrate differences in distributions of response between the demographic groups, as calculated by Pearson's chi-square tests.

	Very important	Important	Slightly important	Don't know	Not at all important	Total
	Gender					
Female	369 (73%)	123 (65%)	55 (76%)	24 (77%)	10 (90.9%)	**581 (72%)**
Male	139 (27%)	66 (35%)	17 (24%)	7 (23%)	1 (9.1%)	**230 (28%)**
Total	**508**	**189**	**72**	**31**	**11**	**811**
						P=0.109
	Age					
18-25 years old	41 (8.0%)	7 (3.7%)	11 (15%)	5 (16%)	2 (18%)	**66 (8.1%)**
26-35 years old	113 (22%)	42 (22%)	16 (22%)	6 (19%)	1 (9.1%)	**178 (22%)**
36-50 years old	147 (29%)	58 (31%)	20 (28%)	8 (26%)	6 (55%)	**239 (29%)**
51-65 years old	147 (29%)	62 (33%)	23 (32%)	8 (26%)	1 (9.1%)	**241 (30%)**
> 65 years old	62 (12%)	20 (11%)	2 (2.8%)	4 (13%)	1 (9.1%)	**89 (11%)**
Total	**510**	**189**	**72**	**31**	**11**	**813**
						P=0.418§
	Approximate Household Income					
< $50,000	189 (37%)	74 (39%)	29 (40%)	14 (45%)	4 (36%)	**310 (38%)**
$51,000 - $100,000	170 (33%)	71 (38%)	24 (33%)	12 (39%)	5 (46%)	**282 (35%)**
$101,000 - $200,000	98 (19%)	28 (15%)	13 (18%)	2 (6.5%)	1 (9.1%)	**142 (18%)**
> $200,000	29 (5.7%)	5 (2.6%)	1 (1.4%)	0 (0%)	0 (0%)	**35 (4.3%)**
Prefer not to answer	24 (4.7%)	11 (5.8%)	5 (6.9%)	3 (9.7%)	1 (9.1%)	**44 (5.4%)**
Total	**510**	**189**	**72**	**31**	**11**	**813**
						P=0.761§
	Highest Level of Education					
High School	119 (23%)	47 (25%)	16 (22%)	12 (39%)	5 (45%)	**199 (25%)**
Community College	146 (29%)	60 (32%)	27 (38%)	10 (32%)	4 (36%)	**247 (30%)**
University degree	245 (48%)	82 (43%)	29 (40%)	9 (29%)	2 (18%)	**367 (45%)**

Total	**510**	**189**	**72**	**31**	**11**	**813**
						P=0.152
	Participant Group					
Canada	175 (34%)	93 (49%)	25 (35%)	17 (55%)	5 (45%)	**315 (39%)**
US	177 (35%)	79 (42%)	42 (58%)	12 (39%)	5 (45%)	**315 (39%)**
Educational Social Media	158 (31%)	17 (9.0%)	5 (7.0%)	2 (6.5%)	1 (9.1%)	**183 (23%)**
Total	**510**	**189**	**72**	**31**	**11**	**813**
						P<0.0001

† *P*-values significant at *P*<0.01

§ Statistical analyses for these data were performed using dichotomised variables as described in the Materials and Methods.

Table 3.7. Participant response to the question "*Do you think antibiotic use in pets poses a risk to people?*" from a survey to assess knowledge, attitudes and influencers of cat owners in North America around antimicrobials and antimicrobial stewardship summarised by demographic group. The *P*-values demonstrate differences in distributions of response across the demographic groups, as calculated by Pearson's chi-square tests.

	Yes	Might or might not	No	Total
	Gender			
Female	159 (70%)	192 (73%)	230 (72%)	**581 (72%)**
Male	68 (30%)	72 (27%)	90 (28%)	**230 (28%)**
Total	**227**	**264**	**320**	**811**
				P=0.800
	Age			
18-25 years old	17 (7.5%)	28 (11%)	21 (6.6%)	**66 (8.1%)**
26-35 years old	71 (31%)	53 (20%)	54 (17%)	**178 (22%)**
36-50 years old	80 (35%)	74 (28%)	85 (27%)	**239 (29%)**
51-65 years old	48 (21%)	79 (30%)	114 (36%)	**241 (30%)**
> 65 years old	11 (4.8%)	32 (12%)	46 (14%)	**89 (11%)**
Total	**227**	**266**	**320**	**813**
				P<0.001

	Approximate Household Income			
< $50,000	67 (30%)	104 (39%)	139 (43%)	**310 (38%)**
$51,000 - $100,000	74 (33%)	91 (34%)	117 (37%)	**282 (35%)**
$101,000 - $200,000	51 (23%)	47 (18%)	44 (14%)	**142 (18%)**
> $200,000	25 (11%)	6 (2.3%)	4 (1.3%)	**35 (4.3%)**
Prefer not to answer	10 (4.4%)	18 (6.8%)	16 (5.0%)	**44 (5.4%)**
Total	**217**	**248**	**304**	**813**
				P<0.001
	Highest Level of Education			
High School	29 (13%)	75 (28%)	95 (30%)	**199 (25%)**
Community College	52 (23%)	77 (29%)	118 (37%)	**247 (30%)**
University degree	146 (64%)	114 (43%)	107 (33%)	**367 (45%)**
Total	**227**	**266**	**320**	**809**
				P<0.001
	Participant Group			
Canada	59 (26%)	103 (39%)	153 (48%)	**315 (39%)**
US	75 (33%)	117 (44%)	123 (38%)	**315 (39%)**
Educational Social Media	93 (41%)	46 (17%)	44 (14%)	**183 (23%)**
Total	**227**	**266**	**320**	**813**
				P<0.001
† *P*-values significant at *P*<0.01				

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4.0 General discussion

The main aims of this research project were to identify which features of an antimicrobial drug North American dog and cat-owners prioritise when their pet is prescribed an antimicrobial, and to establish baseline understanding of antimicrobial resistance (AMR) in the pet-owning population. Dog-owners (Chapter 2) and cat-owners (Chapter 3) were surveyed separately using a combination of simple multiple choice and Likert-style questions, as well as a novel survey technique (conjoint analysis) to assist with quantitative data collection.

4.1 Pet-owner prioritisation of antimicrobial drug features

It is commonly assumed that cost is a significant factor in owner decision making when they are considering treatment options for their pet, but there have been few studies exploring the impact of owner financial constraint on veterinary care, or those that have interviewed or surveyed owners (Brockman *et al.* 2008; Coe *et al.* 2007; Volk *et al.* 2011). This research project demonstrates that medication cost is prioritised highly by the dog- and cat-owning populations surveyed. Cost was the highest priority feature in dog owners (Chapter 2), and was prioritised relatively equally with method of administration by cat-owners (Chapter 3).

As with all studies of this type, care should be taken when interpreting these data, as over three quarters of the study participants in both chapters (76% of dog-owners and 77% of cat-owners) were offered minor financial compensation for participation which may indicate they are more financially motivated than the average cat or dog-owner. However, the results of the conjoint analysis and knowledge, attitude, and influencer (KAI) questions were consistent across all participant groups, which decreases the likely impact of financial incentive on the data. Due to the quantitative nature of both studies, it is not possible to determine the motivations behind participant decision making processes. Despite these minor limitations in the interpretations of our data, this project seems to support the existing evidence that the financial aspects of veterinary medicine have a sizeable impact on the decisions that pet-owners make regarding their animal's care.

Feline owners valued method of administration equally to cost in the conjoint analysis and had a marked preference for the number of times a day an oral medication must be administered in the KAI section (Chapter 3). This is likely due to the perception that cats are more difficult to administer oral medication (Wareham *et al.* 2019). Despite this common perception, no data exist to support this, and the only studies looking at pet-owner compliance with a treatment regimen have been performed in dogs. This may also be due to the perception that research of this type cannot be successfully performed. Our data indicate that owners prefer not to give their cats oral medication, and there may be concerns surrounding cat-owner compliance if an antimicrobial treatment regime requires multiple oral doses in a day. A lack of (or reduced) compliance with an antimicrobial treatment regimen is a risk for the development of AMR. The importance of ease of administration in our study, for cat-owners in particular, indicates there needs to be a focus on training cat-owners on how to safely medicate their animals to maximise treatment compliance or argues for development of single-injection antimicrobials for cats that are lower tier drugs.

The importance of an antimicrobial drug in human medicine was the factor that was least important in both the conjoint and KAI analysis for all recruitment groups in both studies (Chapter 2 and 3). This is unsurprising given that, for the majority of people, AMR is not viewed as a pressing personal concern. In studies of physicians, veterinarians, farmers, pet-owners, and the general public, the threat of AMR is consistently underestimated, along with the impact that an individual's actions may have on the issue (Bakhit *et al.* 2019; Golding *et al.* 2019; Good Business 2015; Smith *et al.* 2018). This study further highlights that prioritisation of AMR is a need in companion animal medicine, and more effort is required to educate pet-owners about the individual impacts therapy choices may have on AMR.

4.2 Baseline understanding of antimicrobial resistance

The majority of participants in this research project were found to have a limited understanding of AMR, especially within the context of veterinary medicine. Less than a third of owners in either chapter (dog-owners and cat-owners) thought that antimicrobial use (AMU) in pets posed a risk to humans (Chapter 2 and 3). This is in agreement with other studies performed in Europe and North America that demonstrated that few cat-owners were aware that AMR was a problem in cats (Stallwood *et al.* 2019), and that no pet owners were concerned that companion animals were prescribed the same drugs as humans (Redding & Cole 2019). In human medicine, patients have been shown to directly contribute to AMR through lack of compliance with treatment regimens (Eells *et al.* 2016; Kardas *et al.* 2005), or indirectly through perceived pressure on general practitioners to prescribe antimicrobials when they are not indicated (Butler *et al.* 1998; Fletcher-Lartey *et al.* 2016). There is also evidence that education of patients and the general public improves stewardship efforts (Huttner *et al.* 2010; Lee *et al.* 2015). Similar pressures on veterinarians to prescribe antimicrobials are reported in companion animal medicine (De Briyne *et al.* 2013; Smith *et al.* 2018), and the few studies of dog-owner compliance demonstrate that many owners do not adhere to their prescription instructions (Wareham *et al.* 2019). Education of pet-owners, particularly relating to the zoonotic nature of some AMR infections in pets, may similarly improve AMS in companion animal medicine.

4.3 Influence of demographics on participant responses

In this research project several demographic factors were shown to have a measurable effect on how participants responded to survey questions. The most notable of these were participant group, and highest level of education. In general participants from the educational social media (ESM) group or those who had a higher level of education were more likely to have a better understanding of antimicrobial resistance. To date, no study of pet-owners has focussed on how participant demographics may impact their responses to a questionnaire (Smith *et al.* 2018; Stallwood *et al.* 2019). One study of

North-American pet-owners surveyed clientele from three clinics with different locations and price points, with the expectation that there would be a difference in the socioeconomic status of participants (Redding & Cole 2019). This was a small study which aimed to survey owners with a range of backgrounds, and no formal analysis on demographic data was performed. Similarly, other studies in human medicine have recorded participant demographics, but not reported or analysed how they may influence their responses to questions about antimicrobials nor their baseline knowledge of the subject (Good Business 2015; Hawkings *et al.* 2007; Mason *et al.* 2018). Our study serves to highlight that study population and participant demographics can have a large effect on survey data, and that the same questions in different populations can yield significantly different results. In addition, further research into how different demographic groups respond to questions about AMR may aid targeted education in future AMS programs

4.4 Conclusions

- North American dog-owners prioritise cost of an antimicrobial over the method of administration and its importance in human medicine (Chapter 2)
- North American cat-owners prioritise cost of an antimicrobial and the method of administration equally (Chapter 3)
- Dog-owners who read an educational veterinary blog site, or have a higher level of education have greater understanding of the importance of antimicrobial drugs in human medicine (Chapter 2)

- Pet-owners who read an educational veterinary blog site are more likely to think AMR is very important in human medicine (Chapter 2)
- Pet-owners who read an educational veterinary blog site, or have a higher level of education are more likely to recognise the risks AMU in pets poses to humans (Chapter 2 and 3)

4.5 Considerations for future research

One of the key limitations (and advantages) of this study is the fact that it was quantitative not qualitative. While this allowed for assessment of a large population of pet-owners, and provided more generalisable data and a more robust statistical analysis than a small scale qualitative study, it was not possible to assess the motivations behind participants' answers. A research project that uses a combination of both qualitative and quantitative results to better investigate the motivations behind antimicrobial decisions in a larger pet-owner population would be a valuable addition to the current literature in this area.

The ESM groups were statistically different to the other groups in this study, both in their demographic make-up and responses to survey questions. The ESM participants were recruited via a veterinary infectious diseases blog targeted at pet-owners, and it is assumed that as a consequence they were engaging with education materials surrounding this topic. It is difficult to discern if the differences among the responses from the different participant groups in this study was due to method in which they were recruited, or due to a greater number of participants with higher education qualifications in the ESM groups. Education is consequently a confounding variable in this study. This limitation could be addressed in future research by more detailed study of the ESM group, through qualitative methods such as in-person or telephone interviews, or through the addition of questions that assess the level of participant engagement with the topic of AMR prior to participating in a study.

In addition to the difficulties in comparing the ESM groups to the general population, one of the limitations of this study is the lack of conjoint data for the feline ESM group. Inferences can be made about their likely conjoint results based on the similarities between the canine and feline ESM groups, however, the lack of data means that statistical comparisons cannot be made. Due to the unique nature of the ESM group it would be challenging to recreate this study, the addition of a conjoint analysis project in a similar cat-owning population would be beneficial in this area of research.

This research demonstrates that further study is needed into the impact of cost on pet-owner decision making. This study provided evidence that cost of medications is important to the majority of pet-owners surveyed, but within a limited context. Drug effectiveness was controlled for in the conjoint scenario in these two studies. It is important to understand how pet-owner priorities change when the effectiveness of an antimicrobial treatment is taken into consideration, as this may be the reality in practice. It would be interesting to assess how these factors interact using conjoint analysis.

This study only investigated the impact of the cost of the antimicrobial drug itself, and not the associated costs. Performing diagnostic testing, such as culture and susceptibility, may improve the effectiveness of the treatment, as well as aid AMS efforts. It is commonly stated by veterinarians that pet-owners do not want to perform diagnostic testing, because it is expensive. However, the limited number of studies performed in pet-owners have provided conflicting information as to how willing pet-owners are to perform these diagnostic tests, and to what extent cost is a limiting factor. A larger scale study to explore how pet owners feel about culture and susceptibility testing, especially how it may improve outcomes for their pet, may help veterinarians feel more confident in making these recommendations to clients.

This research project did not address the issue of cat-owner compliance with antimicrobial prescriptions. Limited studies have been performed in veterinary medicine to assess pet-owner compliance with medications, and these have all been performed in dogs. A study to assess if there a difference between cat and dog-owner compliance with administration of oral medications would be a useful addition to the literature.

More detailed study is needed to identify the motivations of pet-owners when choosing between antimicrobials with different importance in human medicine. Only the canine ESM group preferred drugs that were not important in human medicine, for all other groups surveyed with conjoint analysis the opposite was true. It would be useful to identify why importance in human medicine was considered a desirable trait for these owners, which may highlight gaps in knowledge or misconceptions that can be addressed in future educational campaigns.

One of the primary aims of this project was to establish baseline pet-owner knowledge with regards to AMR in their pets. Gathering these data is important to aid future education campaigns targeted towards pet-owners in an attempt to improve AMS within companion animal veterinary medicine. This study did not identify where pet-owners have gained their current AMR knowledge, nor assess what education methods may be most effective to improve this knowledge in the future. It would be valuable to establish what sources pet-owners are using, and how best to educate pet-owners on this topic on a large scale.

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Appendices

Appendix I Dog-owner survey

Start of Block: Block 1

You are invited to participate in a survey regarding antibiotic use in dogs that is being conducted by Dr. Scott Weese, a Professor at the Department of Pathobiology, Ontario Veterinary College, University of Guelph.

The survey is designed to gather information about pet owners' perceptions and preferences when treating their pet for an infection. The study is funded by the Ontario Veterinary College Pet Trust.

The survey will take approximately 10 minutes to complete. The survey is voluntary and no personal information will be collected. Basic demographic and pet ownership information will be collected, along with answers about your preferences and perceptions for antibiotic treatment of your pet. You will not be contacted about your results.

You are under no obligation to participate. By entering this survey, you indicate that you have read the information provided and agree to participate. There are no direct benefits to you, but results will improve our understanding of pet owners' perceptions and preferences when veterinarians need to treat a pet with antibiotics. You may choose to skip any question(s) you do not want to answer. You can stop completing the survey at any time. If you do not complete the survey, your data will be withdrawn. After completion of the survey, there is no way to withdraw your answers since data are collected anonymously. After the study is completed, a summary will be provided online at http://www.wormsandgermsblog.com, in addition to publication of a scientific paper.

You do not waive any legal rights by agreeing to take part in this study. This study has been reviewed by the University of Guelph Research Ethics Board for compliance with federal guidelines for research involving human participants. If you have any questions about your rights as a research participant in this study (REB#19-03-13), please contact: Director, Research Ethics, University of Guelph, reb@uoguelph.ca; 519-824-4120 ext 56606.

End of Block: Block 1

Start of Block: Country

Q1 What is your gender?

- ◯ Male (1)
- ◯ Female (2)
- ◯ Other (3)
- ◯ Prefer not to answer (4)

Q2 What is your age?

- ◯ 18-25 years (1)
- ◯ 26-35 years (2)
- ◯ 36-50 years (3)
- ◯ 51-65 years (4)
- ◯ >65 years (5)

Q3 What is your approximate household income?

- ◯ <$50,000 (1)
- ◯ $51,000 - 100,000 (2)
- ◯ $101,000 - 200,000 (3)
- ◯ >$200,000 (4)
- ◯ Prefer not to answer (5)

Q4 What is the highest level of education you completed?

- ○ Some high school (1)
- ○ High school (2)
- ○ Community college (3)
- ○ University undergraduate degree (4)
- ○ University professional or graduate degree (5)

Q5 Do you currently own a dog?

- ○ Yes (1)
- ○ No (2)

Q6 Have you had to treat one or more of your dogs with an antibiotic in the past year?

- ○ Yes (1)
- ○ No/don't recall (2)

End of Block: Country

Start of Block: Block 3

Q7 Your dog has an infection and needs to be treated with an antibiotic. You will now be presented with a series of antibiotic treatment options. They will differ by the route of administration (you administering a pill a set number of times a day or a veterinarian giving your dog a single injection) and the cost. Additionally, since antibiotics used in animals are the same as those that are used in people, you will also consider how important the antibiotic is for treatment of infections in people.

There are no right or wrong answers.

Assume all treatment options are equally effective.

End of Block: Block 3

Start of Block: ConjointBlock

C1 (1/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $25
Importance of drug for treating people: Very important

Option 2

How the antibiotic is given: Oral (pill or liquid) twice a day for 5 days
Cost: $60
Importance of drug for treating people: Very important

- ○ (1)
- ○ (2)

C2 (2/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Injected once by your veterinarian
Cost: $60

Importance of drug for treating people: Somewhat important

Option 2

How the antibiotic is given: Injected once by your veterinarian
Cost: $120
Importance of drug for treating people: Not important

- ○ (1)
- ○ (2)

C3 (3/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) twice a day for 5 days
Cost: $120
Importance of drug for treating people: Not important

Option 2

How the antibiotic is given: Injected once a day by your veterinarian
Cost: $25
Importance of drug for treating people: Very important

- ○ (1)
- ○ (2)

C4 (4/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) once a day for 5 days
Cost: $60

Importance of drug for treating people: Somewhat important

Option 2

How the antibiotic is given: Oral (pill or liquid) twice a day for 5 days
Cost: $60
Importance of drug for treating people: Not important

- ◯ (1)
- ◯ (2)

C5 (5/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) twice a day for 5 days
Cost: $60
Importance of drug for treating people: Not important

Option 2

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $60
Importance of drug for treating people: Somewhat important

- ◯ (1)
- ◯ (2)

C6 (6/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Injected once by your veterinarian
Cost: $25

Importance of drug for treating people: Not important

Option 2

How the antibiotic is given: Injected once by your veterinarian
Cost: $120
Importance of drug for treating people: Very important

- ○ (1)
- ○ (2)

C7 (7/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $60
Importance of drug for treating people: Not important

Option 2

How the antibiotic is given: Oral (pill or liquid) once a day for 5 days
Cost: $60
Importance of drug for treating people: Not important

- ○ (1)
- ○ (2)

C8 (8/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) twice a day for 5 days
Cost: $120

Importance of drug for treating people: Somewhat important

Option 2

How the antibiotic is given: Injected ONCE by your veterinarian
Cost: $25
Importance of drug for treating people: Not important

- ○ (1)
- ○ (2)

C9 (9/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $25
Importance of drug for treating people: Somewhat important

Option 2

How the antibiotic is given: Oral (pill or liquid) twice a day for 5 days
Cost: $120
Importance of drug for treating people: Not important

- ○ (1)
- ○ (2)

C10 (10/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $60

Importance of drug for treating people: Somewhat important

Option 2

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $120
Importance of drug for treating people: Not important

○ (1)

○ (2)

End of Block: ConjointBlock

Start of Block: Block 5

Q If you need to treat your dog with an antibiotic, how important do you consider the following factors?

	Very important (1)	Important (2)	Slightly important (3)	Not important at all (4)	No preference (5)
Number of times a day it must be given (6)	○	○	○	○	○
Cost (7)	○	○	○	○	○
Importance of the drug for treatment of infections in people (8)	○	○	○	○	○
Whether or not you need to give your dog a pill (9)	○	○	○	○	○

Q15 How important do you think antibiotic resistance is in human medicine?

- ◯ Very important (1)
- ◯ Important (2)
- ◯ Slightly important (3)
- ◯ Not at all important (4)
- ◯ Don't know (5)

Q16 Do you think antibiotic use in pets poses a risk to humans?

- ◯ Definitely yes (1)
- ◯ Probably yes (2)
- ◯ Might or might not (3)
- ◯ Probably not (4)
- ◯ Definitely not (5)

Q17 Thank you for participating in this survey. A summary of results will be available at http://www.wormsandgermblog.com at completion of the study.

End of Block: Block 5

Appendix II Cat-owner survey

Start of Block: Block 1

You are invited to participate in a survey regarding antibiotic use in cats that is being conducted by Dr. Scott Weese, a Professor at the Department of Pathobiology, Ontario Veterinary College, University of Guelph.

The survey is designed to gather information about pet owners' perceptions and preferences when treating their pet for an infection. The study is funded by the Ontario Veterinary College Pet Trust.

The survey will take approximately 10 minutes to complete. The survey is voluntary and no personal information will be collected. Basic demographic and pet ownership information will be collected, along with answers about your preferences and perceptions for antibiotic treatment of your pet. You will not be contacted about your results.

You are under no obligation to participate. By entering this survey, you indicate that you have read the information provided and agree to participate. There are no direct benefits to you, but results will improve our understanding of pet owners' perceptions and preferences when veterinarians need to treat a pet with antibiotics. You may choose to skip any question(s) you do not want to answer. You can stop completing the survey at any time. If you do not complete the survey, your data will be withdrawn. After completion of the survey, there is no way to withdraw your answers since data are collected anonymously. After the study is completed, a summary will be provided online at http://www.wormsandgermsblog.com, in addition to publication of a scientific paper.

You do not waive any legal rights by agreeing to take part in this study. This study has been reviewed by the University of Guelph Research Ethics Board for compliance with federal guidelines for research involving human participants. If you have any questions about your rights as a research participant in this study (REB#19-03-13), please contact: Director, Research Ethics, University of Guelph, reb@uoguelph.ca; 519-824-4120 ext 56606.

End of Block: Block 1

Start of Block: Country

Q1 What is your gender?

- Male (1)
- Female (2)
- Other (3)
- Prefer not to answer (4)

Q2 What is your age?

- 18-25 years (1)
- 26-35 years (2)
- 36-50 years (3)
- 51-65 years (4)
- >65 years (5)

Q3 What is your approximate household income?

- <$50,000 (1)
- $51,000 - 100,000 (2)
- $101,000 - 200,000 (3)
- >$200,000 (4)
- Prefer not to answer (5)

Q4 What is the highest level of education you completed?

- ◯ Some high school (1)
- ◯ High school (2)
- ◯ Community college (3)
- ◯ University undergraduate degree (4)
- ◯ University professional or graduate degree (5)

Q5 Do you currently own a cat?

- ◯ Yes (1)
- ◯ No (2)

Q6 Have you had to treat one or more of your cats with an antibiotic in the past year?

- ◯ Yes (1)
- ◯ No/don't recall (2)

End of Block: Country

Start of Block: Block 3

Q7 Your cat has an infection and needs to be treated with an antibiotic. You will now be presented with a series of antibiotic treatment options. They will differ by the route of administration (you administering a pill a set number of times a day or a veterinarian giving your cat a single injection) and the cost. Additionally, since antibiotics used in animals are the same as those that are used in people, you will also consider how important the antibiotic is for treatment of infections in people.

There are no right or wrong answers.

Assume all treatment options are equally effective.

End of Block: Block 3

Start of Block: ConjointBlock

C1 (1/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $25
Importance of drug for treating people: Somewhat important

Option 2

How the antibiotic is given: Oral (pill or liquid) once a day for 5 days
Cost: $25
Importance of drug for treating people: Very important

○ (1)

○ (2)

C2 (2/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $45

Importance of drug for treating people: Very important

Option 2

How the antibiotic is given: Injected once by your veterinarian
Cost: $80
Importance of drug for treating people: Not important

- ○ (1)
- ○ (2)

C3 (3/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $80
Importance of drug for treating people: Somewhat important

Option 2

How the antibiotic is given: Injected once by your veterinarian
Cost: $45
Importance of drug for treating people: Very important

- ○ (1)
- ○ (2)

C4 (4/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) twice a day for 5 days
Cost: $45

Importance of drug for treating people: Somewhat important

Option 2

How the antibiotic is given: Oral (pill or liquid) once a day for 5 days
Cost: $45
Importance of drug for treating people: Somewhat important

- ○ (1)
- ○ (2)

C5 (5/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) twice a day for 5 days
Cost: $80
Importance of drug for treating people: Not important

Option 2

How the antibiotic is given: Oral (pill or liquid) once a day for 5 days
Cost: $25
Importance of drug for treating people: Very important

- ○ (1)
- ○ (2)

C6 (6/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Injected once by your veterinarian
Cost: $25

Importance of drug for treating people: Not important

Option 2

How the antibiotic is given: Oral (pill or liquid) twice a day for 5 days
Cost: $80
Importance of drug for treating people: Not important

- ○ (1)
- ○ (2)

C7 (7/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $45
Importance of drug for treating people: Not important

Option 2

How the antibiotic is given: Oral (pill or liquid) once a day for 5 days
Cost: $25
Importance of drug for treating people: Very important

- ○ (1)
- ○ (2)

C8 (8/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) twice a day for 5 days
Cost: $25

Importance of drug for treating people: Somewhat important

Option 2

How the antibiotic is given: Injected once by your veterinarian
Cost: $45
Importance of drug for treating people: Very important

- ○ (1)
- ○ (2)

C9 (9/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $80
Importance of drug for treating people: Somewhat important

Option 2

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $25
Importance of drug for treating people: Very important

- ○ (1)
- ○ (2)

C10 (10/10) Choose your preferred option below:

Option 1

How the antibiotic is given: Oral (pill or liquid) three times a day for 5 days
Cost: $80

Importance of drug for treating people: Somewhat important

Option 2

How the antibiotic is given: Injected once by your veterinarian
Cost: $80
Importance of drug for treating people: Not important

- ○ (1)
- ○ (2)

End of Block: ConjointBlock

Start of Block: Block 5

Q If you need to treat your cat with an antibiotic, how important do you consider the following factors?

	Very important (1)	Important (2)	Slightly important (3)	Not important at all (4)	No preference (5)
Number of times a day it must be given (6)	○	○	○	○	○
Cost (7)	○	○	○	○	○
Importance of the drug for treatment of infections in people (8)	○	○	○	○	○
Whether or not you need to give your cat a pill (9)	○	○	○	○	○

Q15 How important do you think antibiotic resistance is in human medicine?

- ○ Very important (1)
- ○ Important (2)
- ○ Slightly important (3)
- ○ Not at all important (4)
- ○ Don't know (5)

Q16 Do you think antibiotic use in pets poses a risk to humans?

- ○ Definitely yes (1)
- ○ Probably yes (2)
- ○ Might or might not (3)
- ○ Probably not (4)
- ○ Definitely not (5)

Q17 Thank you for participating in this survey. A summary of results will be available at http://www.wormsandgermblog.com at completion of the study.

End of Block: Block 5
