ANTIMICROBIAL DRUG USE AND ANTIMICROBIAL RESISTANCE IN COMPANION ANIMAL MEDICINE

by

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ABSTRACT

Antimicrobial resistance (AMR) is a persistent global public health threat. Antimicrobial drug (AMD) use is a major driver of the development of AMR. AMD use in companion animal medicine in the United States is a relatively unexplored contributor to AMR. Furthermore, the influence of other key stakeholders, such as pet owners, in the AMD prescription process has not been extensively studied. While AMD use in production animal medicine is commonly cited as a major player in the acceleration of AMR, companion animal medicine is typically not included in the conversation, excluding it from the One Health approach to combat AMR.

It is hypothesized that AMDs are over-prescribed in companion animal medicine and that pet owners have a substantial role in the AMD use process. The objectives of this dissertation were to inform a solution using a complex intervention framework. This type of framework is appropriate when the goal is to modify a number of behaviors among diverse targeted groups. In this case, the goal a complex intervention strategy is to improve the way AMDs are prescribed, dispensed and administered in companion animal medicine. As an effective complex intervention requires the efforts of many stakeholders, this dissertation seeks to contribute to the development phase of the iterative complex intervention cycle. By defining the problem, engaging key stakeholders and informing the development of effective interventions, the stage can be set for further intervention development, piloting, evaluation and eventual implementation.

The form and content of this abstract are approved. I recommend its publication.

Approved: Elaine J. Scallan Walter

Dedicated to Dr. H. Scott Hurd and solving the unsolvable by watching the cows

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Antimicrobial drug	AMD
Antimicrobial resistance	AMR
World Health Organization	WHO
Centers for Disease Control and Prevention	CDC
International Society for Companion Animal Infectious Disease	ISCAID
American College of Veterinary Internal Medicine	ACVIM
American Animal Hospital Association	AAHA
American Veterinary Medical Association	AVMA
Urinary tract infection	UTI
Upper respiratory infection	URI
National Association of Public Health Veterinarians	NASPHV
Theory of Planned Behavior	TPB
National Ambulatory Medical Care Survey	NAMCS

CHAPTER I

ANTIMICROBIAL RESISTANCE AS A GLOBAL HEALTH CRISIS

Global scope of antimicrobial resistance

Antimicrobial resistance (AMR) is a worldwide health crisis, refusing to recognize borders and resulting in untreatable bacterial disease across the globe[1]. It is an expanding public health threat that is poised to cause widespread death and economic destruction without swift, effective intervention and mitigation[1]. The development and dispersion of AMR has many causes, some natural and some manmade. A main driver for the acceleration of AMR is the use of antimicrobial drugs (AMDs), encompassing applications in human medicine, veterinary medicine and agriculture. While use of antimicrobial drugs is indicated for various acceptable purposes, unnecessary use of these drugs is of most concern, as this form of use does not treat disease. Instead, inappropriate use exposes commensal bacterial populations to antimicrobial compounds, resulting in excessive resistance development through direct selection pressure and acquisition of mobile genetic resistance elements. Discussion of AMR must start by reviewing the current literature describing the threat to global health and the potential for it to evolve into a pandemic. Focus must also be given to what causes AMR, what accelerates it and what modifiable factors can be intervened upon to manage the threat effectively. An underexplored aspect of AMD use and how it contributes to the AMR predicament can be found in companion animal (i.e., dogs and cats) medicine. The role of AMDs in companion animal medicine, with special attention to the circumstances and factors involved in AMD prescribing, will be thoroughly explored through various methods in this dissertation. Through addressing critical knowledge gaps, this dissertation's aims will advance the overall understanding of AMD use in veterinary medicine. Before focusing specifically on the role of AMD use in companion animal medicine, a brief description of AMR in a global public health framework is provided.

Antimicrobial resistance as a global public health threat

Defined as the lack, or loss, of effectiveness of antimicrobial drugs on microorganisms (i.e., bacteria, viruses and fungi), AMR represents a complicated, dynamic and emerging global public health issue[2]. Antimicrobial resistance has been listed by the World Health Organization (WHO) as one of the top 10 most significant threats to global health. AMR shares this distinction with other global crises, such as climate change and infectious disease pandemics[1]. AMR can be considered an emerging global disease, even though AMR itself is not a recognized as a specific infectious disease agent. AMR is not an emerging disease in the sense that it is novel, in the way a novel influenza virus strain might. Rather, the concern surrounding AMR is the global spread of the already-present serious threat[2]. There will be high costs in terms of both human health and economic losses from the slow-moving global health catastrophe if its consequences continue to be ignored and effective interventions are not implemented. Successful mitigation will require that multiple perspectives and outcomes of AMR be considered[3]. Each perspective adds a layer of complexity, which makes a complete understanding of AMR difficult to comprehend fully. In order gain a holistic grasp of the impact of AMR, medical, microbiologic, economic and political viewpoints and their associated specific metrics need to be explored.

Human health burden

Increased morbidity and mortality can be attributed to AMR around the world. Global disease burden estimates of AMR infections are difficult to determine. However, through regional reports, it can be deduced that disease complicated by resistant pathogens is a serious widespread health issue. Current estimates from the Centers for Disease Control and Prevention

(CDC) suggest that 2.8 million Americans suffer from AMR infections annually, with as many as 36,000 people succumbing to untreatable bacterial infections[4]. The European Centre for Disease Control estimated in 2009 that 25,000 people a year die in Europe from AMR infections and that these infections added an additional 2.5 million hospital days annually[5]. Another European report from 2007 estimated that 400,000 people a year were infected with an AMR pathogen, resulting in 25,000 deaths[6]. Data from China indicates that approximately 80,000 Chinese citizens die each year due to AMR complications[5]. While complete empirical data that would more accurately quantify global deaths attributable to AMR do not exist[7], the magnitude of the threat to human health exhibited by regional studies is too large to ignore and mitigation cannot wait for the delivery of more exact quantitative information. In addition to considering direct morbidity and mortality, AMR can result in a number of negative health outcomes.

AMR threatens the way medicine is currently practiced and can potentially erase some modern medical advances. Medical conditions complicated by AMR infections prolong patients' hospital stays, produce excessive morbidity and can ultimately result in death from a condition that would otherwise be treatable if effective AMDs were available. The rise of AMD ineffectiveness reduces treatment possibilities, increases fatal outcomes and precludes the benefits of other medical treatment advances, such as organ transplant and chemotherapy[8]. Cancer patients' immune systems are commonly suppressed by chemotherapy, making them more susceptible to opportunistic infections, which can include resistant bacteria. Medical advances such as organ transplant and orthopedic surgeries come with the inherent risk of complications due to implant and surgical site infection. If these infections are resistant to AMDs, these advances may fail, or worse yet, may result in significant morbidity and mortality[8]. AMR morbidity and mortality can be exacerbated by other medical and social determinants of immunity, such as socioeconomic status, country of residence and co-morbidities. For example, a patient in a high-income country who has a resistant bacterial infection can be given newer, more expensive drugs to treat the infection, while those in lower-income countries may not have that option[9]. Differences among health determinants highlight the importance of recognizing that marginalized populations with fewer health resources may face a disproportionate burden of AMR disease[9]. While focusing on the direct and indirect effects of AMR on health outcomes, a well-rounded discussion of the topic of AMR should also consider the underlying complexity that arises from its diverse microbiology, steep economic costs and, sometimes, antagonistic political components.

Microbiologic and pharmacologic perspective

In terms of microbiology, the causes of AMR are varied, and resistant bacteria can cause a wide-range of disease, from infected surgical sites to sepsis[10]. Not only is there variation in AMR-related disease, but also in the species of infection-causing bacteria and their associated mechanisms of resistance. Beyond disease and species, there are many routes of transmission that resistant bacteria can take to establish disease, both hospital- and community-centric[8]. While this appears to cause a complexity on the individual level, even more confusion can be seen on a population level when attempting to understand AMR disease development. With individual and population variance in the dynamics of AMR, it is quite reasonable that researchers have not yet been able to adequately define, measure or predict AMR. Given the intricacy of AMR, one general strategy to combat the numerous infection types, species and transmission routes is through the development of novel AMDs, which has proven difficult over the last few decades[11]. The "golden age" of AMD discovery ended in the 1970's; therefore, the emergence of new AMDs is no longer a sustainable option to circumvent the resistance mechanisms that microorganisms have obtained[11]. The pipeline is nearly dry, as pharmaceutical companies have not seen long-term beneficial advancements in new AMD development. The lack of innovation highlights one of the economic aspects of AMR propagation. Drug makers are often focused on the development of more profitable drugs than creating new AMDs, which will likely be rendered ineffective soon after introduction[11,12]. The lack of new AMDs provides evidence that AMR, while commonly cited as a massive public health threat, is not a high economic priority for drug developers. In addition to the lack of motivation for creating new AMDs, other economic outcomes of AMR infections in people compound the problem of increased morbidity and mortality.

Economic burden

Healthcare-associated costs of AMR infections include, but are not limited to, increased intensive hospitalization care, prolonged hospital stays, more diagnostic testing and expensive additional treatment. Estimating the current economic burden of AMR and predicting the future costs if AMR is left unchecked is complicated. A recent report from the World Bank indicates that anywhere from 1 to 4% of a country's GDP could be lost if AMR is allowed to progress at its current pace[13]. Nationally, it has been estimated to cost the United States over $20 billion a year in direct medical costs to treat AMR infections in people[11]. This cost strains patients, healthcare networks and insurance providers[3]. For example, on a more local level, an assessment from a hospital in Chicago found that it cost an estimated additional $30,000 per case, resulting in nearly $5 million in direct medical costs annually for the single hospital location[14]. Not only are the direct costs associated with medical care of AMR increasing, but also the indirect costs associated with lost productivity due to prolonged illness and premature death are rising. The indirect cost to the U.S. economy is over $35 billion a year, almost doubling the direct medical expenditures[15].

Political perspective

Aspects that suggest AMR is not a political priority include the relative lack of funding for AMR-related research, agendas that do not contain any meaningful policy and the numerous persistent knowledge gaps that surround the issue[8]. It has been suggested that the inability to demonstrate the public health consequences of AMR adequately and quantitatively has diminished the importance of aggressively pursuing meaningful change[9,16]. The current slow pace of AMR development coupled with the invisibility of AMR impacts within a complex system make it more difficult to establish meaningful action when compared to more explosive outbreaks such as Ebola or coronavirus. Yet, just because AMR is slower developing , it possesses the potential to be just as serious in terms of mortality and economic repercussions as a fast-moving pathogen. Lack of international political cooperation due to the aforementioned reasons acts as a barrier to a coordinated global effort to predict and mitigate the present and future impacts of AMR[9]. Recognition and acceptance of the threat of AMR by all stakeholders, including lawmakers, and subsequently making mitigation a priority are keys to slowing the progression, and lessening the impact, of AMR[9].

Predictions of future AMR impacts

The future impact of AMR has been framed in dire terms. Words such as “crisis,” “apocalypse,” “post-antibiotic era” and “pandemic” have been used to describe a future in which AMDs are rendered ineffective[17,18,19]. In some experts’ opinions, the period of treatable bacterial infections that humanity has grown accustom to will phase out and be replaced with life-threatening resistant infections[5]. By 2050, it is estimated that, globally, 10 million people will die each year from resistant bacterial infections[20]. The economic consequences are estimated to be just as staggering. While these figures are solely predictions, they still describe a catastrophic situation that society ought to attempt to avoid by recognizing and addressing AMR as a global public health threat.

AMR has the potential to become a pandemic, not much different than a quick-moving respiratory virus and should be treated as such. Experts predict that humanity is only at the proverbial tip of the iceberg when it comes to the full effects of AMR[17]. Instead of a pandemic lasting for months to years, it is reasonable that AMR may emerge into a global issue that persists for much longer, becoming globally endemic like the HIV pandemic. The potential long-lasting, or even permanent, threat of AMR necessitates that a novel approach to managing its effects is needed. Instead of an outbreak being managed through non-pharmaceutical interventions (i.e., social distancing, improved hygiene, closing of businesses and schools) and pharmaceutical interventions (i.e., vaccines, anti-viral medications), an AMR pandemic will likely need to be managed by scaling back on AMD use and by using an effective, sustainable public health campaign that would educate the masses on appropriate AMD use. However, as alluded to previously, changing behaviors may be difficult due to the increasing complexity of AMR, the political barriers to addressing the issue adequately and the current, almost invisible, effects of AMR. While AMR is just serious, if not more, than an acute outbreak of a viral pathogen, AMR fails to elicit the same sense of urgency, which may diminish attention and steer focus away from more aggressive management. Complacency surrounding AMR may remain until its effects are so severe that mitigation with once-reasonable strategies may no longer be viable.

The predictions of the global health and economic consequences of an AMR pandemic are dire and should be enough to make mitigation a real priority. These predictions are based more on hypothetical models rather than empirical data, leading some to a question the specific future impact of AMR[3,13]. Therefore, these models need to be improved through monitoring of AMR, encompassing AMD use surveillance, creating rapid diagnostic tests, implementing effective policy and developing new resistant infection treatments[21]. As discussed in the next section, there are several causes of AMR, many of which are amenable to intervention. These causes include the misuse and overuse of AMDs in humans and animals. However, to grasp adequately how inappropriate AMD use results in AMR and why it is a target for intervention, AMR needs to be examined in a natural history of disease framework.

Natural history of antimicrobial resistance

Bacterial acquisition of resistance to antimicrobial substances is an example of genetic natural selection. Bacteria adapt to survive adverse environmental conditions, which may contain antimicrobial molecules[22]. In other words, AMR is a natural phenomenon that occurs without the contribution of synthetic AMD compounds. Instead of leaning on human contribution as the only cause of AMR, the concept needs to be approached holistically as a part of nature. However, the magnitude of AMR can directly be linked to human activity, as the way we use AMDs results in exponentiated growth of the "pool of resistance". The "pool of resistance" refers to the unknown global quantity of antimicrobial resistant bacteria and associated resistance genes in the ecosystem[22]. Many factors have been cited as driving the increase in magnitude of resistance genes. The overuse and misuse of AMDs in human medicine, inappropriate prescribing of AMDs by health professionals, AMD use in agriculture and the lack of new AMDs all play a role in the development of AMR[23,24]. Regardless of the specific cause of AMD resistance development in an organism, a basic natural history of disease scheme relating to AMD use and resultant resistant organisms can be generally applied (Fig. 1.1). The natural history of AMR development can help to simplify the complex nature of this problem by presenting the phenomenon in a basic manner, making it easier to apply to specific concepts surrounding AMR. The distillation of the issue can then help to frame research questions and guide the development of the study methods, which will ultimately aid in the understanding of AMR. More specifically, a natural history of disease framework is useful when considering one of the most important factors that contributes to AMR: Inappropriate AMD prescribing.

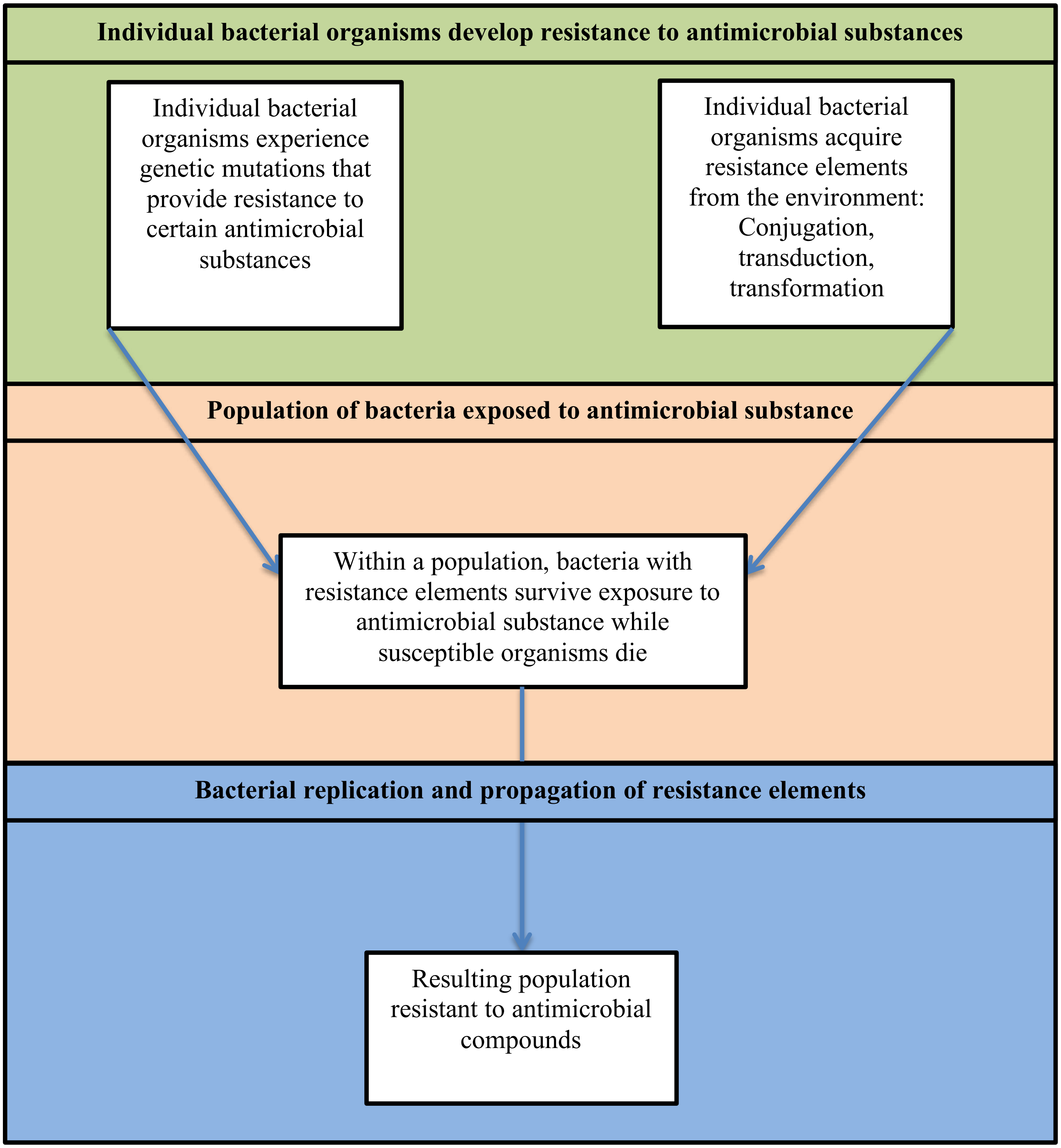

Figure 1.1: A natural history framework for bacterial development of antimicrobial resistance

Inappropriate AMD prescribing

The warnings about the loss of AMD effectiveness subsequent to overuse are nothing new as Sir Alexander Fleming, the scientist credited with the discovery of penicillin, cautioned against the threat in 1945, predicting, “The public will demand the drug (penicillin)” and that “an era of abuse will begin”[12]. There is a substantial amount of evidence in human medicine that shows AMDs are being prescribed inappropriately. There has been significantly less research done in veterinary medicine, but what has been done shows similar trends to human medicine[25-30]. As inappropriate use of AMDs has been suspected as a main culprit in the acceleration of AMR development, it has also been seen as the most modifiable contributor to the issue[9]. Several initiatives have been developed to curb the problem of excessive and inappropriate use of AMDs in veterinary medicine[31-36]. Typically, these efforts have focused on improved recognition of whether or not a medical condition requires an AMD, appropriate prescribing when AMDs are necessary and better surveillance of AMD use on an aggregate level. However, besides the influence of the medical reasons for AMD use, a complex web of social behaviors also contributes to the decision-making process. These medical and social influences not only affect prescribers, but also other stakeholders, including patients, pharmaceutical companies, policy makers and public health officials. Excessive and inappropriate AMD prescribing is not isolated to human healthcare. Given the role animal agriculture plays in everyday life, AMD use in this setting is also of public health concern.

AMD use in agriculture

The use of AMDs in animal agriculture has come under increased scrutiny due to the quantity of AMDs consumed and the reasons for giving livestock AMDs[37-40]. AMDs are used in production animal medicine for the treatment, control and prevention of disease. In the past, AMDs were administered to animals in subtheurapeutic doses to encourage efficient growth, but this practice has largely been outlawed in the United States and in European countries[33,41]. Studies have examined use in livestock and have concluded that it plays a substantial role in the development of resistant bacteria[42,43].These studies have also called out AMD use in livestock as a driver of increased risk for humans contracting AMR infections[42,43]. Attempts to define and quantify the fraction of AMR that is attributable to use in livestock have produced widely different estimates[44-46]. These estimates are typically biased and have yet to produce a reliable and consensus conclusion[44]. While AMD use in animals likely contributes to overall pool of resistance, given what is currently known a quantitative estimation is not currently possible. While a definitive link has not been established, many studies erroneously attribute human risk to misconceptions of AMD use in livestock and food production systems. For example, there are studies[37] that still cite AMD used for growth promotion purposes as a practice that contributes to AMR. However, critically important AMDs are no longer allowed for growth promotion purposes in the United States, as the Food and Drug Administration outlawed this practice in 2017[31-33].

As AMD use has been scrutinized in the production animal sector, criticism for how these drugs are used in companion animal medicine is percolating. However, use in companion animals has not been considered one of the major players, with the thought that it contributes only a small attributable fraction to the overall pool of resistance[22]. With the increasing strength of the human-animal bond and the extensive use of AMDs in companion animal medicine, practices of prescribing AMDs to dogs and cats need to be examined as a possible major contributor to the escalating pandemic.

CHAPTER II

ANTIMICROBIAL DRUG USE AND ANTIMICROBIAL RESISTANCE IN COMPANION ANIMAL MEDICINE

Use of AMDs in companion animal medicine

To date, when veterinary AMD use is discussed in the context of public health, a majority of articles focus solely on the production animal sector. There are few manuscripts dedicated solely to AMD use in companion animal medicine and even fewer that focus solely on the risk to humans[47,48]. The use of AMDs in companion animal medicine and the subsequent development of AMR infections in people are, however, of public health concern[4]. The risk of humans acquiring resistant bacterial infections due to companion animal AMD prescription is not currently quantified[47]. It would be extremely difficult, if not impossible, to quantify this risk accurately given the current state of knowledge surrounding AMD use in companion animals. There are many considerations when assessing AMD use in companion animals and its impact on public health, and, while not completely objective, the qualitatively defined risk is too great to ignore. To quantify the risk to humans of contracting AMR infections subsequent to AMD use in companion animals, a better understanding of how these medications are dispensed is needed.

AMDs are prescribed to dogs and cats every day in the United States, yet factors that influence the AMD decision-making process are only weakly identified. In the veterinary healthcare industry, veterinarians are the most qualified individuals to make appropriate medical AMD treatment decisions for animals and the only ones legally able to do so; however, in the decision-making process, veterinarians must not only consider objective medical findings but also must navigate external influences, such as clients' financial situations, the economic health of their practice and the lack of rapid, cost effective diagnostic tests[49]. All of these factors make the practice of prescribing AMDs in companion animal medicine a complex medical, behavioral and social process[50]. To define clearly how AMDs are used in a real-life clinical context, it is vital not only to understand the medical motivations behind the prescribing of these medications, but also how external factors influence the decision-making process (figure 2.1). The following sections explore how these factors influence the decision of whether or not an AMD is prescribed to a pet. Following a discussion of the factors involved in AMD prescribing, current evidence that can be used to explore the risk of zoonotic AMR organism transfer between people and animals is reviewed. Published consensus companion animal antimicrobial stewardship (AMS) efforts and AMD guidelines are then described, followed by a recognition of gaps in the knowledge and a statement about the need for a better understanding of risks of AMD use in companion animal medicine.

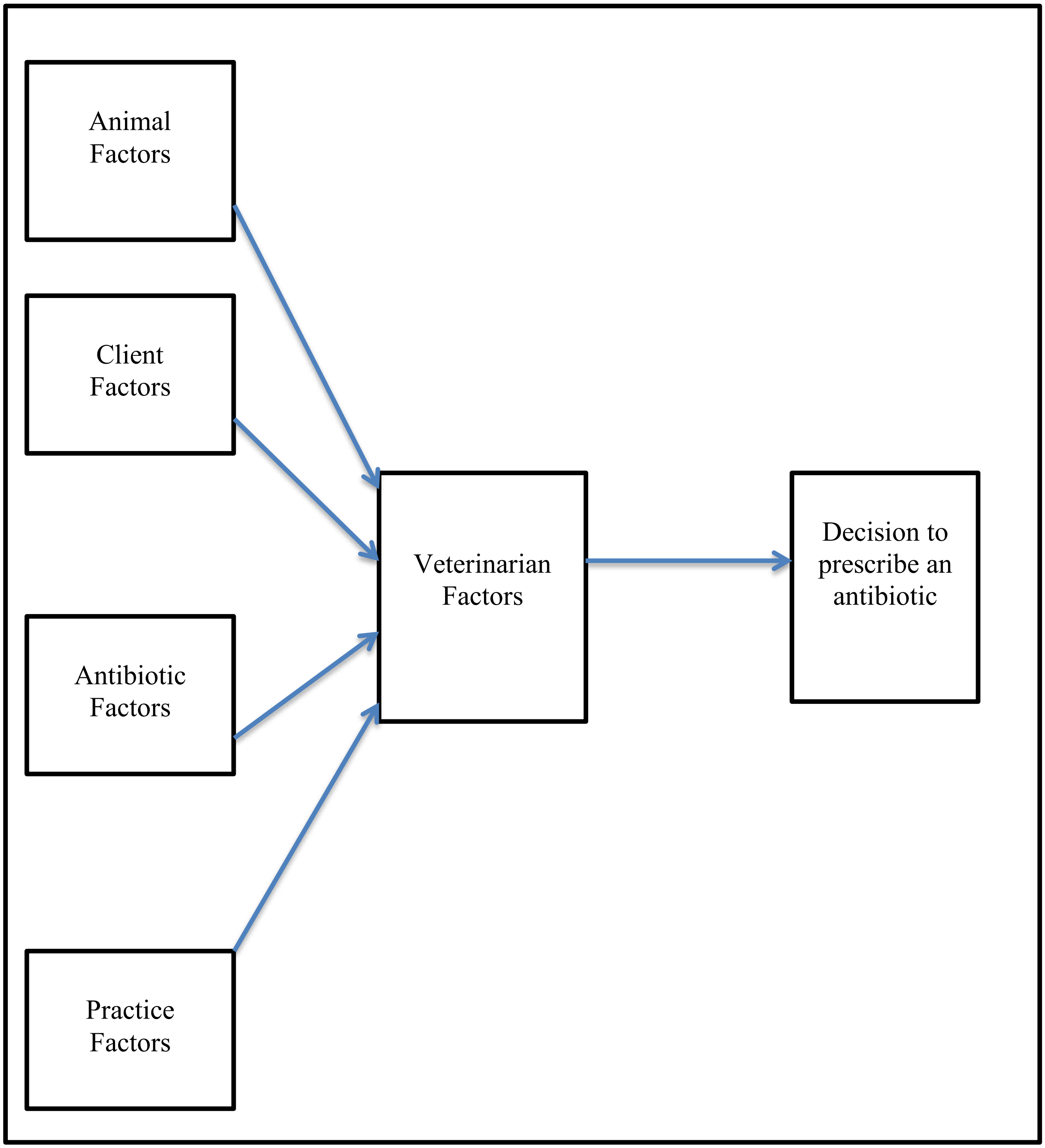

Figure 2.1: conceptual model of factors influencing AMD prescribing. Adapted from Hopman et al[50].

Condition based AMD prescription practices

Utilized for a variety of illnesses in pets, these medications are prescribed appropriately to conditions caused by bacteria and inappropriately to those caused by viruses and etiologies. While AMDs are used extensively in companion animal medicine, a quantifiable measurement of appropriate prescription remains unknown. In contrast to production animal medicine, there are currently neither regulations that dictate how veterinarians should use AMDs in dogs and cats nor nationwide databases that collect information on veterinary AMD prescriptions.

Although AMDs are used to treat numerous illnesses in small animal medicine, the most common clinical presentations for which AMDs are prescribed are urinary tract disease, respiratory tract disease, skin infections and diarrhea[51,52]. AMDs are also used extensively following dental procedures when teeth are extracted[53] and perioperatively for other surgical procedures[54]. While indicated for common bacterial-caused conditions or when the threat of bacterial infection is high, AMDs are also routinely recommended in the absence of bacterial organisms. For example, in cats with urinary tract disease symptoms, the cause of the condition is most likely stress-related and is only rarely of bacterial origin[51]. However, there is evidence that these patients often receive an AMD unnecessarily[55]. In much the same way, animals with upper respiratory symptoms (i.e., coughing, sneezing) are also routinely treated with AMDs even though the most common cause of their symptoms is viral in nature[56]. Dermatitis with a bacterial cause (i.e., pyoderma) is a commonly diagnosed skin disease in dogs and cats that should be treated with AMDs; however, there is concern the dose and duration of these prescriptions is often inappropriate[57]. In cases of acute diarrhea, where animals are otherwise clinically normal, it has become common practice to prescribe metronidazole, an AMD with intestinal anti-inflammatory properties, to help shorten the course of the symptoms[58,59]. Lastly, although not often indicated, it is suspected veterinarians are over-prescribing AMDs for patients after dental procedures as a prophylactic strategy against infected tooth extraction sites[53]. In addition to the unnecessary use of AMDs in common clinical situations, the class of AMD being used inappropriately for these conditions is a concern in the context of public health.

The WHO defines critically important antimicrobials (CIAs) as AMDs with high importance in human medicine and designates classes of AMDs as critically important, highly important or important[60]. CIA classes that are routinely used in veterinary medicine include aminoglycosides, third generation cephalosporins, fluoroquinolones, glycopeptides and macrolides[60]. It is recommended that CIAs be used judiciously in companion animals as their use could theoretically lead to an increased prevalence of resistant bacteria and AMD treatment failures in humans. Based on previous assessments, CIAs account for between 7-36% of all AMD prescriptions for the five most common disease indications in companion animal medicine, mainly through the administration of fluoroquinolones, third generation cephalosporins and macrolides[53,61]. Fluoroquinolones are used frequently in both dogs and cats, while macrolides are used more in dogs and third generation cephalosporins are prescribed more for cats[61]. Cefovecin, an injectable third generation cephalosporin that has a two-week duration of action, is used extensively in cats and studies have noted that there is rarely an indication in medical records that justifies its use[62]. Beyond CIA use in companion animal medicine, numerous studies have examined the most commonly prescribed classes of all AMDs, both in total and by condition, regardless of importance in human medicine.

In a 2018 Belgian study of small animal veterinarians, it was found that potentiated amoxicillins accounted for 43% of all AMD prescriptions, with fluoroquinolones (15%), third generation cephalosporins (11%) and tetracyclines (11%) also frequently recommended[55].

Beyond overall use of specific AMD classes, the study also looked at the most prevalent AMD class by specific disease conditions, including acute gastroenteritis (metronidazole) canine lower urinary tract signs (potentiated amoxicillins), canine acute tracheobronchitis (potentiated amoxicillins), feline URI (doxycycline) and feline bite wound abscesses (potentiated amoxicillins). A 2009 review of AMD prescription practices for cases of skin disease, ear infections and urinary tract symptoms in New Zealand found that potentiated amoxicillins were the most frequently prescribed AMD class, followed by cephalexin, a first-generation cephalosporin, and fluoroquinolones[63]. Skin diseases were routinely treated with either potentiated amoxicillins or cephalexin, while suspect UTIs and ear infections were treated most commonly with potentiated amoxicillins and fluoroquinolones, respectively. A recent European study that assessed AMD use in Italy, Belgium and the Netherlands also noted that potentiated amoxicillins are used most frequently (27% of AMD prescriptions), followed by cefovecin (8%), fluoroquinolones (8%), amoxicillin (8%) and doxycycline (5%)[27]. While these studies describe AMD use among companion animals, little detail on why the AMD prescriptions were recommended is provided. Ideally, the decision to prescribe a particular AMD would be influenced exclusively by the presenting medical condition of the animal. However, a list of owner-related factors, resulting from the bond between owners and their pets, can affect the prescribing process.

Human-animal bond influences on AMD prescription practices

As the exploration of AMR secondary to the use of AMDs in companion animal medicine evolves, it is important to examine the influence of the human-animal bond. The human-animal bond plays a central role in defining the possible risk of people contracting an AMR infection subsequent to the use of AMDs in pets. Without strong interaction between people and their animals, the risk of resistant infections in humans resulting from AMD use in pets would likely be negligible. However, as the bond between humans and animals becomes stronger and as more people obtain pets, so grows the relevance of quantifying the risk that AMD use in companion animals poses to humans. The strengthening of the union between people and pets is exemplified on economic, social and microbiological levels.

According to the American Pet Products Association, 67% of households had a pet in 2018. This number was up almost 10% when compared to 2016[64]. This trend is also exhibited in how much pet owners spend on average each year. Americans spent more than $72 billion dollars on their pets in 2018, which was up 4% from the previous year[64]. More than $18 billion in pet spending went toward veterinary care, while $30 billion was spent on food and $16 billion was put toward pet supplies, such as toys and other accessories. The number of pets that people have and the amount of money they spend on them is evidence that the human-animal bond is an important part of people's lives. The majority of humans who own pets view their animals as part of the family (85%), as indicated in a recent AVMA report[65]. The significance that pet owners place on their pets ensures that there will be close physical contact between the two species, not only at home, but out in the public as well.

Socially, the human-animal bond has been increasingly relied upon for human health benefits, both mental and physical. The health benefits of pet ownership have been explored extensively over the last few decades, and, overall, there appears to be a variety of positive physical effects[66]. Mental health and well-being also appeared to be bolstered by owning a pet as overall happiness was found to be higher among pet owners than in people without pets[67]. According to the AVMA, approximately 85% of dog owners and 75% of cat owners have a close relationship with their pet and consider them to be a family member. This commonly held view of the value of pets has increased from a time when pets were seen merely as property or as only a companion. Describing pets as family members has implications for veterinary care. More emotion and concern from pet owners can occur as a result of this perceived bond, which can influence the pet's healthcare should the owner advocate for use of AMDs when not warranted. Additionally, the connection between a human and his or her pet is not only exemplified by a tight emotional bond, but also a physical bond in the form of sharing microorganisms.

The human microbial environment (i.e., microbiome) of systems such as the skin, gastrointestinal tract and respiratory tract is affected by contact with animals[68]. Studies have shown that microbiome diversity is increased in those who own pets[69]. Other studies have noted similarities between pet and owner skin microbiomes[70]. These observations provide evidence that non-pathogenic and pathogenic bacteria can transfer between human and non-human species, particularly pets. As behaviors such as sharing a bed, sharing food and close contact, which are indicative of a strong owner-pet bond, increase, it is reasonable to assume that the bidirectional transfer of microorganisms will occur on a frequent basis. As pet owners continue to treat their pets like members of the family, the human-animal bond will have an even more prevalent role when defining the impact on people from the use of AMDs in pets. The bond will likely influence how AMDs are used in companion animal medicine and will play a crucial role in the overall improvement of AMD use behaviors.

Other external influences on AMD prescription practices

Besides the objective parameters of a pet's health and the relationship between humans and their pets, it is suspected that other external factors play a role in veterinary prescribing practices. Without recognizing, understanding and addressing non-medical pressures to prescribe AMDs when they are not needed, a veterinary antimicrobial stewardship (AMS) plan has little chance at success. Practice related characteristics, client expectations, client finances and diagnostic uncertainty can all contribute significantly to how a pet's illness is handled and can ultimately result in excessive or inappropriate use of AMDs.

The history of a veterinary practice, along with its current staff, can play a pivotal role in how AMDs are used by individual veterinarians within the practice. If a practice has committed to a culture of reducing AMD recommendations for conditions that do not require them for treatment, a veterinarian may feel supported when withholding AMDs. Furthermore, established clients of a veterinary hospital that practices judicious AMD use may have fewer pet owners' expectations of receiving AMDs for symptoms that suggest something other than a bacterial cause. Quite the opposite may be true in a practice where AMDs are commonly used inappropriately. An individual veterinarian who desires to practice good AMS principles may find it difficult to do so if his or her colleagues routinely dispense AMDs for illnesses that are not warranted for treatment. Likewise, if pet owners are accustomed to having their practice prescribe an AMD for a condition, such as a viral upper respiratory illness, they will likely have a difficult time accepting any recommendation that does not involve an antibiotic. The influence of a veterinary practice on how AMDs are prescribed goes beyond the veterinarian role. For example, how a client care specialist handles the scheduling of an appointment can set the stage for AMDs ultimately being prescribed. If a client makes an appointment to have a pet's urinary tract symptoms evaluated and is told that an AMD will likely be needed, the client may then be primed to expect the medication prior to speaking with a veterinarian. This scenario underlines the importance for all staff to be included in the development, implementation and evaluation of a clinic's AMS plan.

As explored in depth in the upcoming Aim 2 section, pet owners' perceived expectations for AMD prescriptions for their pets is thought to influence the AMD prescription decision-making process[71]. Owners' expectations of whether or not pets should be prescribed an AMD for a given clinical condition are likely formed by such things as past experiences with the illness, medical knowledge from a related healthcare field, advice from other pet owners or personal research done prior to the visit. Owners' preconceptions of the actual cause of their pet's illness and what should be done to treat it can pose a barrier to judicious use of AMDs in order to keep clients satisfied. If owners presents their pets to veterinarians with the preconceived notion that AMDs are needed, veterinarians may potentially face several unpleasant potential outcomes, including clients questioning their medical judgment, having to spend extra time convincing an owner that AMDs are not needed or possibly having to face backlash over not prescribing AMDs when an illness condition has not improved in the absence of a prescription. In addition to keeping clients satisfied, veterinarians may also prescribe unwarranted AMDs for economic reasons. If veterinarians refuse to prescribe an AMD to a pet whose owner is expecting it, the owner may go elsewhere, taking potential future business away from the clinic[72]. In the mind of the prescriber, the perceived relatively small risk of prescribing AMDs when not truly warranted is far outweighed by the potential loss of revenue. Veterinarians may also fear they could face potential litigation or action against their professional veterinary license if AMDs are not prescribed when an owner is certain the drugs are needed. In situations where a veterinarian is uncertain of the cause for a pet's illness, an AMD may be prescribed to give owners the appearance that everything possible is being done for their pet. Ideally, thorough testing would be performed in all animals to rule out bacterial disease. However, unlike human healthcare, availability and/or cost of these tests typically preclude them from being done on a regular basis.

Healthcare for pets differs from human healthcare in many ways, including the use of insurance. Approximately 2% of pets are covered under pet insurance plans[73]. While the enrollment for these programs is increasing, the vast majority of pet owners pay for veterinary services out of pocket. Combined with the increasing prices of companion animal care, most pet owners have a financial limit of how much they are able to spend on their pets' care. This often results in owners declining veterinary diagnostic and treatment recommendations. Especially in the absence of diagnostic testing, uncertainty surrounding a clinical presentation can leave veterinarians guessing about the origin of the pet's illness. For example, in cases of urinary tract symptoms (i.e., stranguria, pollakiuria, dysurina and hematuria), veterinarians typically recommend urine testing and possibly imaging (i.e., radiographs, ultrasound) of the urinary bladder to determine the specific cause, whether it is bacterial cystitis, urinary bladder uroliths or neoplasia. If bacterial cystitis is suspected on the basis of a urine test, a urine bacterial culture may be ordered. Costs for these tests can range from anywhere from $200 to $500, which does not include the cost of the office exam or any treatments. When an owner expresses financial concerns, veterinarians must rely on partial or no diagnostic test results and may ultimately have to offer the owner other options, such as empirical AMD treatment or a "wait and see" approach. Wanting to "treat the treatable," veterinarians many times prescribe AMDs for these patients, even in the absence of evidence of bacterial disease. Of all the causes of urinary symptoms in pets, bacterial cystitis is the easiest and cheapest condition to treat. Besides the cost of certain diagnostic tests, the uncertainty of the cause of a set of disease symptoms can greatly influence the AMD prescription decision-making process.

While the diagnostic capability of veterinary medicine has advanced in recent decades, there is still a substantial gap between human and veterinary medicine. What complicates the lack of reliable testing relative to human medicine is the fact that animals cannot verbally communicate their symptoms. This combination of not being able to question a patient and encountering diagnostic limitations can lead to a list of differential diagnoses rather than a definitive diagnosis. Typically, on differential diagnoses lists, infection is included, whether it be bacteria, viral or fungal. Once the battery of diagnostic tests is exhausted, whether by full execution or an owner's financial limitations, and bacterial infection is still present as a possibility, it is common practice to prescribe AMDs, even if the evidence is not overwhelmingly strong. A frequent example of this phenomenon is a fever of undetermined origin (FUO). In an FUO, an animal presents with a fever, general malaise, decreased appetite and possible gastrointestinal signs. The accepted diagnostic work-up for an FUO starts with a search for a cause of the fever, which can include infectious, inflammatory and neoplastic conditions. A complete blood panel, urine test and radiographs are used to search for conditions such as autoimmune disease, cancer, bacterial cystitis, sepsis and pneumonia. If a cause is found on this initial work-up, the appropriate treatment is instituted. If no cause for the fever is noted, treatment is started and further diagnostics, such as abdominal ultrasound, tick/parasite tests and blood cultures are considered. Initial treatment typically consists of intravenous fluids and, often, AMDs. In the absence of a diagnosis after these second-tier diagnostics, which can take a number of days to complete, the condition is determined to likely be an autoimmune or viral cause. At this time, if there is no improvement with supportive care and AMDs, immunosuppressant drugs are started as an attempt to return the patient back to normal health. In the course of initial treatment and treatment after the second tier of tests, a wide range of AMDs can be used in an attempt to treat a less-than-obvious bacterial infection. It seems that the longer a fever persists, the greater the escalation in AMD class. The longer a fever persists despite

AMD treatment, the less likely bacteria are causing the fever. In less common situations, the longer a fever persists after institution of AMDs, the more likely it is multi-drug resistant. In either circumstance, patients are receiving large amounts of AMDs that are doing nothing but exposing the microbiota to numerous classes of AMDs. The FUO is a prime example of the role diagnostic uncertainty can play in the use of AMDs in companion animal medicine.

The previously described external influences all exert specific pressures to veterinarians, and usually, more than one of these pressures is present at any one time. The previous section does not list all external factors that may have a part in the veterinary AMD decision-making process. Therefore, continued exploration of how different influences factor into a veterinarian's treatment recommendation and how they act in concert with other well-defined factors is needed. The patient's medical condition, human-animal bond and numerous other influences are intertwined in the complex circuitry used when making a decision of whether or not to prescribe antibiotics to a pet. Untangling the individual influences, along with their interactions and dependencies will take much effort. It is possible that the process may not ever be understood in its entirety, but there is much work that needs to be done before that declaration can be made. Not only does the intricacy of the process appear daunting, but also the multiple frameworks that these factors can be viewed in, whether it is public health, animal health or veterinary decision-making, further complicate its understanding. This dissertation will explore the objectives of its three aims through a public health lens, and, will therefore set objectives surrounding the understanding of AMD use in companion animals and the risk to humans. To lay the foundation of the zoonotic potential of AMD resistant bacteria passing between humans and pets, first a review of pertinent pathogens is presented.

Existing evidence of zoonotic risk of AMR

While a direct link between use of AMDs in small animals and AMR infections in humans has not been definitively proven, sufficient evidence to warrant concern about the possible risk exists. There has been insufficient research to perform a quantitative risk analysis that accurately defines the attribution of AMD use in pets to people contracting resistant bacterial infections. Until there is a surveillance system of AMD use in companion animals and a well-collaborated, multidisciplinary effort to determine the risk of AMR infections in humans, veterinary interventions and recommendations on AMD use will continue to be based on the precautionary principle. The absent ability to quantify this risk is especially concerning in the context of the increasing strength of the human-animal bond since the close and consistent contact between pets and their owners provides ample opportunities for transmission of resistant bacteria between them. As the AMR organism prevalence increases in parallel with the strengthening connection between pets and their people, it is suspected that the probability for zoonotic transmission of AMR will also increase. Therefore, it is imperative that the use of AMDs in companion animals and the subsequent risk of owners developing a resistant infection be closely examined. Many events with specific, and likely unknown, probabilities would need to occur in sequence in order for a person to be infected with a resistant pathogen as a direct result of AMD use in pets. Figure 2.2 represent a possible framework for examining the possible path of drug use to resistant infection. A main issue with such a general framework is that it will likely change given the AMD that is prescribed and the pathogen that is being modeled. Therefore, it is important to develop such a model that easily incorporates pathogen specific probabilities and is flexible enough to be adapted to different medication and resistance profiles.

When describing the specific public health threats of different resistant pathogens and how they might relate to AMD use in companion animals, the updated 2019 CDC report of AMR threats will be referenced extensively. In this report, urgent, serious and concerning threats of specific drug-resistant organisms were identified[4]. Among the listed pathogens, many are relevant in the discussion of AMD use in companion animal medicine and the risk to public health, including Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococci (VRE), Carbapenem-resistant Enterobacteriaceae (CRE), EBSL-producing Enterobacteriaceae, Carbapenem-resistant Acinetobacter, drug-resistant Campylobacter and multidrug-resistant Pseudomonas[4,47]. As a result of searching the existing literature, it is clear that bacterial resistance can develop in pets as the result of AMD administration, pets can harbor resistant organisms and bacteria with zoonotic potential, resistant or not, are transferred between pets and people. However, many of the studies referenced in the coming sections are descriptive in nature and of small sample size, and therefore, only lay the foundation for collecting enough data to determine probabilities of pathway events occurring. Additionally, many of the articles referenced in the following sections only focus on one aspect, whether it be AMR development in pets secondary to AMD use, carriage of resistant organisms or transfer of bacteria between animals and humans. However, even given these limitations, it is important to thoroughly examine the currently available evidence for the bacterial threats listed in the CDC AMR threats report.

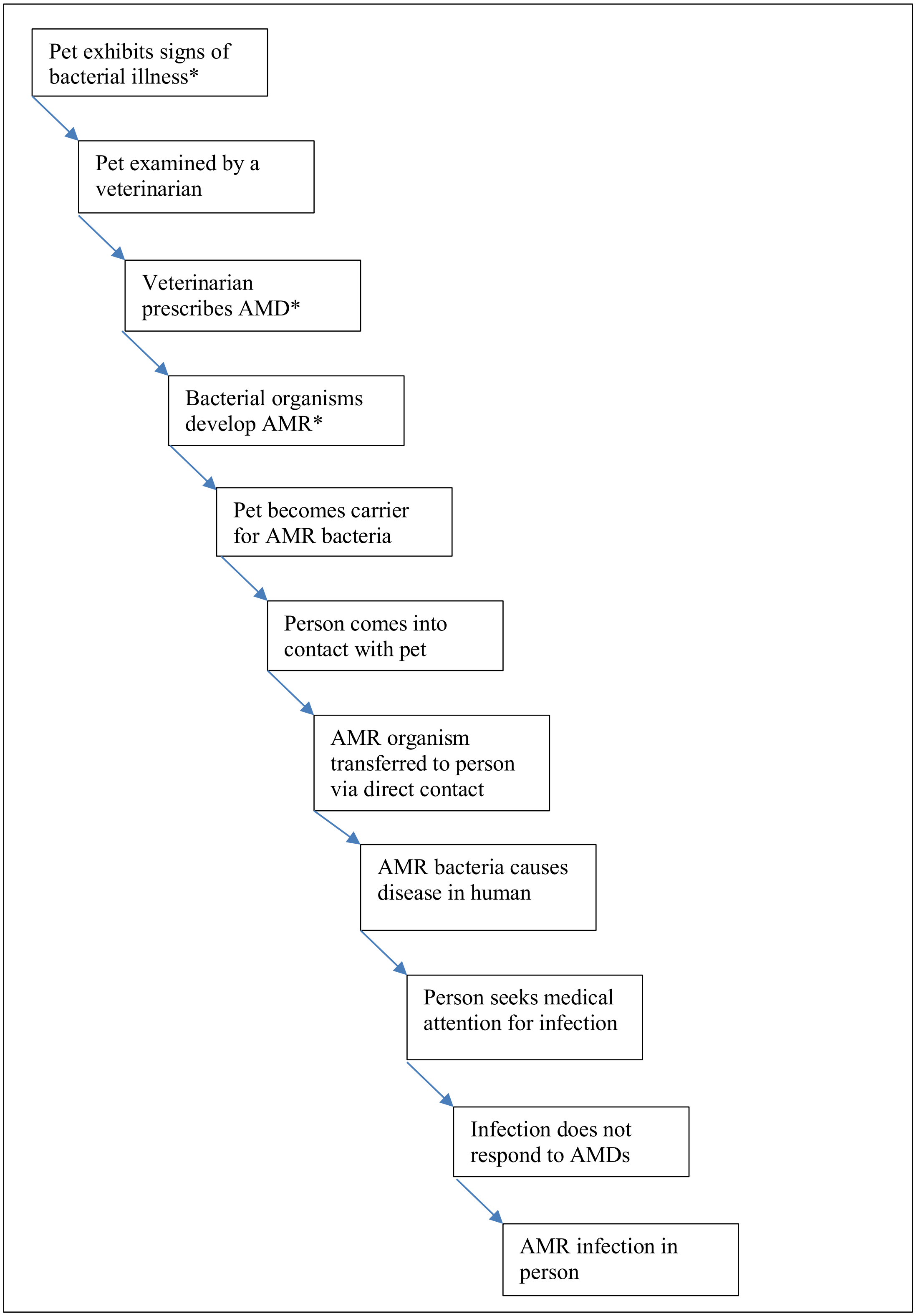

Fig. 2.2: A simple pathway showing how it is possible for AMD use in pets to cause AMR infections in people. *= steps with substantial variation

Methicillin-resistant Staphylococcus aureus (MRSA)

Perhaps the most often studied bacteria in terms of resistance and zoonotic potential is MRSA. This resistant bug is often to blame for hospital- and community-acquired human AMR infections[74]. The CDC estimates that 80,000 severe MRSA infections occur annually in the United States, resulting in approximately 11,000 deaths[4]. *Staphylococci* can be especially harmful as the bacteria can readily acquire resistance genes and form a biofilm of resistant organisms in its host, making infections caused by resistant *Staphylococci* difficult to treat[75]. The typical coagulase positive *Staphylococcus* species to colonize companion animal skin is S. pseudointermedius, a bacterium that rarely causes disease in humans. However, resistant *S. aureus* has also been found in dogs and cats. MRSA has been isolated from diseased skin, surgical wounds and urinary tract infections in companion animals[76]. It has also been found as a commensal on the skin and coats of pets[77]. What makes MRSA a concern is its ability to adapt to different hosts and subsequently cause disease[78]. As *S. pseudointermedius* is more prevalent than MRSA in dogs, there is still concern that S. pseudointermedius can pass on genetic resistance elements to other *Staphylococcus* species, namely *S. aureus*[79]. While little evidence exists for a definitive link between development of MRSA in animals with subsequent transmission to people, the establishment, carriage and transmission of MRSA between pets and people have all been documented separately.

While there has been little substantial research done on risk factors of development or acquisition of MRSA, a handful of risk factors have been identified. One study noted that geographic location, which researchers postulated could represent a variation in prescription practices, might increase the likelihood of colonization of MRSA in dogs and cats[80]. Antibiotic treatment prior to sampling a small study population of dogs has been noted to be a risk factor for testing positive for MRSA[81]. This finding was replicated in an assessment that found dogs were at higher risk of being colonized with the resistant bacteria well after being prescribed AMDs[76]. A visit to a veterinary hospital was also found to be a statistically significant risk factor for obtaining MRSA after controlling for AMD exposure[83]. Other risk factors for canines being colonized with S aureus include being female and being owned by a healthcare worker[84]. Further research in the form of large, prospective studies is needed to solidify the factors associated with the initiation of companion animal MRSA colonization. In addition to the cause of development or acquisition of resistance, the role of pets as a carrier of resistant *Staphylococcus* species is of equal importance.

Numerous studies have noted that both AMR *staphylococci* bacteria and resistance genes have the potential to be harbored by companion animals, typically from the skin, oral cavity and ear canal[81]. It has been postulated that canine *S. aureus* isolates are typically more resistant than human isolates, suggesting that dogs can acquire resistance from sources other than humans[77]. Analysis of *Staphylococcus* samples from cats from 2001 to 2014 revealed that *S. aureus* was present in approximately 10% of samples. Of these samples, 55% were resistant to three or more AMDs. Additionally, there was a significant increase over time when the trend of MRSA was examined[84]. Similarly, a teaching hospital in Australia noted that 15% of canine *Staphylococci* isolates were *S. aureus* and that over half were multi-drug resistant[85]. The study also showed a temporal increase in *S. aureus* resistance to enrofloxacin and potentiated amoxicillin, which are two antibiotics that belong to critically important AMD classes. Another study of 117 dogs revealed that 14.5% of those sampled were colonized with *S. aureus*[86]. The isolates were minimally resistant to AMDs, but this finding does illustrate that dogs can be colonized with the bacteria. As it can likely be assumed that the presence of resistance genes does not make a bacterium more or less able to colonize a species, the finding of minimally resistant *S. aureus* being isolated from pets is still significant. Other studies report prevalences of 6% and 9%[83] of *S. aureus* in dogs. Sample sites with the most common isolation of *S. aureus* in dogs were found to be the oral cavity, skin and perineum, which are areas that are amenable to frequent human contact[87]. Contact with one of these areas is not the only way humans may be exposed to MRSA from their pets as other transmission routes theoretically exist.

With the increase in community-associated MRSA, many studies have recently focused on the zoonotic risk of animals exposing humans to MRSA[72]. *S. aureus* and *S. pseudointermedius* are passed between people and their pets, providing evidence that pets can transmit resistant bacteria to their owners[75]. However, it has been argued that animals serve only as transient carriers of the resistant organism and are actually colonized through contact with humans[88]. A 2018 study that examined MRSA carriage on veterinary staff personnel and animals within their practice found that while a percentage of the staff was colonized with MRSA, the bacteria was not isolated from any of the animals sampled[89]. In other studies, resistant *staphylococci* bacteria isolated from companion animals have been noted to be genetically identical to the most common strains in people[89], indicating a possible bidirectional mode of transmission. While there is good evidence for transmission of MRSA between people and pets, a definition of the role a pet plays in the risk to humans developing an MRSA infection is lacking[90]. As MRSA is an opportunistic pathogen, it is likely that people and pets are likely engaged in a cyclical transfer after one party introduces the bacteria into a household[88]. A pet's role may be less of acting as the primary transmission vector and more of aiding in the maintenance of the pathogen on a commensal level. Pet owners have been found to have a much higher rate of MRSA colonization that the non-pet owning public (18% vs. 2%)[91]. Perhaps diseased animals transmitting resistant bacteria to their owners demonstrate stronger evidence for unidirectional transfer of *Staphylococci*. For example, a study of 13 dogs with deep pyoderma caused by resistant *Staphylococcus intermedius* found that their owners were also colonized with the bacteria[92]. In this study, the resistant bacteria did not cause human disease, as *S. intermedius* rarely establishes infection in people, but it does represent the possibility that *Staphylococcus* species can transmit from diseased animal to healthy human. Not only can a pet's skin disease represent an exposure, but also bites from animals can be a conduit for resistant bacteria. An assessment that examined the resistance patterns of staphylococci in feline oral cavities found that high rates of AMD resistant staphylococci were present and represented a public health threat through the development AMR wound infections after a cat bite[93]. Occupationally, veterinarians and veterinary staff are at increased risk for being colonized with coagulase positive *Staphylococcus* species, likely due to their constant close contact with companion animals and their increased risk for suffering animal bites[89].

As human MRSA infection trends appear to be increasing, it is paramount that the risk of having a pet be thoroughly explored. Investigating how pets acquire resistant *Staphylococci* infections, how they harbor the bacteria and their resistance mechanisms and how pets can pass these bugs on to their owners is needed. Ignoring the strong possibility of bidirectional transfer between people and their pets, it is important to first characterize the pathway that leads from AMD use in pets to resistant infections in people. With so much variability in potential pathways of AMD use in pets to resistant bacteria infections in people, MRSA infections as the result of AMD use in dogs may represent a risk model for which other pathogen pathways could be explored.

Enterococcus

Enterococcus bacteria are thought to possess little capability of causing disease in healthy humans. However, *E. faecium* and *E. facecalis* are considered to be some of the most dangerous hospital-acquired pathogens in people[47]. An estimated 20,000 drug-resistant infections and 1,300 deaths occur annually, typically in hospitalized individuals[4]. What makes *Enterococcus* a dangerous nosocomial infection is the high likelihood that the bacteria are resistant to vancomycin, a strong antibiotic used as a last resort treatment. It has been shown that companion animals can carry enterococci that are resistant to vancomycin[94]. A small study done in 2017 showed that 14% of sampled dogs harbored ampicillin-resistant *E. faecium* in their oral cavities and concluded that resistant bacteria found in the oral microflora of dogs poses a public health risk to humans[95]. Similarly, a report from Europe detected in dogs with bacterial skin infections the presence of a resistant *E. faecium* strain that is a common cause for human nosocomial infections[96]. While the report could not define if the resistance developed as a consequence of AMD use in dogs, it shows that dogs can serve as a vehicle for resistant bacteria. An Italian case study reported the development of a multi-drug resistant *E. faecium* infection in a cat with resistance features not seen before in veterinary medicine[97]. This strain has been shown to cause resistant infections in hospitalized humans. The case report provides evidence that resistant organisms that typically affect humans can develop in animals after extensive AMD use.

Enterobacteriaceae

The Enterobacteriaceae family includes numerous bacterial species that are of human health importance, including *Salmonella* and *Escherichia coli*. These bacteria are to blame for approximately 150,000 illnesses each year, with 26,000 of the cases involving resistant bugs[4]. *E coli* are also responsible for a variety of diseases in dogs and cats. In particular *E. coli* can cause urinary tract, skin and wound infections in small animal veterinary patients[98,99]. Resistance to multiple drugs is becoming more common in the cases of canine *E.coli* infections[100]. As it is also a commensal organism in the canine gastrointestinal tract and excreted into the environment through defecation, it marks a viable route of transmission from animals to people. The persistence residence of commensal *E. coli* in pets makes it amenable to exposure of oral antimicrobial agents, applying a selection pressure to the population of non-pathogenic bacteria[101]. Various studies have examined the development, carriage and transfer of resistant *E. coli* in the context of companion animals.

While risk factors for canine colonization by a resistant E coli strain have not been extensively evaluated, a few risk factors have been postulated to increase the risk for pets acquiring resistant organisms, both infectious and commensal. A reported risk factor for having AMR E coli in the canine gut is the recent exposure to AMDs, showing a probable link between prescribing AMDs to a dog and the development of AMR[101,102]. Another possible risk factor for a dog becoming colonized with resistant bacteria is the feeding of a raw diet. Raw samples taken from pet stores have indicated a high prevalence of Salmonella contamination, with a large percentage of isolates being resistant to multiple AMDs[103]. Feeding a raw diet was also noted as a risk factor in dogs carrying drug resistant *E Coli* and *Salmonella*[104,105]. Coprophagic behavior has been classified as a risk factor for the introduction of AMR bacteria to a pet's commensal microflora as the ingestion of feces results in direct inoculation of the pet's oral cavity and gastrointestinal system[106]. Other pathways for development and acquisition of resistant bacteria or their resistance elements in companion animals likely exist; however, all lead to the transient, or possibly permanent, colonization of resistant bacteria, resulting in a carrier state that could play a role in transmission to humans.

Evaluation of biospecimens from companion animals has demonstrated that pets can harbor resistant bacteria. A 2017 assessment of dog feces found that 30% of sampled dogs had evidence of harboring MDR E. coli in their gastrointestinal tract[107]. Similarly, a Canadian cross-sectional study found that numerous fecal samples contained antimicrobial resistant Enterobacteriaceae[105]. A study of cats, including healthy cats, diseased cats and shelter cats, assessed fecal Enterobacteriaceae shedding. It was found that while healthy cats typically did not excrete Enterobacteriaceae, diseased and shelter cats had a relative high rate of multi-drug resistant Enterobacteriaceae shedding[108].

The transfer of MDR E coli from pets to people is a difficult phenomenon to demonstrate, as there is likely bidirectional transmission among humans, animals and the environment. However, some reports do suggest probable transmission of MDR E coli from pets to people. As pet ownership increases, so does the probability of animal-human transmission of E coli via dog feces, either directly from the animal or indirectly through the environment. The primary vector of possible transmission of MDR E coli is feces, which can act as a conduit for direct transmission or can contaminate the environments that pets and people share. It is accepted that dog feces in highly populated urban areas are of significant public health concern[109]. Assessments have examined specific environments that pets and people co-habitat for the presence of E coli, including veterinary hospitals and dog parks. A sampling of a veterinary hospital noted a concerning prevalence (9%) of environmental samples were contaminated with MDR E. coli[110]. Surfaces in animal shelters are commonly contaminated with resistant E. coli, representing another pathway by which pathogens can transmit between people and pets[111]. A study of feces recovered outside a German veterinary hospital indicated that 10% of fecal samples tested positive for ESBL-producing E coli that were of wound or urinary tract origin, which underlines the importance not just of commensal bacteria, but also infectious clinical pathogens[112]. In addition to veterinary hospital locations, contamination with drug-resistant E coli in public places has been noted as well. A research team in Quito, Ecuador collected dog feces at dog parks and examined the samples for MDR E coli[113]. Researchers found that 40% of samples tested positive for extended spectrum β-lactamase (EBSL) and AmpC β-lactamase genes. This is especially concerning given that these two genes are two of the most MDR E coli strains that cause disease in people and companion animals[113]. Other studies have also found EBSL-containing E coli in canine feces in public areas, but at different prevalence values[114,115,116]. While arguably more significant resistance genes, namely colistin resistance (mcr1) and carbapenemases, were not isolated from the Quito dog park fecal samples, there is concern that the trend of AMD use in companion animal medicine may drive the development and dissemination of the genes. A review article found a higher-than-expected prevalence of companion animals carrying Carbapenem-resistant Enterobacteriaceae, raising concern that companion animals may act as a reservoir for disease causing bacteria that are highly resistant to most AMDs[111]. The contamination of the environment, whether it is a hospital, public area or home, represents a possible pathway of transmission of AMR bacteria or resistant genetic elements from animals to people. In fact, owning a pet and closely sharing an environment has been determined to be a risk factor for human fecal shedding of ESBL-producing bacteria[117].A Chinese case report describes the isolation of a colistin resistant strain of E coli from a urologic patient who owned a pet store. After isolation of the resistant pathogen from the patient, investigators tested the pets at the patient's business and found 10% of the animals were colonized with a clonally similar bacteria[118]. It has also been demonstrated that companion animals and their owners were colonized with the same strains of E. coli in a few instances, which raises the concern the owner or pet may act as a reservoir for disease for the other[118]. An in vitro study of canine-isolated E. coli's ability to invade human urinary bladder cells found that the pathogen was likely able to cause disease in humans, posing a potential zoonotic threat[119].

Acinetobacter

Acinetobacter is a commensal organism in both the oral cavity and on the skin of dogs. Additionally, the bacteria are ubiquitous in the environment and a common cause of human nosocomial infections[47]. It has been shown that not only do animals also develop nosocomial infections due to this pathogen, but that isolated Acinetobacter in hospitalized animals is frequently resistant to many first-line therapies, including 3rd generation cephalosporins, potentiated amoxicillin and fluoroquinolones[120]. There have been warnings for progression of acquired resistance in this organism due to AMD use in animals as the molecular characteristics of resistant bacteria isolated from people are similar in nature. The similarity raises concerns that animals could play a larger role in the dissemination of resistant Acinetobacter among humans[121]. Acinetobacter has a demonstrated capacity to be involved in epidemic spread[122] and the accelerated development of MDR organisms from the extensive use of AMDs in companion animals may enhance that capability. Therefore, further studies on what leads to the development of Acinetobacter resistance in dogs and cats is needed to better characterize the true attribution to the pathogen's enhanced ability to cause human disease.

Campylobacter

Campylobacter is often found in the gastrointestinal tracts of young dogs. A Danish study found that all dogs studied in a longitudinal cohort study were shedding Campylobacter jejuni between 9 and 15 months of age, with 67% of sampled dogs still shedding at 2 years of age[123]. It has been noted that ownership of a puppy increases the likelihood of humans being infected with Campylobacter when compared to those who did not own puppies[124,125]. However, the directionality of this association has not yet been shown[124]. Not only have previous assessments found that the risk of infection of Campylobacter increases with puppy ownership, but documented evidence shows that infection with a multidrug-resistant Campylobacter is no exception. Investigation of an outbreak of human MDR Campylobacter infections traced the causative agent back to a national chain of commercial pet stores, where it is suspected that the MDR bacteria may have developed as a result of medicating puppies with AMDs[126]. Further study is needed to determine a definitive link between giving puppies AMDs and human MDR Campylobacter infections, but the previously presented evidence is strong for a possible link. Therefore, to mitigate the risk of humans contracting an MDR infection from puppies, the use of AMDs in commercial breeding operations needs to be described so that appropriate interventions can be developed and applied. The need to classify AMD use in puppies to prevent undesirable outcomes in humans is a specific example of the overall importance of better understanding AMD use in companion animal medicine to improve human health.

Pseudomonas

Pseudomonas aeruginosa is commonly found in companion animals, causing otitis and pyoderma, as well as hospital-acquired infections[47]. Of the previously described pathogens, resistant Pseudomonas is perhaps the most problematic in clinical small animal medicine, as infections can be notoriously difficult to treat with AMDs[127]. While the level of resistance reported in veterinary medicine does not commonly reach the level of resistance noted in human medicine[47], there is a probability that strains seen in dogs and cats will reach a level where last-resort AMDs, such as imipenem, are the only drugs that will adequately cure infections[128]. This is problematic as imipenem is usually reserved for humans. The use of imipenem in veterinary medicine is not recommended due to the possibility of accelerating resistance and reducing the effectiveness of the medication in humans. Better surveillance of AMD use patterns in common conditions where Pseudomonas infections are prevalent would possibly lead to the improved use of AMDs in companion animal medicine. This, in turn, could reduce the amount of Pseudomonas resistance seen in veterinary medicine.

In conclusion, this brief summary of the development, carriage and potential transfer capacity of drug-resistant bacteria in companion animals demonstrates that there is indeed a risk to people of contracting an AMR infection from bacteria of animal origin. While this risk has not been defined quantitatively, the three main components of risk are present: 1) the hazard (i.e., resistant bacteria), 2) a probability the hazard could cause disease and 3) an impact to those infected with a resistant pathogen. Even in the absence of quantitative risk assessment, the suspected presence of risk has promoted the development of AMD use guidelines and antimicrobial stewardship in companion animal medicine.

AMD use guidelines and antimicrobial stewardship in companion animal medicine

As it has been suspected that AMDs are often over- and misused in dogs and cats, there has been a push to improve use among small animal veterinarians. Several professional organizations within the profession have released guidelines relating to judicious use and AMS. It is important to understand the current recommendations in order to apply them in clinical practice. The following guidelines are central to research presented in this dissertation. As aims of this dissertation utilize current guidelines as both an exposure (Aim 1) and as a method to determine appropriate AMD prescribing (Aim 3), a discussion of pertinent documents is presented.

Specific AMD use guidelines have been developed for a handful small animal disease conditions, including urinary tract disease, respiratory tract disease and bacterial skin infections[129,130,131], which represent conditions for which AMDs are commonly prescribed. The International Society for Companion Animal Infectious Disease (ISCAID) guidelines for urinary[129], respiratory[130] and skin[131] diseases are regarded as the standard in terms of how AMDs should be prescribed in these situations and are used extensively in the development of other organizations' AMD judicious use statements[132,133,134]. While not seen as regulation or a mandate, the ISCAID guidelines are recommendations that were developed with objective data from both human and animal healthcare systems and infectious disease specialists' opinions. Guidelines were developed by panels of internal medicine and infectious disease specialists that came to agreement on recommendations based on the Delphi method of consensus building. The authors of these guidelines recognize that each urinary, respiratory and skin case is, at least slightly, different and ultimately refer to the expertise of the clinician when deciding whether or not AMDs are needed. Additionally, the guidelines do not cover every possible context of these diseases. Rather, the ISCAID guidelines represent expert based recommendations pertaining to diagnostics and treatments that allow practitioners to have a reference in their AMD decision-making process.

As discussed throughout this document, urinary tract symptoms, including stranguria, pollakiuria, dysurina and hematuria, are common in dogs and cats. One of several potential causes for these clinical signs is bacterial infection, which is much more common in dogs than in cats. As this set of symptoms is a common reason to seek veterinary attention, it is also an impetus behind AMDs prescriptions, both appropriate and inappropriate[51,135]. The ISCAID urinary guidelines suggest diagnostic and treatment recommendations for the following: sporadic bacterial cystitis, recurrent bacterial cystitis, pyelonephritis, prostatitis and subclinical bacteruria[129]. The document also touches on management suggestions for urinary catheter management and urological surgery. Of the listed conditions, sporadic cystitis, of bacterial cause, is the most frequently encountered situation in clinical practice. It is suspected that many of these patients are prescribed an AMD without a full diagnostic work-up, which may be declined by the owner due to cost, deemed not necessary by the veterinarian or not possible due to the inability to collect urine for diagnostic testing[136,137]. The ISCAID committee outlines a diagnostic work-up for animals presenting with a history of urinary tract signs, including performing a physical exam, urinalysis and aerobic bacterial culture of urine. The guidelines also strongly suggest ruling out any conditions that might predispose an animal to bacterial cystitis, such as diabetes or uroliths. If, based on the aforementioned diagnostic work-up, a practitioner decides that AMDs are warranted, the document recommends antibiotics to initially prescribe while awaiting the results of a urine culture. Amoxicillin and trimethoprim-sulfadiazine are recommended first-line AMDs for bacterial cystitis and should be prescribed for 3-5 days per the guidelines. If urine culture results, which typically take 3-5 days to receive, indicate that a pathogen is resistant to amoxicillin or trimethoprim-sulfadiazine, the guidelines suggest other classes of AMDs as long as they are included on the urine culture sensitivity profile. The other conditions described in the ISCAID urinary tract disease guidelines, including recurrent bacterial cystitis and pyelonephritis, are much less common in clinical practice. However, the guidelines provide specific diagnostic and treatment guidelines for practitioners to refer to when these conditions are encountered in the clinic. As it is suspected that these conditions collectively do not account for much AMD use in veterinary medicine when compared to sporadic bacterial cystitis, describing the specific diagnostic and treatment regimens is beyond the scope of this discussion.

A range of respiratory disease is covered by the ISCAID respiratory tract disease guidelines. Feline upper respiratory infections (URI) and canine infectious respiratory disease complex (IRDC) (a.k.a. kennel cough) are highlighted in the article. Other conditions such as bronchitis, pneumonia and pyothorax are also covered. Feline URI and canine IRDC are common in small animal medicine and account for a large percentage of AMD prescribing.

Acute feline URI most commonly has a viral cause but can develop secondary bacterial infections in severe cases [138,139]. Evaluation of the amount, color and consistency of nasal discharge in these patients can provide information for the AMD prescription decision-making process. If discharge from the nose is clear, the guidelines state to withhold AMD treatment as the cause is almost certainly viral. In cases where nasal discharge is mucoid or purulent, AMD treatment is still not recommended even though there may be a bacterial component, unless there are systemic illness signs such as fever, anorexia, significant lethargy of the illness that have been lasting more than 10 days. In cases where AMDs are needed, the working group recommends a short list of first-line treatment, including doxycycline. The committee currently recommends against use of third generation cephalosporins and fluoroquinolones based on their importance in human medicine and the threat that widespread resistance to these AMDs poses to public health. In cases of chronic feline upper respiratory disease (i.e., disease that lasts more than 10 days), a full diagnostic work-up is recommended and AMD treatment choice should be dictated by results of bacterial culture and sensitivity.

Just as acute feline URI is common among cats, so is canine IRDC among dogs. Similarly, too, to feline URI, the canine counterpart is also typically of viral etiology. Commonly, canine patients presenting with a cough are prescribed AMDs, regardless of whether or not it is due to a bacterial cause[138]. Most cases of canine IRDC resolve on their own without

AMD treatment within 10 days. ISCAID guidelines state that AMDs should be avoided if the patient does not have a fever, is still eating and has normal energy. If systemic illness signs accompany the respiratory signs, doxycycline is the recommended first-line antibiotic. Follow-up evaluation to ensure clinical resolution should be done within the first seven days of being on the AMD for cases of suspected bacterial involvement since most uncomplicated bacterial IRDC illnesses respond rapidly to AMD treatment.

The third set of ISCAID guidelines lays out protocols for management of superficial bacterial folliculitis, a common bacterial disease of the skin in dogs. There is more opportunity for inappropriate AMD use in companion animals in cases of urinary and respiratory disease when compared to cases of skin disease. This is likely due to the availability of quick and inexpensive diagnostic tests to rule out bacterial skin disease that allows practitioners more accurately to diagnose a bacterial infection. The ISCAID working group focused this set of guidelines on dogs specifically. The decision to prescribe AMDs should be based on physical exam of the skin, which typically reveals pustules, crusting, alopecia and evidence of pruritus. Basic cytology assessment of lesions, which can easily and quickly be done in the clinic, should dictate whether or not AMDs are warranted. The most important reasons to perform cytology on skin lesions is to rule out yeast and parasitic infections, both of which will not respond to AMDs. The ISCAID superficial bacterial folliculitis guidelines give detailed instructions on how to sample different types of lesions. Bacterial culture and sensitivity is not typically recommended for each dermatitis case unless there is no resolution after treatment, there are new lesions present after treatment starts, there are rod-shaped bacteria on cytology or if the patient has a history of multi-drug resistant infections. Antimicrobial treatment of superficial bacterial folliculitis is not contraindicated, but as the guidelines suggest, there are important considerations in terms of drug, dose and duration that need to be followed to maximize positive outcomes and minimize AMR development. Systemic empirical AMD treatment has been extensively practiced for decades and has typically been successful in resolving infections. However, as the authors point out, there is growing resistance among *S. pseudointermedius,* leading to more treatment failures. Topical treatment with shampoos, gels, wipes and other medicated delivery methods should always at least be considered in the treatment of bacterial skin disease. Not only does the use of topical treatment reduce the need for oral systemic AMDs, but it also aids in restoring the health of the skin and resolving infections more quickly. The ISCAID document lists scenarios when topical therapy may be more appropriate than systemic treatment, including in the early stages of the disease, when lesions are localized and to help prevent recurrence after resolution. The committee estimates subjectively that the use of topical treatments is low, likely due to owners' ability to bathe their pet in the correct way. Whether this barrier is perceived by veterinarians or is the reality of pyoderma treatment for owners, focusing on overcoming compliance issues when recommending topical treatment is key. When disease is too severe or extensive and when owner compliance proves to be a non-modifiable issue, oral AMDs are recommended to treat superficial bacterial folliculitis. The working group did not completely agree on the use of certain classes of AMDs and which "tier" to place them in. This lack of agreement is likely due to the dearth of understanding regarding the best drug, dose and duration of oral AMDs to treat superficial bacterial folliculitis. There is concern over the use of third generation cephalosporins and fluoroquinolones in companion animal skin disease in that it has the potential to breed resistant pathogens that could ultimately infect humans. Specifically, in the context of treatment of skin disease in dogs, the use of a third-generation cephalosporin, cefovecin, is of recent public health concern. Cefovecin was released in 2008 and is labeled for the treatment of soft tissue and skin infections in dogs and cats. Its main advantage is that it is active in the body for 14 days, thus eliminating the need for daily oral dosing. It ensures the pet is receiving the medication appropriately because it is given in the veterinary clinic. While eliminating the issues of owner compliance, there is still opportunity for this drug to be used inappropriately in the veterinary community for illness other than skin disease. Therefore, it is suggested that cefovecin be used as directed for labeled indications only. As superficial bacterial folliculitis is common in canine patients and routinely treated with oral AMDs, it presents an opportunity to improve use by considering topical treatments prior to oral medications and choosing the correct drug, dose and duration when systemic AMDs are indicated.

The American College of Veterinary Internal Medicine (ACVIM) has developed a consensus statement on the use of AMDs in veterinary medicine[134]. This 2015 document outlines a number of considerations to achieve better treatment outcomes when using AMDs and provided detailed thoughts on stewardship in companion animal medicine. While the document does not specifically address any certain disease conditions, species or medications, it describes a general framework to apply in the AMD decision-making process. Much like the ISCAID guidelines, it does not take into account the influence of external factors, like client finances, on the decision-making process. However, this statement provides consensus objective guidance from specialists to refer to and make an informed AMD decision.

The ACVIM statement underlines the importance of the challenge of AMR, but also emphasizes that there needs to be balance between judicious AMD use and animal welfare. While recognizing the strong evidence for AMR development in people secondary to AMD use in veterinary medicine, the authors point out that there is no conclusive data to definitively support the connection. The potential for transmission is, however, important from a public health perspective, and therefore, the committee favors a “precautionary principle” approach for which a qualitative risk assessment is the foundation. The committee provides three general strategies for mitigating the development of AMR from AMD use in veterinary medicine: 1) preventing disease, 2) reducing the use of AMDs and 3) improving AMD use when indicated. Disease prevention through vaccines, improved environmental hygiene and regular medical care can reduce AMR by not allowing bacterial pathogens to establish infection in the first place. Overall reduction in AMD use can be achieved by not prescribing AMDs inappropriately, such as in the case of a viral infection or in cases of non-systemic illness (i.e., acute, self-limiting diarrhea). Other ways to reduce AMD use include de-escalation of AMDs based on bacterial culture, shorter duration of AMD courses[129,140] not treating subclinical bacteruria[129,141], not using AMDs for suspected non-antimicrobial therapeutic uses (i.e., doxycycline for URI, metronidazole for diarrhea) and avoiding the use of AMDs in moribund patients[134]. Finally, improved use of AMDs when they are indicated can decelerate selection pressure on bacterial pathogens and the commensal microbiota. Understanding the specific pathogen that is causing disease and what AMDs is it susceptible to greatly improves the use of AMDs. Use of culture and sensitivity is aggressively advocated for in the ACVIM document. While there are factors that preclude the routine use of culture and sensitivity (i.e., cost)[136], the committee recommends counseling pet owners about the importance of this test. Emphasizing the value of culture through the reduced morbidity, mortality and associated costs has been suggested as a method to get owners to accept the cost and time delay of bacterial culture use. Another way of improving the use of AMDs is through the delivery of the medications. The document recommends topical and local administration of AMDs when the option exists. This local or topical administration circumvents the systemic effects of oral AMDs. When oral AMDs are indicated, using the right drug, at the right dose for the correct duration is recommended.

The ACVIM statement outlines other recommendations to improve AMD use in veterinary medicine aside from disease prevention, AMD use reduction and AMD use improvement. The committee discourages the use of compounded AMDs. Compounded AMDs are commonly used to increase palatability for pets, accommodate various body weights, increase owner compliance of giving the medication and reduce medication costs to the owner. However, the FDA does not regulate these drug formulations, meaning the pharmacodynamics, efficacy and safety are not evaluated. In one example, compounded doxycycline, which is routinely used for small dogs and cats with URI, is only stable at its stated concentration for seven days[142]. Therefore, when this formulation is prescribed to a patient more than seven days after being compounded, it, at best, is providing a subtheurapeutic dose where, at worst, it no longer contains active doxycycline, possibly leading to ineffective and ultimately delayed treatment of a bacterial disease, resulting in increased mortality, morbidity and expense. For much the same reasons, the committee also recommends steering away from the use of generic medications that do not have a PK/PD profile for animals. This practice is routinely employed in an effort to reduce the costs of prescribing a more costly medication. A common example is the use of human generic ciprofloxacin, a critically important AMD in human medicine, in favor of the more appropriate veterinary-formulated enrofloxacin, which is much more expensive, especially for larger animals. Much like the use of compounded medications, the use of a human generic that lacks an animal use profile may lead to a delay in effective treatment, resulting in poor outcomes, while exposing the commensal microbiota to a higher tier AMD and selecting for more resistant bacterial populations.

The discussion outlined in the ACVIM document advocates for judicious use of AMDs in veterinary medicine, both large and small animal. Where the document differs from other reports calling for improved use of AMDs in veterinary medicine is that is also focuses on the need for continued responsible AMD use to ensure animal welfare, a safe food supply and the financial interests of owners/producers. With the stated need for AMDs, the committee also issues a stern warning that AMDs will continue to come under strict restrictions, effectively controlling what veterinarians can prescribe, unless the profession self-regulates voluntarily. Without the profession taking it upon itself to reduce inappropriate AMD use, the committee states that regulation is justified. However, with any significant restrictions, the committee also calls for robust and sustainable tracking methods to document the effects of regulation objectively.

The American Animal Hospital Association (AAHA) has been a major player in raising awareness of AMR in veterinary medicine and has advocated extensively for judicious use of AMDs. In guidelines released in 2014, along with the American Association of Feline Practitioners (AAFP), AAHA made many similar recommendations as those in the ACVIM consensus statement[133]. The AAHA document is substantially shorter and lacks the specialty commentary that the ACVIM document presents; it is more focused on a broad framework that practitioners can use in their AMD prescription decision-making process. The framework contains recommendations on how best to prevent disease, which is also outlined in the ACVIM statement. AAHA has published extensive vaccine guidelines for veterinarians to follow when making vaccine recommendations[143]. AAHA guidelines advocate for specific AMD use and specifically state that most cases of lower urinary tract signs in cats, upper respiratory infection in dogs and cats and pancreatitis in dogs and cats are not of bacterial origin and, therefore, do not warrant antimicrobial drug therapy. In cases of suspect bacterial infection, it is recommended to make a definitive diagnosis before prescribing AMDs. When a true diagnosis is made, looking for therapeutic alternatives prior to AMD prescription should be considered per the guidelines. Once the decision is made to prescribe AMDs, culture and sensitivity should be employed and the most-narrow spectrum drugs should be used until a culture result is available. Furthermore, the shortest possible course of AMDs should be prescribed while avoiding drugs that are meant for more serious infections in people and animals. Engaging the client to ensure proper administration of the drugs is encouraged and periodic monitoring of the patient's condition are also part of AAHA's guidance. Finally, the AAHA guidelines stress the importance of accurate documentation describing the use of AMDs in patient medical records. While these recommendations are much more succinct than the ACVIM statement, AAHA does specifically address the role of AMDs in routine veterinary dentistry in detail in another guidance document.

The 2019 AAHA dental care guidelines for dogs and cats outline recommendations for complete dental care of pets[132]. This includes how and when to use AMDs for these procedures. There is suspect widespread use of AMDs in the context of companion animal dentistry, most of which is thought to be inappropriate[144]. The AAHA dental guidelines allow for more subjective assessment by the clinician when compared to the previously discussed sets of guidelines. AAHA recommends that the decision to prescribe AMDs for a dental patient be assessed on a "case-by-case" basis instead of making them a part of every dental procedure's protocol. Dentals are considered to be clean-contaminated procedures and, therefore, systematic AMDs are not warranted in most cases. AAHA does recommend the use of post-operative systemic AMDs when there is radiographic findings of osteomyelitis or evidence of widespread oral infection. By referring to these recommendations, veterinary practitioners will likely reduce their use of AMDs for dental procedures, thus reducing overall use.

Recently, the American Veterinary Medical Association (AVMA) developed and adopted consensus core principles of AMS[145]. The principles set forth by the AVMA mirror those that were developed for human outpatient medicine by the CDC in 2016[146]. The AVMA defines AMS in veterinary medicine as maintaining animal welfare through effective disease prevention and treatment, using an evidence-based approach when deciding on AMD use and managing the treatment course while considering the client's resources[145]. The Veterinary Checklist for Antimicrobial Stewardship was created by the AVMA's committee on antimicrobials and was developed using the previously discussed guidelines, as well as other research. The checklist outlines five main areas of AMS: committing to stewardship, preventing common diseases, selecting and using AMDs judiciously, evaluating AMD use after prescription and educating clients, staff and one's self.

Extensive efforts have been put into developing and distributing AMS and AMD use guidelines. All previously discussed resources are freely available to practicing veterinarians. However, it is unknown if veterinarians are widely aware of these guidelines and how effective they are practiced. The lack of awareness and effectiveness is key to improving AMD use in veterinary medicine. Other gaps in knowledge, such as how AMDs are used in small animal practice, how pet owners influence the AMD decision-making process and how AMDs are used for pets compared to human medicine, are also important to fill if there is to be improved AMD use in veterinary medicine.

Gaps in understanding AMD use in companion animal medicine

As previously discussed, there is concern that the misuse and overuse of AMDs in companion animal medicine may be contributing to the human risk of acquiring a resistant bacterial infection. Relatively little attention has been paid to AMD use in companion animal medicine when compared to production animal medicine. Although concern for the threat to human health from using AMDs in companion animals has emerged[47], literature on the topic of AMD use in companion animal medicine remains limited. Researchers postulate the reason for the dearth of literature on AMD use in companion animals is likely due to the prior lack of recognition of the public health importance of AMR in companion animals[147]. Specifically, little is understood about how veterinarians use AMDs in companion animal medicine, how pet owners influence the AMD prescription process and how misuse in veterinary medicine interacts with human medicine. Previous studies that have examined AMD use in companion animal medicine have not specifically addressed general practice veterinarians in the United States. The publications are generally from other countries [26,55,148,149,150], academic institutions[147,151,152] or specific corporate practices[153]. While these studies have provided important insight into the way AMDs are used by veterinarians, the results cannot be generalized to the wider population of all U.S. veterinarians. As results cannot be externally generalizable to the larger population of U.S. veterinarians, accurate estimates of their AMDs prescription practices cannot be made. Without a better understanding about how AMDs are prescribed among the general population of practicing companion animal veterinarians, quantifying the problem and, subsequently, developing and implementing effective interventions will be difficult.

Not only is the way veterinarians prescribe AMDs not adequately described, but the role pet owners play in the AMD decision-making process is also unknown. The decision to recommend AMDs is typically made in the exam room of a veterinary hospital after a pet is examined. The intimate setting of this real-time decision has three primary stakeholders: The pet, the pet's owner(s) and the veterinarian. Outside of this group of primary stakeholders, other individuals and groups have a vested interest in the use of AMDs in pets, including practice owners, pharmaceutical companies, veterinary organizations, researchers, public health officials and human medical professionals. While the entire stakeholder network is important to consider, the primary group of the pet, owner and veterinarian are central to the decision to prescribe an AMD. Currently, there has been little published regarding pet owners' attitudes and perceptions of AMD use in veterinary medicine and AMR. Studies that have been published are mainly exploratory and qualitative in nature, and there have been no quantitative assessments done in the United States. The little amount of work that has been previously done on this topic leaves questions about how pet owners view AMD use and AMR. An understanding of how pet owners perceive AMD use and AMR are vital to fully describing the AMD decision-making process. Exploring AMD use in companion animal medicine without filling the critical knowledge gap of how pet owners perceive AMD use and AMR will lead to an incomplete picture and insufficient intervention efforts.

A key component of mitigating the threat of AMR is viewing it in a One Health framework. This framework looks at the human, animal and environmental aspects of AMR and is instrumental in both understanding and controlling the threat. AMR has been called the "quintessential" One Health issue, as there are obvious connections between animals, humans and the environment[154]. However, it is suspected that the value of putting AMR into a One Health framework is underappreciated when considering efforts to reduce the spread[155]. By comparing AMD prescribing in human and animal health, a more global perspective of AMR can be gained. Instead of looking at the components of One Health in a compartmentalized manner in the context of AMR, exploring it on a holistic level can possibly be of more value. There is currently a lack of understanding of how AMR can be viewed in a quantifiable One Health framework. There is also a gap in knowledge of the true value of comparing the two health care systems. By comparing rates of inappropriate AMD prescribing, perhaps the impact of inappropriate AMD prescribing and how it relates to AMR can be attributed more clearly. Furthermore, a global understanding of AMD prescribing may provide perspective that could lead to improved prescribing practices in both human and animal medicine.

The need to understand AMD use in companion animal medicine

As AMR continues to threaten global public health, several efforts on the international stage have sought to mitigate its effect. In order for such interventions to be successful at decelerating the growth of the resistance pool, they need to identify and address the barriers that prevent appropriate use of AMDs. Many of the recognized barriers to judicious AMD use involve a behavioral component and improving AMD use in companion animal medicine will require a change in stakeholder actions. Proponents argue that sustainable prescribing changes cannot be made without considering the behavioral component involved in the AMD decision-making process[156].To date, very few studies in veterinary medicine have examined AMD prescribing in a social and/or behavioral context[157,158]. In the human medicine realm, there is a better understanding of how human behavior can be modified through the development of complex interventions[159,160], which has been applied to developing interventions that encourage judicious AMD use[156,161].

A complex intervention (Figure 2.3) is an iterative process to improve outcomes through interventions that have multiple interacting mechanisms, required behaviors and targeted groups[159]. This process has the potential to be adapted and applied in veterinary medicine to address AMD prescribing. Guidelines have not yet focused on the behavioral aspect of AMD use in veterinary medicine. That is not to say that a novel approach that attempts to change AMD prescribing behavior in veterinary medicine should re-write use guidelines.

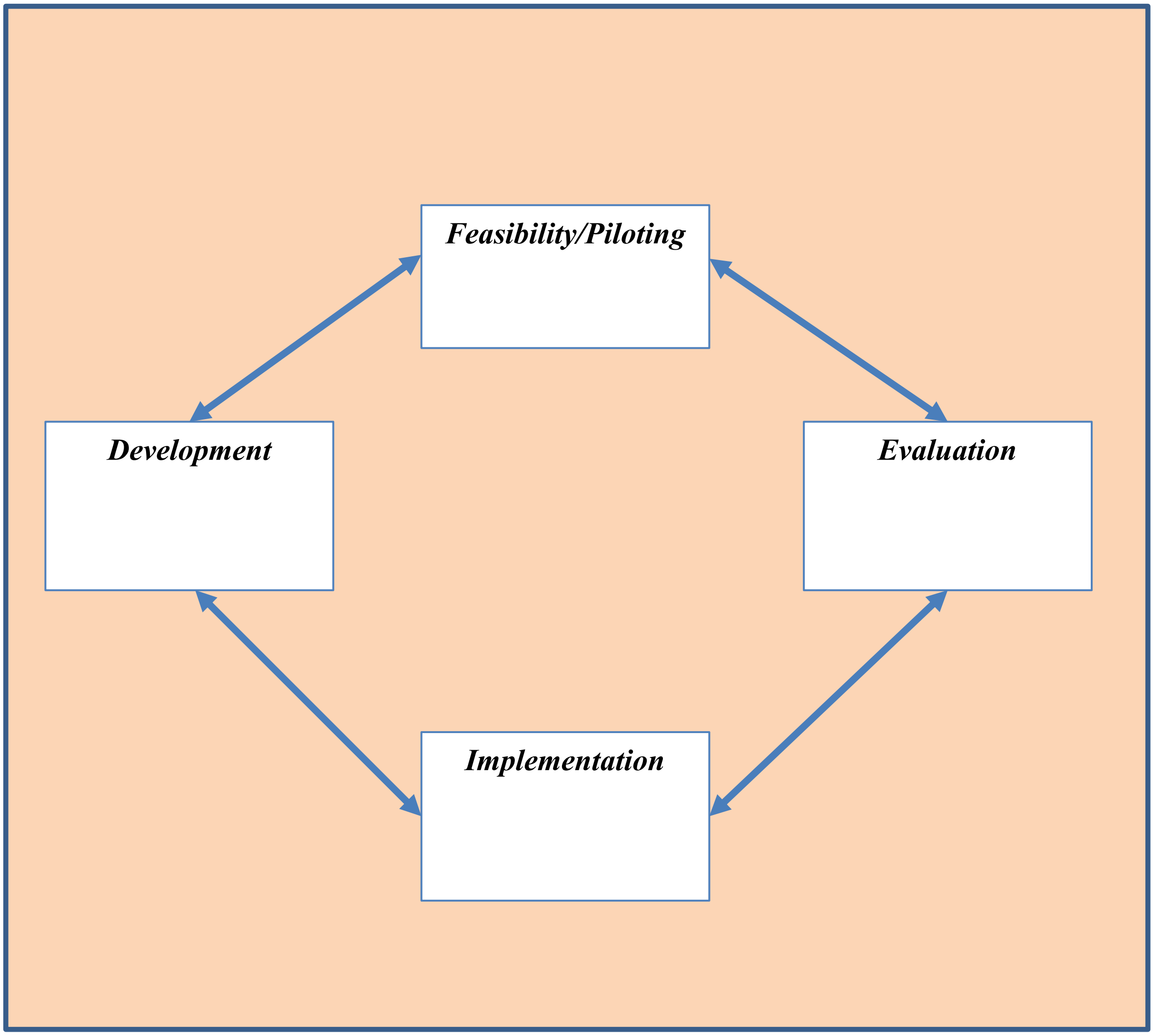

Figure 2.3: Complex intervention framework representing the iterative cycle among development, feasibility/piloting, evaluation and implementation

Rather, it might optimize placement that will maximize effectiveness through the development-piloting-evaluation-implementation framework[160]. The complex intervention cycle starts with the development phase before moving into the piloting-evaluation-implementation stages. The development stage must be done well to avoid a failed intervention[160]. Beyond the broad development step, a systemic approach must be chosen to begin the complex intervention cycle[162]. The development step starts with identifying a problem that needs to be solved, followed by obtaining knowledge of the problem. The next tasks are to decide where changes can be made in the process, designing the actual intervention, refining the intervention and planning for evaluation of the intervention[162]. Before embarking on the development phase, proponents of the approach recommend deciding on a systematic category in which the development takes place. These categories involve such methods as partnership intervention development, stepped development and a combination approach among others[162]. The aims described in the remaining dissertation were designed with a complex intervention framework in mind. It is strongly suspected that AMDs are being widely mis- or overused in companion animal medicine. Therefore, it is of value to design an effective intervention to improve AMD use. Such an intervention should include input for key stakeholders (i.e., veterinarians and pet owners) as they will be the end users of the product. AMD prescribing for companion animals represents a complex process and any intervention that addresses problems with this process should be a collaborative effort from a variety of partners. As this is a novel approach within veterinary medicine, the overall goals for this dissertation are to a) identify the problem and reiterate the call for intervention, b) understand the problem from the perspective of key stakeholders through existing evidence and the collection of new data, c) recommend areas where interventions may be most effective and d) based on results, propose possible interventions and identify existing theories of behavior change to inform the actual intervention. Steps typically taken later in the development stage, and beyond, will not be addressed in this body of work, but rather upcoming aims will hopefully provide a foundation for the complex intervention process to continue in future work.

As outlined earlier, there are many gaps in understanding the way AMDs are prescribed and used in small animal veterinary medicine. If an adequate understanding of this complex process is not defined, then interventions designed to increased adherence to judicious AMD use principles will likely fail to be effective. The lack of efficacy of flawed interventions will continue to allow veterinary medicine to contribute to the pool of resistance at its current rate, possibly increasing the risk to human health and propagating the consequences of AMR. The aims of this dissertation will work to address the knowledge gaps of a) how veterinarians prescribe AMDs b) the role pet owners play in the AMD prescription decision-making process and c) how AMD prescribing in veterinary medicine compares to human medicine. The first two aims of this dissertation will add to the understanding of this complex AMD prescription process by examining the perspectives of the main stakeholders: the veterinarian and the pet owner. Additionally, the first two aims will identify aspects of the process that may be most amenable to intervention. Aim three will compare current AMD prescription practices between veterinary and human medicine in order to attempt to understand veterinary prescribing in a similar framework in which human prescription patterns are studied. By comparing the two systems, ways to improve prescribing in companion animal medicine can emerge. Aim three will also establish methods that can be used to evaluate complex interventions in the future, whether it be during the piloting phase or implementation phase.

CHAPTER III

COMPANION ANIMAL VETERINARINS' ANTIMICROBIAL PRESCRIBING PATTERNS AND THE EFFECT OF ANTIMICROBIAL DRUG USE GUIDELINES ON PRESCRIBING

Introduction

AMDs are used to treat a variety of illnesses in companion animals (i.e., dogs and cats), including common clinical presentations such as urinary tract disease, respiratory tract disease, skin infections and diarrhea[48,163]. Any use of AMDs in companion animals, whether appropriate or not, will result in the selection of a population of resistant bacterial organisms (both pathogenic and commensal), which have the potential to propagate and can theoretically be transferred among different species and their environments. As the human-animal bond has become stronger, so has the concern that AMD use in pets may pose a risk of resistant bacterial infection in their owners[47,164]. While AMDs are a necessary component of treatment for some illnesses and their use cannot be completely avoided, it is suspected that companion animals routinely receive AMDs unnecessarily, resulting in excessive production of resistant organisms and release of genetic resistance elements into the environment. This proliferation in resistance, in turn, could possibly increase the risk to humans of coming in contact and contracting a resistant bacterial infection. While an exact measurement of excessive AMD usage in companion animal medicine does not yet exist, there are assessments that have explored the issue on a smaller scale.

A previous review of medical records from a teaching hospital revealed that 38% of AMD prescriptions did not have a documented indication of why they were being recommended, indicating that use might not have been justified[147]. Additionally, this study found that 45% of

AMD prescriptions were based on suspicion of bacterial disease and not objective diagnostic test results. In companion animal medicine, there are a number of diseases that are often treated with AMDs when there is not an indication for them. Animals often receive AMDs for urinary tract disease symptoms, upper respiratory symptoms (i.e., coughing, sneezing), dermatitis with a bacterial cause (i.e., pyoderma), acute non-hemorrhagic diarrhea and dental extractions[165]. Examination of AMD use in these common clinical situations indicates there is clear opportunity to reduce the unnecessary use of AMDs in companion animal medicine, thereby theoretically reducing the risks of resistant bacterial infection to humans.

In the absence of U.S. regulations, several organizations have produced guidelines for use of AMDs in companion animals (ISCAID, ACVIM, AAHA), which were described in section 2.3. These guidelines address common clinical scenarios, including treatment of urinary tract symptoms, skin infections, respiratory illness (ISCAID), acute diarrhea (ACVIM) and dental procedures (AAHA) and provide insight as to when AMDs should be used or should be withheld. While there has been widespread promotion of these guidelines by veterinary epidemiologists, professional organizations and veterinary specialists, there have been no prior large-scale studies that evaluate if guidelines have an impact on the veterinary prescription decision-making process. The few studies that have examined the effect AMS guidelines have on veterinary prescription practices generally show improved AMD use when the guidelines are applied[166,167,168]. However, these studies are often isolated to specific institutions, regions or corporations. Furthermore, in the United States, there have been no peer-reviewed reports of evaluation of AMS programs and/or guidelines.

With little being known about veterinary practitioners' AMD prescription patterns for companion animal diseases in the United States or veterinarians' awareness of existing AMD use guidelines and recommendations, this aim is significant in that it 1) gathered data on companion animal veterinarians' AMD prescription patterns for five common clinical situations and 2) assessed awareness of existing AMD use guidelines and recommendations and determined how awareness affects AMD prescription practices in the United States.

Aim 1 explores AMD prescription practices for five common clinical companion animal disease scenarios (i.e., feline urinary tract symptoms, canine pyoderma, feline upper respiratory disease, canine acute diarrhea and canine dental extractions) that do not have evidence of bacterial disease. Through this aim, information regarding veterinarians' AMD prescribing practices was gathered using an online, anonymous survey tool. The significance in this aim lies in its ability to describe the problem of AMD over-prescription in companion animals and how it relates to AMR in a public health context. Specifically, this aim establishes a baseline of AMD prescription practices among veterinarians in the United States. This baseline of veterinary AMD prescription habits can serve a handful of purposes, including informing clinical interventions meant to improve AMD use and acting as a benchmark for future comparisons.

Beyond measuring AMD use for commonly encountered clinical situations, this aim also explores the awareness and impact of antimicrobial stewardship efforts in the form of AMD use guidelines. Guideline impacts need to be evaluated to ensure the effectiveness of judicious AMD use interventions. This objective of the aim is significant in that it is the first study in the United States to assess awareness of AMD use guidelines among a large sample population of practicing small animal veterinarians. It is also significant in evaluating how prescription practices differ among those who reported guideline awareness with those who did not.

Materials and Methods

In order to assess AMD prescription practices among companion animal veterinarians in the United States and how AMD use guidelines affect these practices, a cross-sectional survey was used to collect data using a non-probabilistic convenience sample. Data were analyzed in a descriptive manner, and logistic regression models were built to assess for an association between awareness of AMD use guidelines and appropriate AMD prescribing.

Cross-sectional survey

Cross-sectional survey development

An anonymous, online survey link was made available to practicing companion animal veterinarians in the United States from December 1, 2018 to March 1, 2019. The National Association of Public Health Veterinarians (NAPHV) was engaged and agreed to assist in the distribution of the survey. Participants were invited to complete the survey through correspondence from their state's public health veterinarian (i.e., electronic newsletters, state veterinary medical association email listservs or other electronic resources). By opening the survey link and completing the questionnaire, veterinarians self-selected into the study. The survey tool was comprised of three sections: (a) demographic information (years in clinical practice, state of primary practice, role in practice (i.e., owner, associate, other) and employment setting (i.e., general, specialty, emergency)); (b) five standardized common companion animal disease scenarios that solicited veterinarian diagnostic and treatment recommendations; and (c) questions regarding awareness and utilization of any AMD use guidelines and recommendations.

Hypothetical scenarios assessed diagnostic and treatment recommendations for five common clinical situations in which AMDs are thought to be frequently inappropriately prescribed (i.e., feline lower urinary tract illness, canine pyoderma, feline upper respiratory illness, canine acute diarrhea and perioperative canine dental procedures) (Box 3.1). Respondents were able to provide recommendations for all five scenarios or to indicate that they did not routinely see the case described by a particular scenario in their practice. Recommendation options for each scenario were multiple choice (including empirical antimicrobial drugs, diagnostic tests, other support care measures, etc.) and multiple answers could be selected. The option of selecting "other" treatments was also provided. If respondents chose to recommend a particular diagnostic test (i.e., x-rays, blood work, lesion cytology, urine culture), the results were presented to them prior to asking if an AMD would be recommended. If an AMD was ultimately recommended, the survey tool collected additional information about the prescription, including medication and duration.

Table 3.1: Hypothetical clinical scenarios in the antimicrobial drug use survey
Scenario 1- Feline lower urinary tract disease- 4 year old castrated male domestic short hair with a 3-day history of frequently producing small amounts of bloody urine outside of the litter box. **Scenario 2- Canine pyoderma-** A 2-year-old castrated male golden retriever presents for a 5-day history of itching, hair loss and rash on his abdomen. **Scenario 3- Feline upper respiratory disease-** 1-year-old spayed, fully vaccinated, indoor only domestic short hair with a 2-day history of clear nasal discharge and some sneezing some at home. Patient is still eating/drinking. **Scenario 4- Canine acute diarrhea**- A 3-year-old spayed, fully vaccinated female mixed breed dog with a 2-3 day history of non-bloody diarrhea. The patient is still eating/drinking, has not had any vomiting and is acting normally. **Scenario 5- Canine dental**- 8-year-old spayed female healthy Australian shepherd with a total of three teeth extracted due to furcation exposure. Dental x-rays do not reveal any tooth root abscesses or retained roots.

Data Analysis and logistic regression models

Questionnaires that contained a response (i.e., recommendation of a treatment or indication that the type of presentation was not typically seen by the respondent) for each of the five scenarios were included in the final dataset. The demographic characteristics of respondents submitting completed surveys were analyzed descriptively and compared with those submitting incomplete questionnaires to identify missing data patterns in order to determine if values were missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). The demographic characteristics of respondents who were and who were not aware of AMD guidelines and recommendations were also compared using a chi-square test with a p-value of <0.05 used as the threshold for statistical significance.

Frequency of AMD prescribing and the types of medications typically recommended were assessed descriptively for each scenario. Frequencies of AMD prescription for each scenario were weighted by geographic location and a 95% confidence interval was calculated for each scenario's estimate of the proportion of AMD prescribing. Likewise, a proportion and corresponding 95% confidence interval was calculated for the most frequently recommended medications for each scenario.

Aim 1 analyzes data that had previously been collected. Therefore, a sample size (n=2,115) had already been determined prior to analysis. A power calculation to determine the minimum effect size (odds ratio) that can be detected given the sample size, a desired power of 80% and a significance level of 0.05 was performed. A minimum detectable odds ratio was calculated and found to be 1.20 for each of the five hypothetical clinical disease scenarios[169](Table 3.1).

Table 3.2: Minimum detected odds ratio at varying powers and significance levels.

Power	Significance level	Minimum detected odds ratio
60%	0.05	0.87
70%	0.05	0.84
80%	0.05	0.80
90%	0.05	0.74
60%	0.01	0.62
70%	0.01	0.56
80%	0.01	0.51
90%	0.01	0.44

A logistic regression model (equation 3.1) was developed for each of the five hypothetical disease scenarios to assess how an awareness of AMD use guidelines/recommendations affected AMD prescribing. The outcome of each model was whether or not an AMD was recommended (yes/no) while the exposure of interest was whether or not the respondent reported awareness of existing AMD use guidelines and recommendations (yes/no). Other covariates (Table 3.2) were added to the models in a stepwise fashion, and if a covariate had a significant effect on the association between the outcome and exposure, it was included in the final model. All analyses were performed in R statistical software.

(Equation 3.1)

$$\mathit{Logit}\ [\pi(X)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots.. + \beta_p X_p$$

Where β_0 = the outcomes value when all other covariates are zero or reference

Where β_p = the beta coefficient covariate X_p

Results

In total, 2,410 survey responses were submitted. Of these, 88% (2115/2410) of submissions were complete and included in the final dataset used for analysis. The demographic characteristics of those who only partially completed the survey did not significantly differ from those who completed it (Data not shown). All 50 states were represented and were grouped into American Veterinary Medical Association (AVMA) regions. The largest percentage (433/2115 [20%]) of responses came from region 6 (Montana, North Dakota, South Dakota, Minnesota, Iowa, Wisconsin) (Table 1). Approximately half (1064/2115[51%]) of respondents had 11+ years of clinical experience, most (1761/2115[83%]) reported working in a general practice setting and 72% (1519/2115) identified as an associate veterinarian. The majority (1279/2115 [60%]) of respondents reported that they were aware of AMD use guidelines and recommendations, with specialist veterinarians reporting a significantly higher proportion (126/165[76%]) of awareness than general (1045/1761[59%]) and emergency (104/184[56%]) practitioners (p <0.01). Awareness of guidelines did not vary by other demographic factors including years in clinical practice, geographic location, or role within a practice.

The frequency of AMD prescriptions for each of the hypothetical scenarios, along with the most frequently prescribed medications are given in Table 3.3 and Figure 3.1, respectively. AMDs were most frequently prescribed in cases of canine pyoderma (83%, 95% C.I. 81-85%), followed by acute canine diarrhea (55%, 95% C.I. 53-58%), feline lower urinary tract illness (48%, 95% C.I. 46-50%), canine dentals (35%, 95% C.I. 33-37%) and feline upper respiratory illness (28%, 95% C.I. 26-30%). The most commonly recommended AMDs for each scenario were cephalexin (canine pyoderma), metronidazole (canine diarrhea), amoxicillin-clavulanic acid (feline lower urinary tract and feline upper respiratory symptoms), and clindamycin (canine dental procedure).

The odds ratios and corresponding 95% confidence intervals for each scenario's univariate logistic model and multivariable model are included in Table 3.4. Prescribers who were aware of existing AMD use guidelines and recommendations were significantly less likely to prescribe AMDs for the following scenarios: feline lower urinary tract symptoms (odds ratio=0.67, 95% C.I. 0.55-0.81), feline upper respiratory illness (odds ratio=0.66, 95% C.I. 0.53-0.81) and canine acute diarrhea (odds ratio=0.79, 95% C.I. 0.66-0.96). Awareness of AMD use guidelines and recommendations remained significantly associated with less AMD prescribing after controlling for AVMA region, years of clinical experience, role in practice, and employment setting. While awareness of AMD use guidelines and recommendations was associated with less prescribing in cases of canine pyoderma (odds ratio=0.82, 95% C.I. 0.64-

1.05) and for canine perioperative dental procedures (odds ratio=0.94, 95% C.I. 0.77-1.16), these associations were not statistically significant in the univariate or multivariable models.

Table 3.3: Demographic characteristics of practicing companion animal veterinarians in the United States who completed the antimicrobial drug use survey.

Demographic characteristics **Years in clinical practice**	**Number of respondents n (%)**
10 years or less	1049(49.6)
11-20 years	522(24.7)
More than 20 years	544(25.7)
Region[a]	
Region 1- (ME, NH, VT, MA, CT, RI, NJ, PR)	183(8.6)
Region 2- (NY, PA, DE)	209(9.9)
Region 3- (WV,MD,VA,DC,NC,SC)	149(7.0)
Region 4- (TN,MS,AL,GA,FL)	142(6.7)
Region 5- (MI,IN,OH,KY)	129(6.2)
Region 6- (MT,ND,SD,MN,IA,WI)	438(20.7)
Region 7- (NE,KS,MO,IL)	123(5.8)
Region 8- (TX,OK,AR,LA)	171(8.1)
Region 9- (NV,CO,UT,AZ,NM,WY,ID)	241(11.4)
Region 10- (WA,OR,CA,HI,AK)	330(15.6)
Practice type,	
General practice[b]	1764(83.4)
Specialty practice[c]	166(7.8)
Emergency practice	185(8.7)
Practice role,	
Practice owner	534(25.2)
Associate	1519(71.8)
Other[d]	62(2.9)

[a]=American Veterinary Medical Association (AVMA) regions
[b]=general small animal, general mixed animal, shelter medicine, feline only practice, mobile practice, relief veterinarian, retired, unemployed
[c]=specialty practice and academic teaching hospital
[d]= relief, medical director, independent contractor

Table 3.4: Frequencies of AMD treatment recommendation for each of the five hypothetical clinical scenarios presented in the antimicrobial drug use survey by participant self-reported awareness of AMD use guidelines.

	Yes, aware of guidelines	No, not aware of guidelines	Total	p-value
Feline urinary scenario, n (%)	**1267(60.4)**	**831(39.6)**	**2098[a]**	<0.01
Antibiotics prescribed	558(44.0)	452(54.4)	1010(48.1)	
No antibiotics prescribed	709(55.6)	379(45.6)	1088(51.9)	
Canine pyoderma scenario, n (%)	**1226(60.0)**	**817(40.0)**	**2043[b]**	0.05
Antibiotics prescribed	1003(81.8)	695(85.1)	1698(83.1)	
No antibiotics prescribed	223(18.2)	122(14.9)	345(16.9)	
Feline upper respiratory scenario, n (%)	**1254(60.2)**	**829(40.0)**	**2083[c]**	<0.01
Antibiotics prescribed	300 (23.9)	276(33.3)	576(27.6)	
No antibiotics prescribed	954 (76.1)	553(66.7)	1507(72.4)	
Canine diarrhea scenario, n (%)	**1249(60.1)**	**829(39.9)**	**2078[d]**	<0.01
Antibiotics prescribed	663(53.1)	491(59.2)	1154(55.5)	
No antibiotics prescribed	586(46.9)	338(40.8)	924(44.5)	
Canine dental scenario, n (%)	**1119(59.8)**	**753(40.2)**	**1872[e]**	0.31
Antibiotics prescribed	380(34.0)	273(36.3)	653(34.9)	
No antibiotics prescribed	739(66.0)	480(63.7)	1219(65.1)	

[a]= 17 participants reported not seeing feline urinary cases in practice
[b]= 72 participants reported not seeing canine pyoderma in practice
[c]= 32 participants reported not seeing feline upper respiratory cases in practice
[d]= 37 participants reported not seeing canine diarrhea cases in practice
[e]= 243 participants reported not performing dentals in practice

Table 3.5: Odds of AMD prescription for those who reported an awareness of existing AMD use guidelines compared to those who reported no awareness for a) univariate logistic regression models and b) multivariable logistic models after controlling for years in clinical practice, AVMA region, practice type and practice role.

	Univariate model		**Multivariable model**	
	Odds ratio	**95% C.I.**	**Odds ratio**	**95% C.I.**
Feline urinary scenario	0.66	(0.55-0.79)	0.67	(0.55-0.81)
Canine pyoderma scenario	0.79	(0.62-1.03)	0.82	(0.64-1.05)
Feline upper respiratory scenario	0.63	(0.51-0.77)	0.66	(0.53-0.81)
Canine diarrhea scenario	0.77	(0.65-0.93)	0.79	(0.66-0.96)
Canine dental scenario	0.9	(0.74-1.1)	0.94	(0.77-1.16)

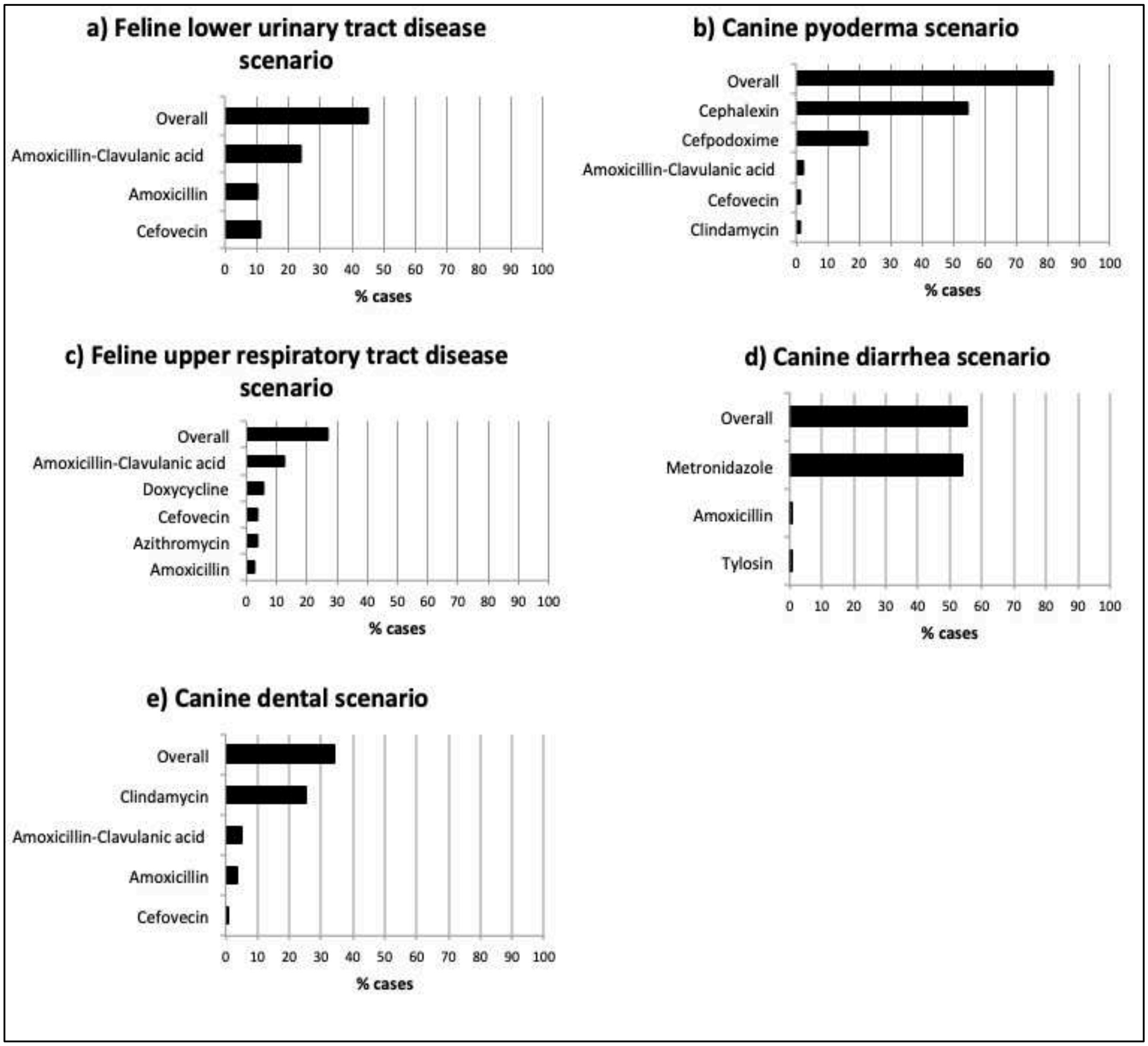

Figure 3.1: Frequencies of antibiotic prescribing and most common medications by scenario:a) feline lower urinary tract disease b) canine pyoderma c) feline upper respiratory tract disease d) canine diarrhea and e) canine dental procedures

Discussion

The results from this nationwide survey support our hypothesis that AMDs are being overprescribed in companion animal medicine for common clinical presentations. While the level of overprescribing varied by disease, results consistently indicate that AMDs are not being prescribed in accordance with existing AMD use guidelines. However, veterinarians who reported awareness of AMD use guidelines were found to be significantly less likely to prescribe AMDs for some clinical presentations when compared to those who were not aware, highlighting the need to promote AMD use guidelines further. Findings of this study contribute to the understanding of an important knowledge gap, which, when addressed, can improve AMD prescription practices among companion animal veterinarians and mitigate AMR development.

Without evidence for bacterial disease, AMDs were routinely recommended for the hypothetical common clinical disease presentations. Existing AMD use guidelines recommend that AMDs should be withheld in the absence of evidence for bacterial disease[129-134]. For this reason, four of the five scenarios used in this survey (i.e., feline lower urinary, feline upper respiratory, canine acute diarrhea, and canine dental procedure scenarios) were designed to emphasize the lack of evidence for bacterial disease. However, participant recommendations for these fours scenarios suggested frequent and inappropriate AMD prescribing, which aligns with results of previous studies. In one study, over half of the dogs admitted to a U.S. teaching hospital had been prescribed at least one AMD[170]. Another U.S. teaching hospital assessment noted that 38% of AMD prescriptions were made without documented evidence of bacterial infection and 45% of prescriptions were made solely on suspicion of bacterial disease[147]. Our study provides further evidence that there is opportunity for improved AMD prescription practices in companion animal medicine by referring to established guidelines and prescribing AMDs only when necessary.

Amoxicillin-clavulanic acid was the most frequently recommended AMD in the feline lower urinary tract and upper respiratory tract disease scenarios, followed by cefovecin and amoxicillin. Studies in Belgium, Switzerland and Canada also found amoxicillin-clavulanic acid to be the most frequently prescribed AMD for cats with respiratory disease[51,55,150] whereas a Finnish study found amoxicillin was prescribed most often in these presentations[148]. Both amoxicillin and amoxicillin-clavulanic acid are suitable AMD choices in cases of lower urinary tract and upper respiratory tract disease when the cause is found to bacterial[129,130]. Cefovecin, a third-generation cephalosporin, was also routinely recommended for feline urinary tract and feline upper respiratory symptoms. Other studies have found widespread use of cefovecin, a member of a critically important class of AMDs, for similar disease conditions [28,61,62]. The prevalent use of third-generation cephalosporins is likely a product of the availability of a single, long-lasting injection that alleviates the burden of having to orally medicate cats, which has been shown to be an influencer of AMD prescriptions[52]. The use of cefovecin in cases where AMDs are not warranted is concerning given the importance of third generation cephalosporins in both animal and human medicine. As is the case in many feline urinary and upper respiratory tract presentations, the cause is not typically bacterial in origin, likely rendering any AMD medication an inappropriate choice. In order to preserve these important AMDs, efforts should be made to use these medications only as directed and to reserve them for clinical cases where bacterial infection is confirmed through objective evaluation and diagnostic testing.

Findings from this study indicate that AMDs are commonly recommended for cases of canine acute diarrhea, and that metronidazole is prescribed almost exclusively. Previous studies also indicate a high rate of use of metronidazole, but alongside other AMD classes such as amoxicillin and amoxicillin-clavulanic acid[52,55,171]. Metronidazole has gastrointestinal anti-inflammatory properties in addition to its antimicrobial action, which makes it a logical choice when choosing an AMD for acute diarrhea[172-174]. However, it is thought that metronidazole use should be reserved for when there is an actual indication to use it (i.e., protozoa infections, clostridium infections). Furthermore, clinical trials have found conflicting evidence on metronidazole's ability to shorten the course of diarrhea [174,175]. Results from the current study, combined with results from the previously referenced studies, indicate that metronidazole may be over-prescribed and may not provide patient benefit in cases of canine diarrhea.

These survey data indicate that clindamycin is most often prescribed after dental extractions, with it comprising approximately 75% of all dental AMD recommendations. An Australian survey also found a high rate of AMD prescribing after dental procedures, but noted that clindamycin and amoxicillin-clavulanic acid were prescribed equally[53]. It is recommended by the American Veterinary Dental College to use systemic AMDs only in immunocompromised pets or in cases of severe dental disease, which is a subjective parameter[176]. The American Animal Hospital Association dental guidelines indicate that AMDs are not typically needed, unless there is evidence of osteomyelitis[132]. While there have not been controlled studies in veterinary dentistry to determine if AMDs are truly beneficial, assessments in human dentistry indicate that prophylactic use of AMDs should be limited[177]. Given the current thought surrounding AMD use in companion animal dentistry, practitioners should judiciously prescribe AMDs on a case-by-case basis while further research is needed to inform more concrete consensus guidelines for practitioners.

An AMD was recommended in over 80% of the responses to the pyoderma scenario, with cephalexin being the most frequently chosen medication. For cases where an oral AMD was not prescribed, topical treatments, such as shampoos, were recommended instead. Oral cephalexin use in canine pyoderma is not inappropriate per the guidelines[131], but pyoderma does represent a bacterial infection that can be treated with targeted topical treatments rather than systemic oral AMDs. Past studies of prescription habits in cases of pyoderma found frequent oral AMD use and that cephalexin was the most common medication choice[52,178,179]. Veterinarians in New Zealand prescribed oral AMDs in 98% of pyoderma cases, choosing cephalexin 43% of time and potentiated amoxicillin for 44% of cases[180]. Besides medication choice, guidelines also provide recommendations for dosage, frequency and duration of treatment. Information regarding dosage and frequency was not collected in the current study, but previous studies have demonstrated the need for improvement[52,178]. Combined with results from other assessments, there appears to be an opportunity to utilize more targeted topical treatments for pyoderma over systemic oral AMD therapy.

Across all scenarios, respondents with an awareness of AMD use guidelines were less likely to prescribe AMDs than those who did not report awareness. While the number of veterinarians who were aware of AMD use guidelines in this survey is higher than what a 2015 AVMA survey found (12% vs. 60%)[181], there is still a clear opportunity to increase awareness and subsequently improve prescribing practices among companion animal veterinarians. Previous studies have shown that guidelines and other resources positively affect AMD prescribing. In Belgium, veterinarians who referenced scientific resources when making an AMD prescription decision were more likely to prescribe appropriately than those who did not utilize such resources[55]. Similarly, a retrospective records review at a Canadian teaching hospital found improved AMD prescribing after antimicrobial stewardship guidelines were implemented[166]. Likewise, a Danish study showed that guidelines had a positive impact on the prescription practices in companion animal medicine[167]. Guidelines can be useful in the AMD prescription decision-making process as they provide expert consensus on when and what AMDs should be used. Furthermore, guidelines can help troubleshoot complicated clinical cases and give veterinarians a strong scientific foundation to refer to during the complex AMD prescription decision-making process.

Limitations and strengths

Limitations

There are numerous sources of bias in this aim, including selection bias, information bias, unmeasured confounding and possible clustering of responses. No epidemiologic study is without these sources of bias and the assessment of AMD use among small animal veterinarians and the effect of AMD use guidelines is no exception. Examples of possible bias, the possible effect on the results and ways to adjust for these biases are discussed by the bias source category.

Selection bias

The strategies used to collect data in this assessment do open the study to sources of selection bias that could ultimately prevent generalizing the results from the study sample to the broader veterinary population. In an effort to obtain as many completed surveys as possible, a "shotgun" approach was used to recruit small animal veterinarians. This collection strategy did not give everyone in the source population an equal chance of participating in the survey. The discrepancy in opportunity came from three main sources: unequal effort among state public health veterinarians to reach their constituents, failure to reach veterinarians who do not use the internet and self-selection in the study. Though it is difficult to assess which source of selection bias has the biggest impact on the results, it is suspected that self-selection into the survey may have had the most influence. Selection bias in this study could have occurred by "censoring" on a variable that is the effect of the exposure and a cause of the outcome (figure 3.2)[182]. By allowing veterinarians to self-select into the study, bias is introduced through non-randomization. In a random sample, self-selection cannot occur because an exposure has not been knowingly assigned to the participant[182]. The non-random sample has the possibility of being fundamentally different from the source population. Figure 3.2 illustrates how an association between awareness of AMD use guidelines (E) and appropriate AMD prescribing (D) can be induced through a self-selection bias (C).

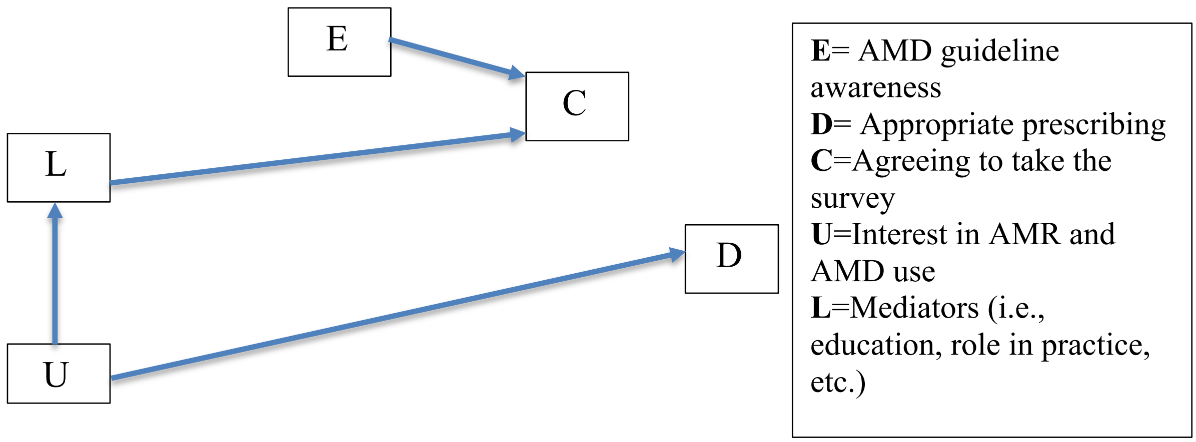

Figure 3.2: Directed acyclic graph (DAG) showing how conditioning on agreeing to take the survey can induce an association between awareness of AMD use guidelines and appropriate AMD prescribing

Information bias

As the case with selection bias, the design of a questionnaire and the way in which data were gathered could have both introduced an information bias. An information bias in this particular study may have resulted in inaccurate estimates of association due to an over- or underestimate of the true odds ratios[183]. More specifically, social desirability bias may have been at play. As AMD use can be seen as a sensitive topic, participants may have been more likely to report an awareness of AMD use guidelines when they were not truly aware of them. This bias may have resulted in an over-estimated proportion of AMD use guideline awareness, resulting in a possible differential misclassification of exposure. However, a self-reported awareness of guidelines is likely more of a measurement of perspective since the question assessing awareness only asked if the participant was aware of any guidelines, not asking them to provide specific examples. Possible ways to address if this source of bias truly exists are through internal and external validation studies. As there were not any other data collection instruments used in addition to the survey tool, internal validation is not possible. However, external validation of the survey tool could be accomplished by examining medical records written by the participants or by observing their prescription habits in a practice environment. Ideally, this type of validation should be considered prior to data collection and not after the analysis has been completed[183]. Another method for overcoming social desirability bias could have been to incorporate questions into the survey that measured social desirability. While this technique could have eliminated responses that scored high on the social desirability scale, it would have added additional time burden for the participants and would have reduced the sample size.

The use of hypothetical clinical disease scenarios is likely both a limitation and strength of the study design. The consistency of the scenario produced a rigidity that made it impossible to capture the effect of several sources of variation, including client, pet and veterinary practice factors. While the use of a consistent hypothetical scenario made it simpler to collect recommendations for common disease presentations, it also limited the amount of information captured, which ultimately leads to other questions. New techniques described by Hur et al. show that medical record data can be used to identify AMD use in companion animal practice[25]. The use of these methods, which include free text analysis and natural language processing, are novel in veterinary medicine and show the power of large data sets in creating accurate estimates. While studies that employ these more sophisticated methods are better able to capture the whole story when exploring AMD use in companion animal medicine, they are only possible in countries that have sources of large datasets created through surveillance. Australia and the United Kingdom have both invested heavily in the creation of networks capable of collecting a large amount of data through submission of medical records from volunteer practices[25,26]. While the methods and applications described by Hur et al. are in their infancy in veterinary research, they represent an example of a more complete way to analyze data in veterinary medicine. For pet-related data to be collected and analyzed in this way in the United States, a reliable surveillance network with a representative sample of participating hospitals needs to be created. With the consolidation of veterinary practices into large corporate entities, the possibility for creation of such a network exists, however, not without logistic and proprietary barriers.

Unmeasured confounding

In this survey, demographic information, such as geographic location and years in clinical practice, was collected. In an effort to control for possible confounding, models were constructed using these demographic variables. The demographic information collected by the survey tool was determined by both previous literature and expert opinion and represented covariates that were most likely to confound the relationship between the exposure and the outcomes. Ultimately, no significant associations were noted between the demographic variables (i.e., years in clinical practice, geographic location, role in practice and employment type) and the prescribing outcomes for each scenario. However, there is a probability that other variables that were not captured by the survey tool may have an effect on the association between the exposure and the outcome. If this were truly the case, then the significant associations noted between awareness of AMD guidelines and inappropriate prescribing may not be real.

Clustering of responses

A fourth limitation of the study design is that data analysis did not take into account the possible effect of clustered responses. Veterinary hospitals typically have multiple clinicians and it is possible that survey responses were clustered around certain hospitals. The possible correlation in responses is due to the fact that veterinarians in the same hospital may practice similar medicine, including prescribing AMDs in a similar manner. Given the information that the survey tool collected, there is no way to know if a set of responses came from the same clinic or hospital system. Therefore, there is not a post hoc method of accounting for correlation of responses. The lack of accountability for correlated responses comes from the sampling methodology. To properly address the concern of correlated responses, a more rigorous sampling scheme would need to be employed. Eliminating the possibility for correlated response is seen in human AMD assessment study sampling, where only one practitioner per site is selected to participate in the survey[184].

Strengths

The study design, data collection and analysis have a list of strengths that increase the validity and precision of the study results. The survey was designed to maintain consistency through the use of the hypothetical scenarios. While the use of the same scenario for each participant could also be seen as a limitation, the scenarios were designed to represent common clinical presentations that practitioners see on a frequent basis. In addition, the use of hypothetical scenarios controlled for variations in other factors that might have played a role when deciding whether or not to recommend AMDs for a particular scenario. For example, in the hypothetical scenarios, client finances were not a barrier to diagnostic testing, allowing the participant to recommend diagnostic tests prior to deciding on AMD treatment. Other external factors that were controlled for by the use of a consistent hypothetical scenario included client expectations, patient co-morbid conditions, time of day and pressures of the appointment schedule. While it is true that these factors do play a role in the AMD decision-making process, the objective of the hypothetical scenarios was to establish a baseline of AMD use. It will be important for future research to explore how these factors affect the AMD decision-making process and how to mitigate their effect.

Perhaps the biggest strength is the sample size. Using a convenience sampling technique, more than 2,400 responses were gathered. The estimated population of practicing companion animal veterinarians in the United States is approximately 70,000. To date, no veterinary AMD assessment performed in the United States has had more veterinarians participate. Furthermore, the sample population represents a diverse group of veterinarians in terms of geographic location, years of clinical experience, role within the practice and practice type. While a complete census of companion animal veterinarians does not exist, some pertinent demographic information is available that can be compared to our sample population. For example, the U.S. breakdown of veterinarians in general practice, specialty practice and emergency practice matches that of the sample population. The size of this diverse sample population increases the likelihood that results can be generalized to the source population. The sample size represents approximately 3% of the companion animal veterinarians in the U.S., which decreases the likelihood for a Type 1 error (i.e., rejecting the null hypothesis when the null hypothesis is true).

Future directions

The aim provides a previously unreported baseline of AMD use for five common clinical scenarios among companion animal veterinarians in the United States and describes the impact of an awareness of AMD use guidelines. Future studies can build off of these findings and subsequently improve upon methods used here. Instead of prescription practices being measured with a hypothetical scenario, widespread representative retrospective records review or prospective data collection methods could be used. This would allow for the stepwise progression of allowing more variation in case presentation and for assessing how this variation affected AMD recommendations. The use of real case presentations would also allow for external factors such as client finances and practitioner schedule to impact AMD use. Similarly, a more rigorous measure of AMD use guideline utilization could be developed to assess the specific resource that was referenced and how it was used. A better measure of guideline use and awareness would reduce the bias created by the self-reported variable used in this survey. A random, probabilistic sampling approach could be employed to ensure better representation of the entire source population. This sampling strategy would also allow for the assessment of non-response and would provide a better foundation for the assessment of missing data. An example of how this sampling scheme is used in human medicine and could be applied to veterinary medicine will be explored in the Aim 3 section. Ultimately, the creation of a nationwide sustainable surveillance system that could capture actual use of AMDs among companion animals is needed, and results from this study are sufficient for aiding in the development of such a system. Results from the current study could also be compared to results from future studies, further validating the use of a cross-sectional survey of hypothetical clinical scenarios for future assessments.

CHAPTER IV

COLORADO PET OWNERS' ATTITUDES AND PERCEPTIONS OF ANTIMICROBIAL DRUG USE IN COMPANION ANIMALS

Introduction

The pet owner plays a significant, yet underappreciated, role in the veterinary AMD prescription process. Understanding the role of this important stakeholder is key in better defining how AMDs are used in companion animal medicine. An owner's decision to have a pet examined at a veterinary hospital and their expectation of receiving medications for their pet can influence the veterinarian's decision of whether or not to prescribe antibiotics. Additionally, owner compliance of administering medications as directed introduces potential barriers to appropriate AMD use in companion animals. Ignoring the role of the pet owner in the AMD prescribing process may render judicious AMD use efforts ineffective. Furthermore, not adequately understanding factors associated with pet owners' compliance of administering AMDs may perpetuate misconceptions that veterinarians have about pet owners, leading to continued suboptimal AMD prescribing and use. Continued inappropriate AMD use in companion animals accelerates bacterial resistance to AMDs, which poses a potential threat to pet owners' health. To date, a handful of studies have interviewed pet owners to develop an understanding of their AMD knowledge and understanding[71,185].

In the United States, a qualitative assessment in Philadelphia found a low level of concern for AMR among pet owners. Also noted in this assessment was pet owner desire for antibiotics in times of diagnostic uncertainty, even when pet owners were counseled by veterinarians about the likely ineffectiveness of AMDs[185]. Findings from this study suggest that the veterinarian-client relationship can be instrumental in improving AMD prescribing once the role of the pet owner in the AMD prescription process is better understood. In a separate study from the United Kingdom, interviews with veterinary practitioners discovered that pet owners affect the decision-making process through their expectations for AMDs, ability to pay for care and compliance of administering treatments[186]. While veterinarians cited client expectations for receiving AMDs as an external influence on dispensing AMD prescriptions, another study suggested that clinicians misinterpret client expectations and perceive demands that are not truly there[71]. Another study from the United Kingdom specifically asked cat owners about their knowledge of and experience with AMDs[187]. The previously referenced studies not only describe the pet owner role in the AMD decision-making process, but also illustrate the potential for qualitative methods to be applied to a wide array of veterinary research questions. When used in conjunction with quantitative methods in a mixed-methodology framework, qualitative methods can provide a deeper understanding of the phenomenon being studied.

Mixed methods have gained popularity in public health research over the last two decades. The methodology emphasizes the strengths of different data collection and analysis strategies to gain a better understanding of public health issues, especially in the context of social and behavioral questions[188]. Mixed methods confer benefits such as trustworthiness of the data, credibility of the results and confirmability of the findings. This rigorous approach to answering research questions, especially where little previous data is available, makes it a popular choice among social and behavioral researchers. Several examples of the application of mixed methods in human medicine exist, while it has been employed sporadically in veterinary medicine. The decision of whether or not to prescribe AMDs to a pet is complex, in terms scientific, social and behavioral aspects and mixed methods provides a framework to build on previous studies' findings. Specifically, a sequential explanatory strategy allows for the results of a quantitative cross-sectional survey to inform the qualitative study design before results from both techniques are integrated to explain a research question[189]. The use of a sequential explanatory model has been employed to explore human patient beliefs around AMDs and awareness of appropriate AMD use[190,191]. Examples of sequential explanatory mixed methods typically begins with a quantitative cross-sectional survey, which is then connected to qualitative methods such as semi-structured interviews, focus groups and direct observation[189]. As there are likely similarities between AMD prescribing in companion animal medicine and outpatient human medicine, briefly reviewing selected findings from studies that employed mixed methods to explore human AMD use behavior can be useful when designing a mixed methods approach to address these knowledge gaps in veterinary medicine.

It has been demonstrated that consumer expectations for AMDs drive inappropriate prescribing through a variety of mechanisms, including fear of litigation, concern for a patient not returning for care if not clinically improving and lack of time for proper patient education[192-194]. From a patient perspective, there is often confusion surrounding aspects of AMD use, such as what illnesses AMDs are used for and the importance of taking medication as directed[195]. Much of provider performance is measured by patient satisfaction[196], which can be affected by a clinician denying patient requests for medications and diagnostic tests[197]. The desire among clinicians to perform well in terms of patient satisfaction may result in unnecessary AMD prescriptions in order to keep patients happy. Beyond perceived patient expectations and the need to maintain patient satisfaction, past assessments have also identified that patients routinely do not use AMDs as intended[198,199]. This combination of expecting AMDs when not necessary and then subsequently not consuming them as directed compounds the issue of excessive AMD prescriptions. These studies all demonstrate, in one form or another, that AMD prescribing and patient compliance have behavioral components. Therefore, a framework that incorporates a proven behavior theory should be considered when exploring topics related to antibiotic use in veterinary medicine.

The Theory of Planned Behavior (TPB) has gained popularity in the analysis of a wide range of behaviors and has been found useful to assess behaviors regarding health[200,201]. The TPB framework has been shown to predict how people will behave in a certain context by estimating their intention to behave a certain way[202]. This intention to behave in a certain way is explained by three main constructs: a) attitudes and beliefs, b) subjective norms and c) perceived behavior control. In addition to the three constructs, studies have found that knowledge of a certain topic is directly associated with attitudes and beliefs[203]. As a consequence, when knowledge of a certain topic is the exposure of interest, it is usually incorporated into the final model as an interaction term due to its correlation with the attitudes and beliefs construct[200]. In the context of AMD use in dogs and cats, it is reasonable that the TPB can be used to show that compliance in giving a medication to a pet (behavior outcome) is directly influenced by a pet owner's intention to behave in a certain way (i.e., not giving medications as directed by a veterinarian). A pet owner's knowledge of AMD use, attitudes/beliefs around giving AMDs as directed and their perception of subjective norms, or the perception of how others view appropriate behavior, likely contribute to the intention to behave in a certain manner. Additionally, a pet owner's perceived control over their pet's health (i.e., obtaining AMDs for their pets and giving AMDs to their pets correctly) can play a role in behavior outcomes. The connection between the three constructs and behavior for this aim is diagramed in figure 4.1.

Given the lack of studies in the veterinary arena, the topic of pet owner AMD perceptions and attitudes and how they relate to compliance with veterinary instruction is ripe for a detailed exploration through the use of mixed methods. This is significant in that it will attempt to explain a previously unexplored topic using a combination of methods which has not yet been employed in veterinary medicine research. The objective of this aim is to a) measure, quantitatively, Colorado pet owner knowledge, perceptions and attitudes related to AMD use in companion animals, b) explore the quantitative findings in more depth with qualitative interviews and c) integrate findings of the quantitative and qualitative components to provide an explanation of the compliance behavior of pet owners.

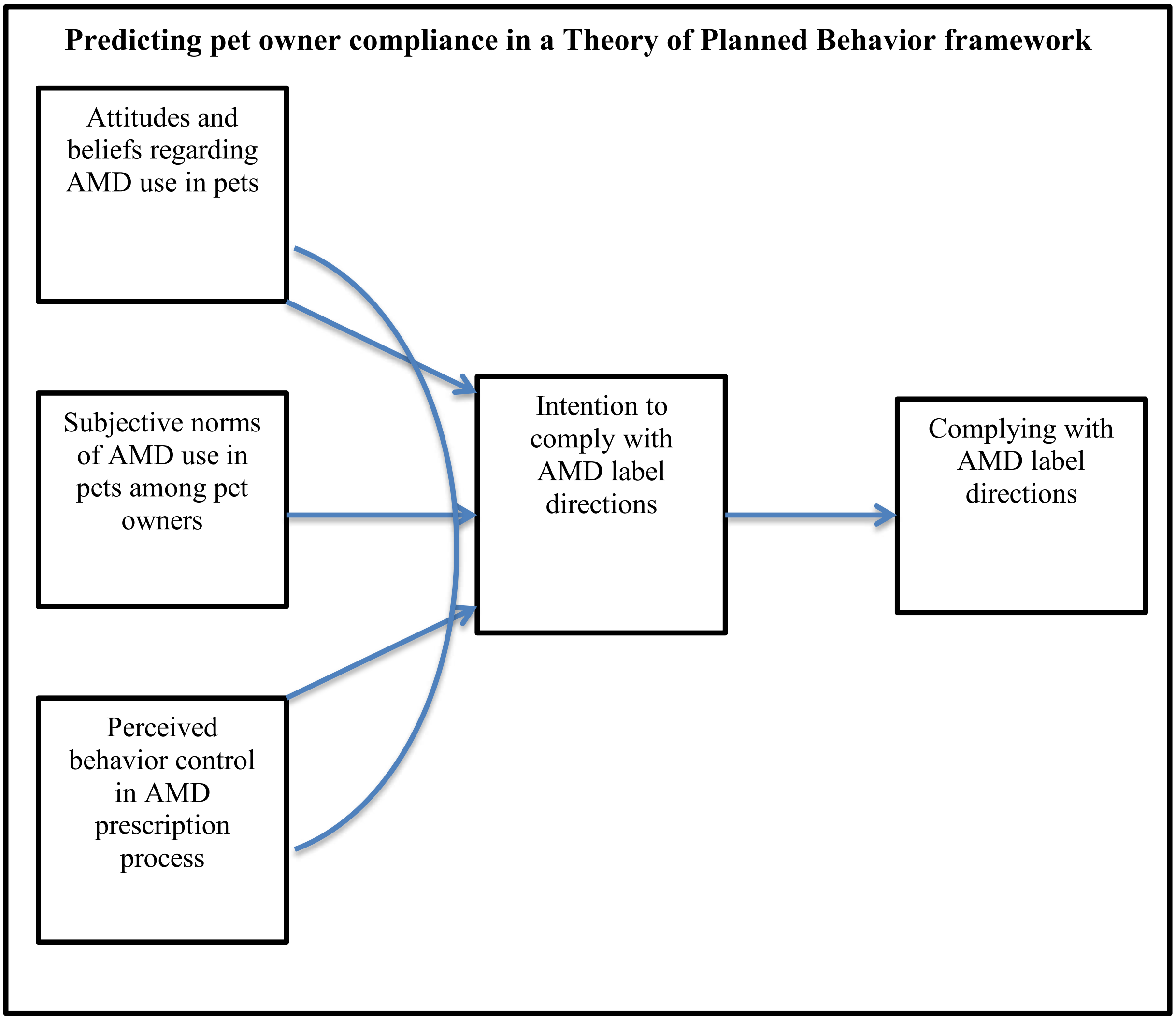

Figure 4.1: A representation of the Theory of Planned Behavior (TPB) in the context of pet owners' expectations for AMDs and compliance of giving medications as directed. (Adapted from Byrne et al. 2019)

Materials and Methods

To understand what influences pet owners' behavior in complying with veterinary directions when administering an AMD to pets, a mixed methods approach was applied. Quantitative and qualitative methods were used sequentially to explain the phenomenon of pet owners' experiences with AMD prescriptions for their pets (figure 4.2). The quantitative component of the aim used a TPB approach and results then informed development of the semi-structured interview guide of the qualitative arm. Finally, results from the quantitative and qualitative techniques were integrated and interpreted.

Quantitative component

An anonymous survey with two time points served as the data collection tool for the quantitative component of this aim. The survey was administered at five different veterinary hospitals across the state of Colorado. Hospitals were recruited to participate based primarily on the demographic they serve in an attempt to match key characteristics of the sample population to the source population. The hospitals included in the sampling included an urban general practice, two suburban general practices, a rural general practice and a lower-cost urban clinic. At each hospital, a key individual (i.e., hospital manager) was recruited to manage the data collection aspects among their clients. This key individual was responsible for inviting clients to participate in the survey, informing participants of the purpose of the study and administering the survey tool. This individual also served as the direct link between the hospital and the research team, providing contact information when questions about the project arose.

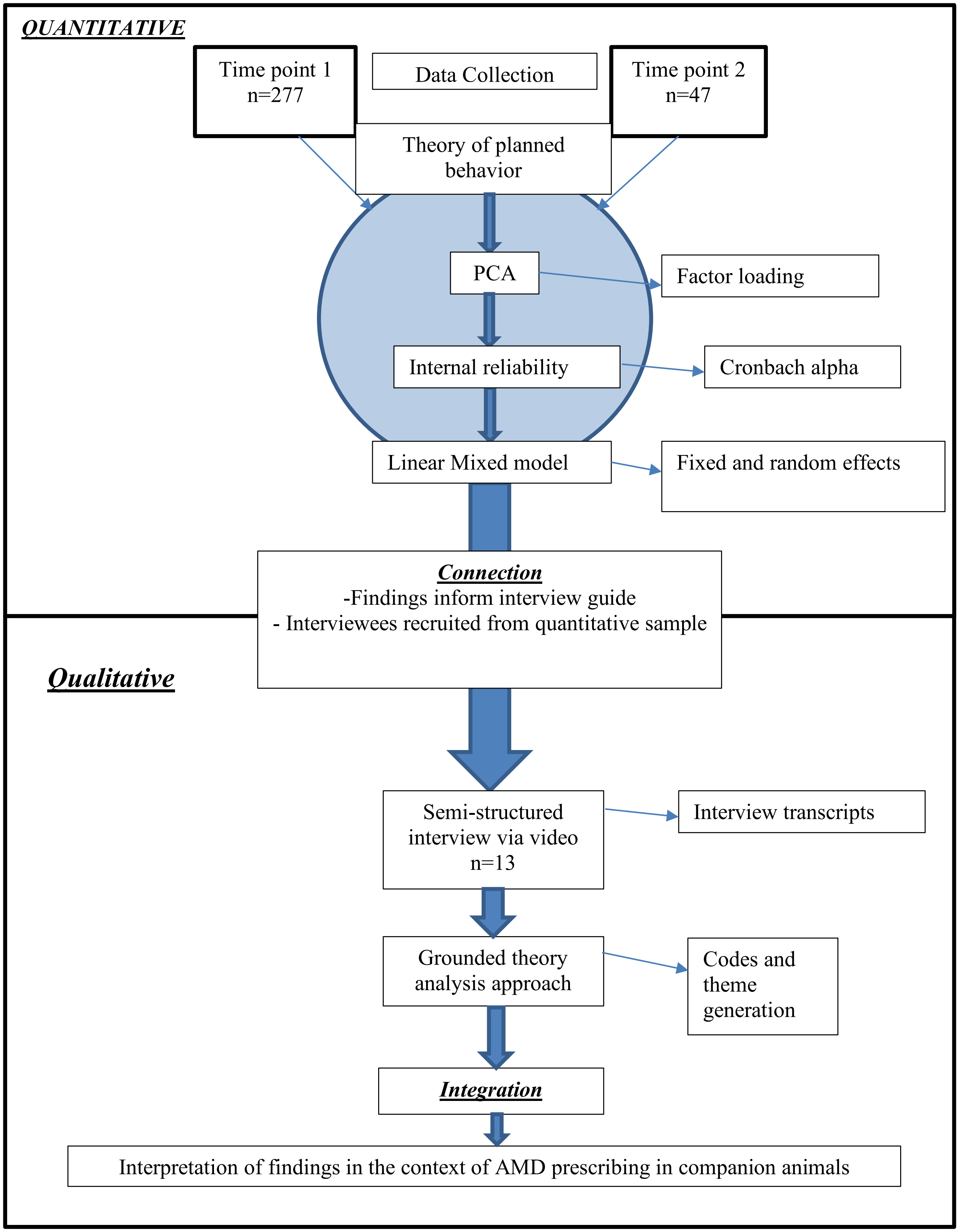

Figure 4.2: A model for the sequential explanatory mixed methods study design

At the time of pets' veterinary visits, clients were asked about their willingness to participate in a brief survey about antibiotic use in veterinary medicine. Willing clients were able to complete the survey either on paper or on their own electronic device by visiting the survey website. Initially, hospitals had the choice to administer the survey in the paper format, electronic format or a combination of both. However, due to the coronavirus pandemic, all hospitals were encouraged to switch to an electronic format midway through the data collection phase. Once a client finished the survey, the response was saved automatically using the Qualtrics survey platform if completing on an electronic device or handed back to the key individual, if completing the survey on paper. All paper surveys were stored in a secure location within each hospital, ensuring no path for tracking responses back to a specific client. Data gathered from paper surveys was ultimately entered manually into an Excel spreadsheet by the research team and merged with data from the online surveys.

The survey tool at the time of a pet's initial veterinary visit (time point 1) collected a) information about the reason for the visit b) attitudes and perceptions regarding medication compliance c) knowledge of AMD use and AMR in veterinary medicine and d) demographic information of the owner. Knowledge, attitude and perception questions were answered on a Likert scale and key demographics captured in the survey included the pet owner's gender, age, education, and work experience in a medical field. The survey ended by asking the participants if they would be willing to complete a follow-up survey 7-10 days later via email. Participants were able to provide an email address for the follow-up survey, with the assurance that information would be kept confidential. The follow-up survey (time point 2) asked similar questions to the first survey in order to gather information on a) whether or not the client's pet was prescribed an AMD at the visit b) attitudes and perceptions regarding medication compliance and c) knowledge of AMD use and AMR in veterinary medicine. The second time point survey ended by gauging willingness to sit for a semi-structured interview that would ask detailed questions regarding AMD use in pets. Responses for the second time point were recorded automatically using the Qualtrics survey platform.

In order to analyze how knowledge of AMD use in veterinary medicine (exposure of interest) affected compliance of giving medications, a TPB framework was used. The pet owner questionnaire contained 17 items, which represented components of the four dimensions of the TPB (i.e., attitudes/beliefs, subjective norms, perceived behavior control and intention to behave a certain way) and the exposure of interest (i.e., knowledge of AMD use in veterinary medicine). In order to determine onto which construct each questionnaire item was to be loaded, orthogonal principal component analysis with varimax rotation was performed, as was utilized by Byrne et al. in an assessment of human AMD-related behavior[200]. This analysis ultimately allowed a large number of variables to be reduced to five variables, including an exposure of interest (knowledge), three TPB constructs and the outcome (compliance behavior). The outcome construct was used to calculate scores to indicate AMD compliance behavior by summing the factor loading values for the behavior construct. Lower scores indicated more appropriate compliance behaviors. Once the constructs were loaded, Cronbach alpha was used to assess internal reliability of the items that formed each construct.

Once the TPB constructs were loaded with the questionnaire items and assessed for internal reliability, a linear mixed model was constructed to explore the associations between the exposure of interest and each of the three TPB constructs with the compliance behavior outcome of interest at the two time points. The fixed effects incorporated into the initial model were owner knowledge of AMD use in veterinary medicine (exposure of interest), the three TPB constructs, time point, age, gender, education level and work experience in a medical field. The random effects in the model were represented by a three-level nested structure: Repeated measures was nested in subjects, which was nested in the hospital location. The structure of the model was determined using a stepwise fixed effect variable selection process. AIC values were used to assess the model fit and to ultimately select the final model. Next, the quantitative and qualitative components were connected by allowing the results from the quantitative portion to inform the qualitative data collection tool. The two components were also connected in that participants for the qualitative interview were recruited from the sample that completed the cross-sectional surveys.

Qualitative component

The qualitative arm of this mixed methods approach was executed after the longitudinal survey component. The final question in the second time point survey recruited interview participants by asking their willingness to sit for a 15-20 minute interview regarding AMD use in pets. The interview guide was developed through analysis of numerical information regarding the exposure, TPB constructs and outcome and was subsequently transformed into semi-structured interview questions. By proceeding in this manner, the sequential explanatory model methodology was satisfied. The interview questions sought to develop a deeper understanding of the quantitative findings. For example, analysis of the data from the survey found that owners “strongly agreed” that pets should be medicated with AMDs in accordance with instructions from a veterinarian. To explore this result in more detail, a question pertaining to compliance was crafted for the semi-structured interview that asked interviewees to describe their memory of the last time their pet was prescribed a medication. Questions were designed to be open-ended, neutral and non-leading. Interviewees were encouraged to answer the questions by describing recent experiences rather than listing factors that contribute to their AMD knowledge and administration compliance. Probing questions were designed to gather more information from participants in order to learn as much as possible about their previous experiences.

A maximum variation sampling strategy was used to select participants based on hospital type (i.e., general vs. specialty practice vs. low cost vs. rural). This strategy allowed for exploration of differences among different practice types and aided in determining a sample size. Interviews were conducted until saturation was achieved and no new codes or themes emerged. A sample group of 13 participants (7 from general practices, 5 from low-cost practices and 1 from rural practices) agreed to participate in the interview process. Interviews were conducted over email or over video-conferencing software, depending on preference of the participant. Video interviews were recorded via the video-conferencing software recording function. Once an audio recording was complete, transcription of the file was completed by hand. In order to ensure accuracy of the transcription, portions of two interviews were re-transcribed and compared. After the quality control step, the audio files were securely destroyed and any identifying information including the transcript was deleted.

The qualitative analysis portion of Aim 2 followed a described method known as the "data analysis spiral"[204]. With this technique, data are collected, analyzed and interpreted in concert. As a rigid "spiral" does not exist, the qualitative analysis plan will be unique for each qualitative research aim[204]. The analysis in this case started with organizing the text data into de-identified text files that were double-spaced and contained numbered lines. Once organized, each text file was read and re-read several times to obtain an overall sense of the interview before developing and applying codes. After reviewing the first few transcripts, pieces of text were consolidated into the initial codes to describe emergent ideas found within the interview. Codes were listed with a description and example text before being reviewed. Redundant listings were consolidated into single codes. Once a final code list was created based on the first two interviews, the code list was applied to the remaining transcripts and analyzed for major themes. A final codebook resulted from the analysis and included the major themes, codes within those themes, definitions of the code and examples from transcripts where the code was applied. Themes, or a collection of codes representing a common idea, were ultimately interpreted to garner a better understanding of how pet owners perceive AMD use in veterinary medicine and how it influences their behavior. Interviews were conducted and analyzed until a saturation of themes was noted, which in this study included all 13 interviews.

Once the quantitative survey and qualitative interview data were analyzed, findings were integrated to provide a detailed explanation of pet owners' perceptions of AMD use in veterinary medicine and how they affect compliance of giving AMD medications to their pets as directed. The integration of the quantitative and qualitative findings is key in mixed methods[189] and ultimately results in a takeaway message from this aim. To integrate results, a diagram showing exactly how compliance scores were informed through the three TPB constructs was constructed. Constructs were tagged to quoted text representing the three TPB constructs to illustrate pet owners' thoughts associated with high and low compliance scores.

Results

Quantitative results

In total, 334 responses were collected from five Colorado hospitals. Of the total responses, 83% (277/334) questionnaires were completed and included in the final dataset. Hospital 4 (a suburban general practice) had the most responses [76, (27.4%)], followed by hospitals 1 [75, (27.1%)], 2[56, (20.2%)], 5 [41, (14.8%)] and 3 [28, (10.1%)]. The 25-34-year-old age group had the most responses [84, (30.3%)] and females accounted for 61.7% of the completed questionnaires. Most respondents indicated they had a bachelor's degree [125, (45.1%)] and were not currently or previously employed in a medical field [193, (69.7%)] (table 4.1).

Table 4.2 illustrates a descriptive analysis of participating pet owner survey responses. Most respondents believed that AMDs did not treat viruses [137, (49.4%)] and most were unsure if pets received the same AMDs as people [116, (41.9%)]. Overall, surveyed pet owners did not think AMDs should be available over the counter [178, (64.2%)] and most agreed that a pet should be examined by a veterinarian prior to being prescribed AMDs (225, (81.2%)]. The majority of pet owners agreed that AMD use in pets could cause resistant bacteria, while most participants were unsure if resistant bacterial infections were a problem in pets and if resistant infections could be passed on to humans. Most [248, (89.5%)] owners expressed a trust in their veterinarian and thought veterinarians should be experts on AMD use [222, (80.1%)].

Principal component analysis loaded the 17 survey items onto five factors. Specific questions and the construct onto which they were loaded are presented in table 4. Four questions were loaded onto the compliance construct, while four questions were loaded onto each of the attitudes/beliefs and perceived behavior control constructs. Three questions and six questions were loaded onto the knowledge and social norms constructs, respectively. Cronbach alpha analysis showed only fair internal reliability for each explanatory construct (AMD knowledge= 0.64, social norms= 0.58, attitudes/beliefs= 0.65, perceived behavior control= 0.55 and compliance= 0.75).

The compliance score was calculated by summing the factor loading coefficients from the compliance behavior construct (Table 4.2: Statement 9 (0.56) + Statement 13 (0.71) + Statement

14 (0.72) + Statement 16 (0.80)). The sample population had a mean compliance score of 4.55 (SD= 1.87), with lower scores indicating better overall compliance behavior.

Table 4.1: Demographic characteristics and sample compliance score

Demographic variables (n=277)	**n**	**%**
Age, years (n,%)		
18-24	17	6.1
25-34	84	30.3
35-44	69	24.9
45-54	50	18.1
55-65	26	9.4
Over 65	30	10.8
Gender (n,%)		
Female	171	61.7
Male	105	37.9
Education (n,%)		
High School equivalent or lower	24	8.7
Some college	46	16.6
Associates	23	8.3
Bachelors	125	45.1
Masters	49	17.7
Doctorate/Professional	10	3.6
Medical Field (n,%)		
Yes	79	28.5
No	198	71.5
Hospital		
1- urban, lower cost hospital	75	27.1
2- suburban general practice 1	56	20.2
3- rural mixed practice	28	10.1
4- suburban practice 2	76	27.4
5- urban general practice	41	14.8
Species		
Dog	220	79.4
Cat	57	20.6
Reason for visit		
Healthy exam	135	48.7
Illness exam	108	39.0
Surgery	20	7.2
Other (i.e., recheck exam)	14	5.1
	Mean	**SD**
Compliance score (range: 2.79-13.15)	4.55	1.87

Table 4.2: Responses to survey questionnaire statements

Questionnaire statements	Yes, n (%)	No, n (%)	Unsure, n (%)		
Statement 1: Antibiotics are effective against viruses	107 (38.6)	137 (49.4)	33 (11.9)		
Statement 2: Pets receive the same antibiotics that humans are prescribed	68 (25.4)	93 (33.6)	116 (41.9)		
Statement 3: Antibiotics should be available over-the-counter without a prescription	63 (22.7)	178 (64.2)	36 (13.0)		
Statement 4: In the past, I have discussed appropriate antibiotic use with a veterinarian	171 (61.7)	76 (27.4)	30 (10.8)		
Statement 5: It is easy to give mt pet a medication by mouth	143 (51.6)	108 (39.0)	26 (9.4)		
	Strongly agree, n (%)	**Somewhat Agree, n (%)**	**Neither agree nor disagree, n (%)**	**Somewhat Disagree, n (%)**	**Strongly Disagree, n (%)**
Statement 6: Antibiotic use in pets can create bacteria that are resistant to antibiotics	57 (20.6)	116 (41.9)	79 (28.5)	19 (6.8)	6 (2.2)
Statement 7: Antibiotic resistant bacterial infections are a problem in pets	43 (15.5)	80 (28.9)	134 (49.5)	14 (5.0)	6 (2.2)
Statement 8: Antibiotic resistant bacteria can spread from animals to people	28 (10.1)	53 (19.1)	129 (46.6)	41 (14.8)	26 (9.4)
Statement 9: It is important to give antibiotics to pets as directed by a veterinarian	203 (73.2)	46 (16.6)	13 (4.7)	10 (3.6)	5 (1.8)
Statement 10: Just to be safe, it is OK to give antibiotics when the cause for a pet's illness is unknown	14 (5.0)	55 (19.9)	75 (27.0)	65 (23.5)	68 (24.5)
Statement 11: Most pet owners I know give antibiotics as directed	83 (30.0)	90 (32.5)	80 (28.9)	18 (6.5)	6 (2.2)
Statement 12: I trust veterinarian advice as to whether or not my pet needs antibiotics	173 (62.4)	75 (27.1)	20 (7.2)	8 (2.9)	1 (0.4)
Statement 13: Veterinarians should be experts on antibiotic use	116 (41.9)	106 (38.8)	38 (13.7)	11 (4.0)	6 (2.2)
Statement 14: Veterinarians should prescribe antibiotics only when necessary	182 (65.7)	68 (24.5)	20 (7.2)	4 (1.4)	3 (1.1)
Statement 15: Antibiotics will help resolve cold symptoms (i.e., sneezing coughing) in most cases	22 (7.9)	28 (10.1)	96 (34.6)	47 (17.0)	84 (30.3)
Statement 16: It should be required for a veterinarian to examine a pet before an antibiotic is prescribed	150 (54.1)	75 (27.1)	29 (10.5)	20 (7.2)	3 (1.1)
Statement 17: Antibiotics are overprescribed by veterinarians	23 (8.3)	28 (10.1)	144 (52.0)	62 (22.4)	20 (7.2)

Table 4.3: Factor loading for survey questions. **Bold** indicates which construct item is associated

Statements included in survey	Compliance score construct	Attitudes and beliefs construct	Social norms construct	AMD use knowledge	Perceived behavior control
Statement 1: Antibiotics are effective against viruses	-0.02	0.33	-0.06	**0.67**	0.19
Statement 2: Pets receive the same antibiotics that humans are prescribed	-0.04	0.15	-0.4	0.01	**0.61**
Statement 3: Antibiotics should be available over-the-counter without a prescription	0.26	0.01	0.11	**0.52**	0.09
Statement 4: In the past, I have discussed appropriate antibiotic use with a veterinarian	0.14	0.13	0.16	0.08	**0.63**
Statement 5: It is easy to give my pet a medication by mouth	-0.03	-0.16	0.22	-0.03	**0.62**
Statement 6: Antibiotic use in pets can create bacteria that are resistant to antibiotics	0.06	**0.71**	0.03	0.31	0.01
Statement 7: Antibiotic resistant bacterial infections are a problem in pets	0.22	**0.72**	-0.03	-0.01	0.2
Statement 8: Antibiotic resistant bacteria can spread from animals to people	-0.1	**0.76**	0.11	0.04	-0.03
Statement 9: It is important to give antibiotics to pets as directed by a veterinarian	**0.56**	0.2	0.54	0.13	0.01
Statement 10: Just to be safe, it is OK to give antibiotics when the cause for a pet's illness is unknown	0.19	-0.08	-0.08	**0.74**	-0.06
Statement 11: Most pet owners I know give antibiotics as directed	0.12	0.06	**0.61**	-0.11	0.25
Statement 12: I trust veterinarian advice as to whether or not my pet needs antibiotics	0.4	0.06	**0.7**	0.12	0.1
Statement 13: Veterinarians should be experts on antibiotic use	**0.71**	0.01	0.11	-0.03	-0.01
Statement 14: Veterinarians should prescribe antibiotics only when necessary	**0.72**	0.12	0.24	0.19	0.1
Statement 15: Antibiotics will help resolve cold symptoms (i.e., sneezing coughing) in most cases	-0.08	0.01	0.17	**0.75**	-0.09
Statement 16: It should be required for a veterinarian to examine a pet before an antibiotic is prescribed	**0.8**	0.01	-0.05	0.1	0.02
Statement 17: Antibiotics are overprescribed by veterinarians	0.13	0.37	**-0.59**	-0.27	0.11

TPB constructs, the knowledge construct, visit variables and demographic variables with compliance scores. None of the demographic (i.e., age of owner, gender of owner, education level or work experience in the medical field) or visit (i.e., species of the pet, reason for the veterinary visit) variables was significantly associated with the compliance score. The social norms construct, and the attitudes/beliefs construct significantly predicted the compliance score. Perceived behavior control, AMD use knowledge and the interaction between knowledge and attitudes/beliefs were not significantly associated with compliance, nor was survey time point (table 4.4).

Table 4.4: Fixed effect estimates of the final model with standard errors and 95% confidence interval

	Estimate	**Standard error**	**Lower 95% CI**	**Upper 95% CI**
Intercept	4.57	0.33	3.93	5.24
Attitudes/beliefs	0.2	0.1	0.1	0.8
AMD use knowledge	0.21	0.1	-0.01	0.44
Perceived behavior control	0.11	0.1	-0.08	0.31
Social norms	0.33	0.1	0.13	0.55
Attitudes/beliefs*AMD use knowledge	-0.1	0.1	-0.28	0.11
Time point	0.1	0.23	-0.37	0.54

As indicated by the linear mixed model, social norms and attitudes/beliefs regarding AMD use in companion animals are significant predictors of complying with veterinary instructions when administering AMDs to pets. Original survey question items that were loaded onto these two constructs were used to formulate semi-structured interview questions in order to explore the effect of the constructs in more detail. While past research in human medicine suggests that perceived behavior control also informs the intention to behave a certain way, it was found not to be significant in the present model. However, as it has been shown to be a significant predictor in human AMD use studies, the survey question items loaded onto the PBC construct were also used in the development of interview questions.

Qualitative results

In total, 13 individuals who completed the cross-sectional survey tool at both time points agreed to participate in the qualitative interviews. Nine participants were female, four were in the 35-44 year age group and four reported work experience in a medical field. Five came from hospital 1, while seven came from hospital 2 and one came from hospital 3. No pet owners from hospital 4 and 5 chose to participate in the interview process. The data analysis spiral described previously identified four emergent themes from the data relating to pet owner AMD compliance behavior: 1) communication from the veterinarian 2) social norms of trust and other pet owners' behavior 3) guidance of development of attitudes and perceptions related to AMD use and 4) involvement of the pet owner in the AMD prescription decision-making process.

Veterinary communication

When asked what veterinarians could do to ultimately gain acceptance of their recommendation of whether or not to prescribe an AMD, pet owners perceived that an important strategy was to communicate, clearly, facts surrounding AMD use in companion animal medicine. The more pet owners knew about appropriate AMD use in dogs and cats, the more willing they were to comply with veterinary instruction, which reflects an owners' perceived level of control in their pets' medical care. It is also suspected that communication directly affected a client's attitudes/belief and knowledge of AMD use in pets. Participants described varying levels of satisfaction over communication from veterinarians.

> *" My vet always takes the time to explain and discuss treatment and alternatives. They then ask for my input and if it is okay to treat them as discussed. It is very important to know all the facts. I feel better the more educated I am."*

> *"I've never been told anything about antibiotic use in pets. I would like to know if antibiotic resistance is a common issue in pets like it is for humans. I would want to know how likely antibiotic resistance is to occur in my pet based on the use of antibiotics. I would want to know if there are other options available if my pet does become resistant to antibiotics."*

Only talking about AMD use in dogs and cats was not enough to improve clients' compliance behavior. Clear reasoning for their decision also appeared to be required in the promotion of appropriate AMD compliance behavior. Pet owners' perception a veterinarian's explanations of reasoning pertaining to whether or not an AMD was recommended appeared to be key not only because it enabled pet owners to hear the information a veterinarian presented during consultation, but also in that it seems it allowed pet owners to follow the veterinarian's lead in the decision-making process.

“*My veterinarian has always told me the reason why she prescribed any antibiotics for my dogs. Along with being told why my dog is being prescribed antibiotics, my vet has always reiterated the dosing instructions and any possible side effects.”*

Promotion of the trust and societal social norms

The owner’s perception of universal trust in the veterinary professional along with a notion of how other pet owners behave were found to possibly influence a client’s intention to give AMDs as directed. Trust in the veterinarian, both overall and specifically in terms of AMD expertise, was thought to be a key component of client commitment to listen and learn from a veterinarian. When trust was not present, owners suggested they would seek a second veterinary opinion or turn to secondary sources of information, such as Google.

“My following prescription directions depends on how much I trust my vet. If I trust my vet and they tell me that there is a high likelihood of one outcome verses another, I am more inclined to pursue the treatment as discussed with my veterinarian.”

“Pets are challenging because they cannot tell us what is wrong- there is a lot of guess work involved and I have to trust my vet to be well informed and make informed decisions regarding my pet’s care. If I don’t trust my vet, I would probably be more apt to seek a different vet than to question accepting their recommendation.”

Pet owners appeared to value their trust in a veterinarian when it came to the health of their pet. It also seemed that they relied on their perceptions of what their fellow pet owners think. Most interviewees thought that other pet owners gave medications as directed. Participants cited financial reasons, benevolence and time factors for why they thought other pet owners complied with veterinary medication instruction.

> *" I think most pet owners are very good about following instructions. Everyone I know is very good about it and are very responsible pet owners. I think if someone cares enough to take their pet to the vet and pay for medications, they are mostly responsible enough to administer it properly."*

Interviewees who thought other pet owners did not follow veterinary instructions were typically those who demonstrated a lower AMD use knowledge. Additionally, owners who perceived that other pet owners did not always follow veterinary instruction were ones who demanded more involvement in the AMD decision-making process. Opinions of other pet owners not complying with veterinary instruction often reflected a poorer personal compliance score than those who felt owners generally administered AMDs correctly.

> *" I think most pet owners start off well but after a few days tend to dwindle, miss a dose here and there, sometimes not completing the course."*

Education related to AMD use

To varying degrees, pet owners demonstrated a need to be better informed regarding AMD use and AMR in both companion animals and humans. This could be interpreted as an opportunity to form correct client attitudes and perceptions as responses indicated that owners either did not know much about this topic or had misconceptions on basic tenets of AMD use and AMR. Analysis identified two codes that inform this theme, outlining targets where client education may be most effective. Perceptions of using AMDs in times of diagnostic uncertainty emerged as a topic that needs to be addressed. Owners were often contradictory in their statements, accepting the use of AMDs when the cause of an illness could not be determined, but also acknowledging the medications may not make their pet better. While often contradictory in their statements that expressed concern for inappropriate AMD use, but still accepting AMD treatment, interviewed pet owners ultimately wanted their pet to return to a normal state and were willing to try any treatments, even if there was little promise of any true benefit.

> *"I would be extremely comfortable with the decision of prescribing antibiotics if the cause of the illness is not known. Use of antibiotics is not always a bad thing, but over-prescribing is. If there is a question, I feel better to treat with antibiotics and hope that it cures the illness rather than allowing something to get worse because it's untreated."*

Owners who expressed acceptance of using AMDs in times of diagnostic uncertainty often had assumptions about the concept of AMR that were not consistent with scientific tenets of AMR. For example, some owners thought that patients become resistant to AMDs, instead of bacterial organisms becoming resistant. This sentiment was typically accompanied by a willingness to risk the possible development of AMR in their pet, especially if AMDs had been sparingly used in the past.

> *" The body builds up a tolerance to an antibiotic, possibly making it less likely to be as effective."*

Involvement in the decision-making process

Finally, given that owners preferred clear communication, concise education and the best possible care for their pet, the last theme to emerge from the data was owners' desire to be included in the AMD decision-making process for their pets. Above all, it appeared that if owners did not feel like they were involved in their pet's healthcare, compliance behavior may be reduced.

> *"Ideally, I would like to be given all the options with the pros and cons for each, as well as the vet's recommendation and the rationale for any course of treatment. Explaining my options and the pros and cons for each help me make an informed decision"*

The four themes that emerged from the interview data are each important on their own but need to be considered together when trying to improve pet owner compliance behavior. This is true because leaving out even one aspect (i.e., involving owners in the decision-making process) renders the other components less effective. Figure 4.3 represents how the results from the quantitative and qualitative compartments were integrated to develop a well-rounded explanation of what affects pet owners' AMD use compliance. When examining the text data from the qualitative interviews, coded text segments from the four themes were compared to the interviewee's compliance scores. A higher quantitative compliance score was potentially explained by qualitative text that indicated if a participant had been educated by a veterinarian about appropriate AMD use. Similarly, pet owners who expressed a trust in their veterinarian and believed that other pet owners administered AMDs as directed appeared to have higher compliance scores. The same was true for owners who held correct beliefs regarding AMD use in pets and AMR and who felt they were involved in the AMD decision-making process.

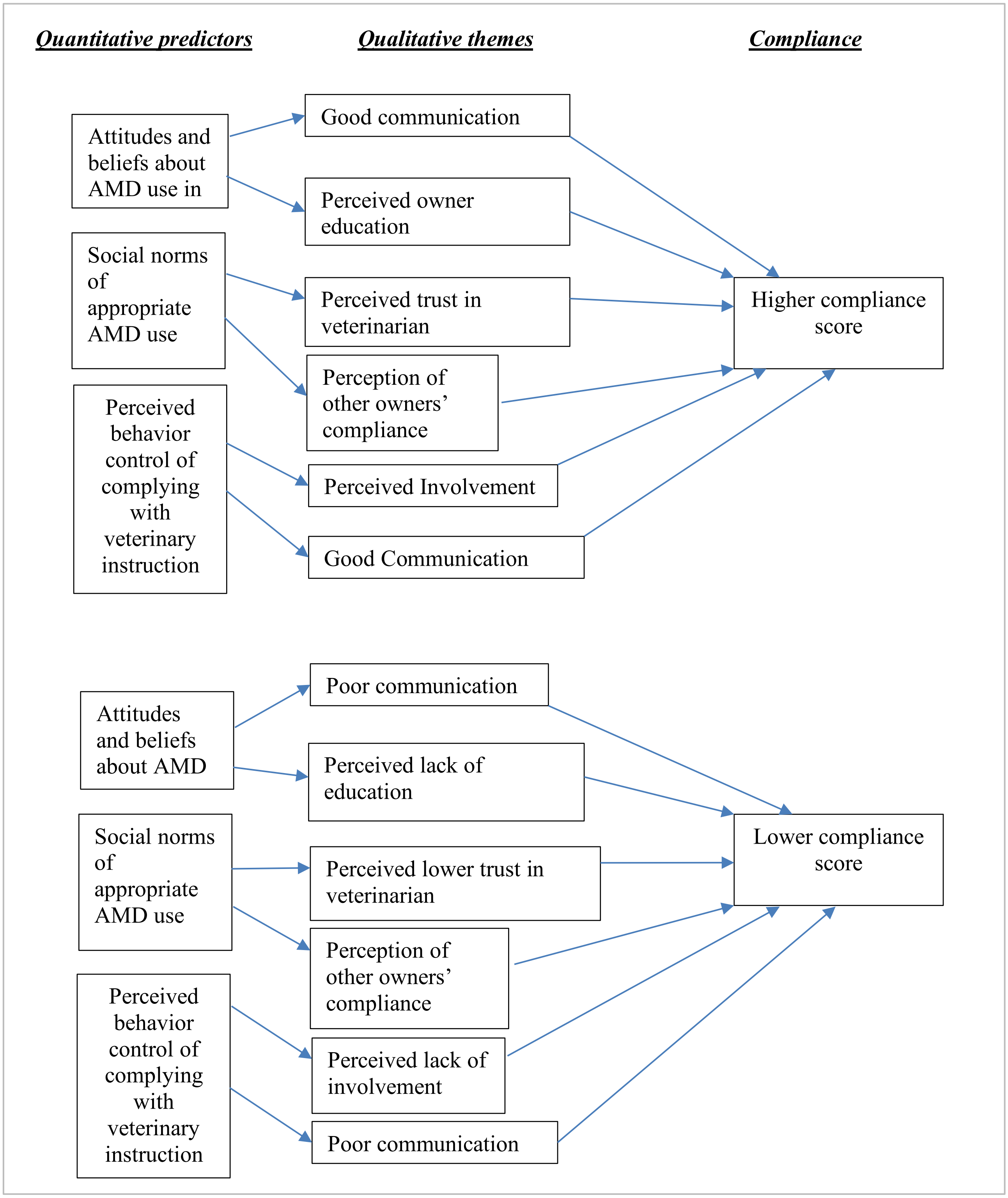

Figure 4.3: Integration of the quantitative and qualitative findings to explain pet owner AMD compliance behavior scores

Discussion

Colorado pet owners in this study demonstrated variable levels of compliance adherence behavior when administering AMDs to their pets. Further insight into why a pet owner may or may not comply with veterinary instruction was gathered through semi-structured interviews. Integrated quantitative and qualitative findings explain that a pet owner's intention to behave a certain way can be explained through a TPB framework and that a client-centered approach can improve this behavior. Results from the mixed methods sequential explanatory study fills a critical knowledge gap. Previous studies have addressed pet owner AMD compliance through the use of qualitative interviews, but findings from this study provide a more in-depth look at how pet owners behave in terms of compliance and what influences their intention to behave a certain way.

The social norms and attitudes/beliefs constructs used in the TPB are significant in predicting how well a pet owner will comply with veterinary instructions. In this study, the perceived behavior control construct and exposure of interest, knowledge of AMD use, did not significantly predict compliance behavior. In a previous assessment of human AMD compliance behavior, all three TPB constructs predicted a person's intention to behave in a certain manner[200]. In this model, a greater knowledge of appropriate AMD use was associated with better compliance. However, this association was not significant. Previous studies in human medicine found mixed results when looking at the impact of knowledge on AMD use behavior. A few studies indicated that lower levels of knowledge were associated with poor compliance[205,206] while another showed poor compliance associated with increased knowledge[207]. Further, as in this aim, a handful of studies failed to show a significant association between knowledge and behavior[208-210]. Contra to results from this analysis, other studies have found that being involved in the medical field or having a close relative in the medical field improved AMD use behavior[200]. The current study purposefully avoided surveying those with a background in veterinary medicine, and, therefore, any possible effect of working in the veterinary profession on AMD use behavior was not explored. It is possible that even though people had experience in the human medical field, appropriate AMD use knowledge did not translate to their pets' healthcare. Another possible reason for experience in the medical field not significantly predicting appropriate AMD use behavior is that the specific type of medical experience was not recorded, reducing the granularity of the covariate and resulting in possible residual confounding.

Analysis of the semi-structured interview data determined that owners want to be involved in the decision-making of their pets' healthcare. This involvement can be instrumental in improving compliance as it provides an opportunity to communicate and educate pet owners while validating trust in their veterinarians and perceptions of what "good pet owners do.". Given that pet owners play a decisive, yet sometimes unsaid, role in whether or not their pets receive an AMD prescription, it seems reasonable to explicitly include owners in the decision-making process. Much research done on provider-patient relationships in human medicine has found that "relationship-centered care" leads to improved patient satisfaction and improved health outcomes[197,211]. The premise behind relationship-centered care establishes that patients perceive medical issues in terms other than just objective parameters and that providers need to be sensitive to individual patient perceptions[212]. Additionally, relationship-centered care outlines the importance of a mutually respectful relationship between provider and patient where there is a common understanding of the disease and treatment goals[213]. This same concept can also be applied to veterinary medicine and, specifically, to the AMD prescription decision-making process, which can be improved through a relationship-centered care approach[214]. By engaging pet owners and by satisfying their need for autonomous participation in the decision of whether or not their pets are prescribed an AMD, pet owner acceptance and compliance of AMD-centered recommendations can be improved[215]. While research involving relationship-centered care is not common in veterinary medicine, Kuper and Merle outline four factors that appear to be most important in the delivery of quality medicine that also leads to client satisfaction[214]: Information giving, communication, empathy and shared decision-making.

For a relationship-centered care framework to exist, the authors argue that information giving must exist, in order for the pet owner to adequately participate in the decision-making process[214]. Having information explained to them at a level that is understandable to them also helps clients deal with the inherent uncertainty of illness issues and prognosis[216]. This is directly relatable to the concept of diagnostic uncertainty that can so often lead to inappropriate AMD use. As noted in the results of the current study, most owners were in favor of their pets having an antibiotic "just in case". How this information is presented is also of interest. Studies have shown that veterinarians traditionally tend to communicate in a "paternalistic" manner when educating clients, delivering information laced with technical medical terms in a hurried fashion[217,218]. This method of communicating vital information is thought to preclude a trusting relationship between the veterinarian and pet owner[214]. In the context of AMD prescribing, if the process of giving information regarding AMD use in veterinary medicine is done in a rushed, technical, obscure or judgmental manner, pet owners will likely not embrace a veterinarian's recommendation that "no antibiotic is needed." Results from this assessment indicate that most pet owners trust their veterinarians in terms of when an AMD would be needed, but also express the desire to understand a veterinarian's thought process in order to justify it. In addition to effective communication, pet owners also expect veterinarians to have empathy toward their pets and its situation[213,219]. The lack of empathy can erode a trusting client-veterinarian relationship, leading to decreased understanding and compliance. When deciding not to prescribe AMDs for a pet who clearly has a condition not caused by bacteria, the veterinarian should show empathy toward the pet's condition in order to maintain the trust of the client and have that client agree that AMDs are not warranted. As exhibited by pet owners in the qualitative interviews, worry dominates a client's thought process and the effective delivery of important information from an empathic veterinarian can ease a client's anxiety about a pet's illness. Finally, by providing accurate, easy-to-understand information in an empathic manner, veterinarians build a framework of trust with clients concerning their pets and that sets the foundation for shared decision-making[214]. Shared decision-making has gained popularity in human medicine and leads to improved health outcomes, better patient compliance and augmented patient knowledge of their medical conditions[220]. In veterinary medicine, qualitatively it has been shown that owners prefer to be part of the process when making decisions for their pets and prefer to have different diagnostic and treatment options presented to them[221]. However, the concept of shared decision-making does not work unless there is a relationship between the interested parties that relies on the clear exchange of accurate information.

The results of the current study outline pet owner AMD perceptions and compliance behaviors. The results also suggest potential barriers that clients can bring to judicious AMD prescribing. Given that little was previously known about pet owner AMD perceptions, the data gathered in this study will help to develop new interventions as well as aid in evaluating current methods and tools for veterinarians. By understanding the role of pet owners in the AMD decision-making process, identifying what predicts their AMD compliance behavior and incorporating those findings into a relationship-centered care framework, pet owners can be seen as part of the process instead of being expected to accept a directive from an authoritative-type figure (i.e., the veterinarian). The feeling of control a pet owner may experience after being involved in the AMD decision-making process will not only increase knowledge of AMD use in companion animals, but will also maintain client satisfaction, which has been noted to be a potential driver of AMD use in veterinary medicine[157].

Factors that were not measured in the TPB framework may also affect client compliance in giving medications correctly at home. For example, not having enough time during a consultation to completely explain all aspects of an illness and its treatments may reduce compliance[222]. Human patients who felt their consultation time was inadequate ultimately reported that their compliance with medical recommendations was reduced[223]. Physicians also reported that shortened consultation times led to an inability to explain adequately all necessary topics and that more pressing health concerns were prioritized[224]. Similarly, in veterinary medicine, owners report that an adequate consultation time is key in developing a trusting relationship, which is vital in the framework of shared decision-making[214].

Limitations and strengths

Limitations

The approaches used to test the hypotheses of Aim 2 have both limitations and strengths. The limitations of the approach include the possible lack of generalizability to pet owners outside of Colorado, the selection of pet owners who completed the survey and the inability to determine the role of social desirability in the survey responses. Additionally, TPB constructs had only fair internal reliability, which forces researchers to question if all survey items for a given construct were indeed measuring the same thing. The limitations in the study design, implementation and interpretation can introduce several biases and potential confounders, which can threaten the validity of the results.

As this survey for this aim was only administered in the state of Colorado, results may not be generalizable to the rest of the country. Colorado has a high rate of pet ownership and may view veterinary healthcare differently than those in other states. To remedy this potential lack of generalizability, a larger separate cross-sectional survey of pet owners from across the country could be done to assess if there are differences among different demographic variables. While this comparison of Colorado's sample population to the broader nationwide sample population would not ensure external generalizability of the longitudinal Colorado study results, it would at least indicate that baseline responses from both groups are similar or different.

Possible selection bias could have occurred due to the way in which pet owners were recruited to participate in the survey. Pet owners were asked about their willingness to take the survey at the veterinarians' offices and, therefore, selection was conditioned on bringing a pet to the veterinarian for medical care. This selection could have induced an association between a high level of knowledge of AMDs in veterinary medicine and good compliance score outcomes. It is possible that owners who do not bring their pets to the veterinarian may have different levels of AMD knowledge and would score differently in expectation and compliance than those who bring their pets in for medical care.

Social desirability in survey responses can lead to differential misclassification. If a participant in reality only sometimes gives medications as directed but indicated that he or she always gives pet medications as directed in order to appear in line with what is seen as "correct", an over-estimation of that participant's compliance score could result. This misclassification could result in a biased association between knowledge of AMD use in veterinary medicine and compliance of giving medications as directed, moving the association toward or away from the null. This source of potential bias could have been avoided in the survey design phase by adding social desirability questions, which was the method employed in Byrne et al. Participants in that assessment were removed if they scored too high on a social desirability scale. While the effect of social desirability has not yet been explored in pet owner and AMD assessments, results from this study indicate that there is potential for it to have an effect as 87% of respondents indicated they "always" give medications to their pets as directed by a veterinarian. There is evidence this is not true based on previous assessments of pet owners' compliance of giving medications[225,226].

Strengths

Strengths of this aim include the unique research questions, aspects of the study design, and the mixed methods approach. How pet owners perceive AMD use in pets and how it affects AMD compliance behavior is largely absent in the literature. While a handful of studies address pet owner opinions and attitudes regarding AMD use, a large assessment has not yet been attempted. In exploring pet owner perceptions of AMD use and AMR in veterinary medicine, a better understanding of the pet owner's role in the AMD decision-making process can be obtained. Methods to explore pet owner attitudes of AMD use in dogs and cats are also a strength of this aim. The quantitative component of the aim used correlated data analysis methods to account for clustering of responses by hospital and the correlation of repeated responses from those who participated in both survey time points. The linear mixed model built to analyze the data from the 277 Colorado pet owners who completed the survey represents a flexible, yet complete way of explaining the data while accounting for non-independent responses. A mixed methods sequential explanatory approach explored pet owner perceptions and attitudes in a more detailed manner than either quantitative or qualitative methods could do alone. As more social and behavioral research questions are being asked in veterinary medicine, methods from this aim can serve as an example of how a mixed methods approach can be applied.

CHAPTER V

COMPARING VETERINARY AND HUMAN OUTPATIENT VISITS WITH INAPPROPRIATE ANTIMICROBIAL DRUG PRESCRITPIONS FOR VIRAL UPPER RESPIRATORY ILLNESS

Introduction

A recognized contributing factor to the development of AMR is inappropriate AMD use in both humans and animals[227,228]. Specifically, there is evidence that AMDs are routinely dispensed unnecessarily to both humans and companion animals in cases of viral upper respiratory disease[55,148,229,230]. Estimating the proportion of visits where AMD use is considered inappropriate, overall and by specific disease condition, can serve several purposes in human and veterinary medicine. Tracking AMD use over time and assessing the effectiveness of AMS interventions is important and can be assessed with proportions, which illustrates the utility of such measures[231,232]. The proportion of visits where AMDs are inappropriately prescribed by a provider have not previously been compared between human and veterinary healthcare systems. Several studies in human medicine have attempted to estimate AMD use on a population level, while this type of measure is lacking in companion animal medicine.

The absence of reliable surveillance data in companion animal medicine prevents nationwide measures of AMD use for patients or by providers from being estimated. Estimates of the number of pets in the United States are available[233], but a complete count has proven difficult due to fractured pet licensing systems and a lack of funding. Without nationwide AMD use estimates, the current state of AMD prescription practices is difficult to define. Additionally, without these estimates, AMD use cannot reliably be tracked over time, making it difficult to define current trends of AMD use in companion animal medicine. Given that risk of AMR infections in pets and people subsequent to AMD use in companion animals [47,48] is a concern, it is important to investigate and measure the occurrence of AMD prescribing among veterinarians. As there is a list of conditions where AMDs are frequently inappropriately prescribed (i.e., respiratory conditions), it is logical to initially assess prescribing patterns for these common presentations. This assessment would not only develop a method to judge trends of AMD use in veterinary medicine, but also would help determine the effectiveness of AMS interventions. The lack of a standard method for estimating AMD use in companion animal medicine on national level is reflected in the fact that only a few studies, which employ different AMD use outcome measures, have assessed the impact of AMS interventions.

The lack of studies assessing the impact of AMS programs is surprising given the attention the veterinary profession has paid to the issue of AMR and the effort it has put into developing national AMD use guidelines and stewardship principles[45]. It may be, in part, that the dearth of nationwide data and the lack of agreement on what the most appropriate AMD use outcome should be has precluded large-scale evaluation assessments from being performed. What studies do exist are typically isolated to a particular population of veterinary practitioners, usually defined by the institution in which they are employed. In a study from a Canadian academic teaching hospital, a decrease over time in prescriptions of AMDs per 1,000 hospital admissions was noted after the implementation of AMS principles, which were based on existing AMD use guidelines[166]. Another prospective assessment in Belgium found that, while AMD prescriptions for dogs and cats decreased after the implementation of guidelines, the association was not statistically significant. Contrarily, a significant increase in the use of critically important AMDs was noted after guidelines were introduced[234]. Research from Switzerland found that AMD use guidelines promoted through an online tool generally reduced AMD prescribing among companion animal practitioners, but that adherence to guidelines when AMDs were indicated was not improved[168]. The previously referenced studies all utilized a records review to determine change in AMD prescription patterns secondary to AMS implementation and results lack in external generalizability. Furthermore, with these studies occurring in Canada, Belgium and Switzerland, conclusions from the assessments cannot necessarily be applied to practitioners in the United States. In an attempt to establish a baseline for appropriate AMD prescriptions in the United States, a large veterinary corporation reviewed approximately 70,000 medical records and found that 67% of urinary tract presentations and 79% of upper respiratory presentations received an AMD in concordance with AMD guidelines[235]. While this study is unique in that it attempts to describe baseline appropriate AMD use, it assumes that all documented urinary and upper respiratory presentations were of bacterial origin. This study is also not generalizable as it analyzed records from a non-representative group of practicing U.S. veterinarians. A method to estimate inappropriate AMD use nationwide would provide the advantage of better describing an entire population, leading to a more reliable baseline of AMD use that can be used for tracking AMD use trends and in evaluation of AMS program effectiveness.

Prior to the execution of Aim 1, there was a deficiency of comprehensive information regarding AMD use in companion animal medicine in the United States. As the results from the cross-sectional survey in Aim 1 demonstrate, there is evidence of widespread AMD prescribing among companion animal veterinarians in the United States. Moreover, survey results indicate that AMDs are routinely being prescribed for non-bacterial infections, such as feline upper respiratory disease, that do not have a bacterial cause. Not only does the data generated from the companion animal survey tell a story of AMD overuse, but it also can be used to calculate a nationally representative estimate of the proportion of visits where AMDs are prescribed by veterinarian. The utilization of this data to generate use estimates presents a method for addressing AMD prescribing questions and fills a critical gap in knowledge.

The first objective of Aim 3 is to calculate an estimate of the proportion of feline upper respiratory illness visits where a veterinarian inappropriately prescribed AMDs. Determining this proportion is significant in that a proportion estimate of visits where veterinarians prescribe AMDs contra to existing guidelines will describe the magnitude of AMD overuse for a condition where AMDs are commonly dispensed. Additionally, in calculating a proportion for a specific scenario, the methods used in Aim 3 can serve as a framework for examining other disease conditions for which AMDs are often overused. Understanding how AMDs are being used for scenarios in which they are commonly prescribed will be useful in promoting judicious AMD use principles and interventions to veterinarians. In circumstances in which there appears to be room for significant improvement in adherence to prescribing guidelines, organizations, such as AVMA, AAHA and ISCAID, can use a targeted educational campaign to increase veterinarian awareness of the issue. An estimate that describes the proportion of visits where AMDs are inappropriately prescribed will be able to aid these organizations in determining future targets for application to other common disease conditions. Lastly, such estimates can allow stakeholders to judge the effectiveness of various AMS initiatives, from nationwide interventions to single hospital AMS programs.

Unlike the current state in companion animal medicine, there is a plethora of research done in the United States human healthcare system that attempts to measure the inappropriate use of AMDs on a population level. Prevalence rates of AMD prescribing for human patients are commonly reported to track trends over time[231,232]. Reported rates describe both overall [184,237] and condition-specific prescribing[184,229,238] as well as specific geographic, specialty and hospital network rates[236, 239,240]. The CDC has long instituted a system for estimating AMD use by administering an annual survey of patient visit records. Developed in 1973, the National Ambulatory Medical Care Survey (NAMCS) uses a complex survey design to randomly select outpatient practitioners across the United States. The patient data generated from these surveys are used in a diverse range of national estimates, including AMD use, as seen in a 2016 example that examined AMD prescribing habits and was able to determine population AMD prescription incidence rates by illness condition[184].

A second objective of Aim 3 is to calculate a proportion of visits were inappropriate prescribing by physicians for viral upper respiratory conditions occurred using data from the 2016 NAMCS data. Methods for calculating AMD measures of use do exist, primarily on the patient or population level. However, this objective is still significant in that it adds another method for estimating inappropriate AMD use in human medicine. Viewing different estimates simultaneously can also possibly lead to synergistic improvement in AMD prescribing practices in both settings.

Prior reports and reviews have called for more interdisciplinary collaboration in the area of AMR research[241]. Recognizing the interconnectedness of people, animals and the environment, creating integrated solutions to reduce unnecessary AMD use will lead to less genetic selection pressure on bacteria[154]. Looking at the problem of AMR from a holistic viewpoint acknowledges interdependence among humans, animals and the environment. Therefore, there is significant One Health value in not only describing AMD prescribing in companion animal medicine, but also comparing these estimates to those in human medicine. Currently, referenced AMS strategies in human medicine expand to include other healthcare fields, mainly dentistry, but fail to incorporate veterinary medicine in the collaboration[242]. By not recognizing veterinary medicine as a contributor to AMR, a key component is being ignored. Continued compartmentalization of the prescribing patterns in human and veterinary medicine will result in a missed opportunity to improve the AMD use in both systems and to slow the overall growth of AMR.

The third objective of this aim will compare the previously calculated veterinary and human proportions of upper respiratory visits where an AMD was inappropriately prescribed. Additionally, this aim will compare the human and veterinary measures by utilizing novel methods that have not yet been applied to this type of question. This collaborative study starts with the acceptance that veterinary and human medicine, especially outpatient human medicine, share a list of common influences in the AMD prescription decision-making process. Upper respiratory infections represent a common situation in both veterinary and human medicine in which AMDs are excessively prescribed. The exploration of rates can promote discussion about the common factors in the AMD prescription decision-making process between the two systems. Methods for reducing AMD use through interventions that have been successful in one profession could ultimately be adapted in the other in an attempt to replicate the reduction. Also, a more accurate description of the relative roles of each profession in regard to inappropriate AMD prescribing can be cultivated from results of such a comparison[155]. While ideal data sources do not exist for either healthcare system, this aim will use the best available datasets to compare prevalence rates, while emphasizing the limitations of the datasets and analysis in order to guide future assessments that determine and compare inappropriate AMD prescribing.

Materials and Methods

To accomplish the three objectives of this aim, a Bayesian approach was used to estimate the proportion of upper respiratory visits ($Prop_{visit}$) where a prescriber, either outpatient human physician ($Prop_{visithuman}$) or veterinarian ($Prop_{visitvet}$), recommended AMDs contra to respective existing professional guidelines for non-bacterial upper respiratory symptoms was estimated from large, representative nationwide datasets. $Prop_{visit}$ was calculated by dividing the number of visits that received AMDs ($Visit_{AMDvet}$ and $Visit_{AMDhuman}$) by the total number of visits ($Visit_{totalvet}$ and $Visit_{totalhuman}$) (equation 5.1) for each healthcare profession.

(Equation 5.1)

$$Prop_{visitvet} = Visit_{AMDvet} / Visit_{totalvet}$$

$$Prop_{visithuman} = Visit_{AMDhuman} / Visit_{totalhuman}$$

Finally, posterior sample distributions for $Prop_{visithuman}$ and $Prop_{visitvet}$ were compared using numerical integration methods to determine which had a lower proportion of visits where providers prescribed AMDs unnecessarily for non-bacterial upper respiratory illness. In this analysis, a system with a absolute lower $Prop_{visit}$ was judged to prescribe fewer AMDs for a suspect viral upper respiratory condition. Figure 5.1 describes the data sources, analysis and outcomes used in this aim.

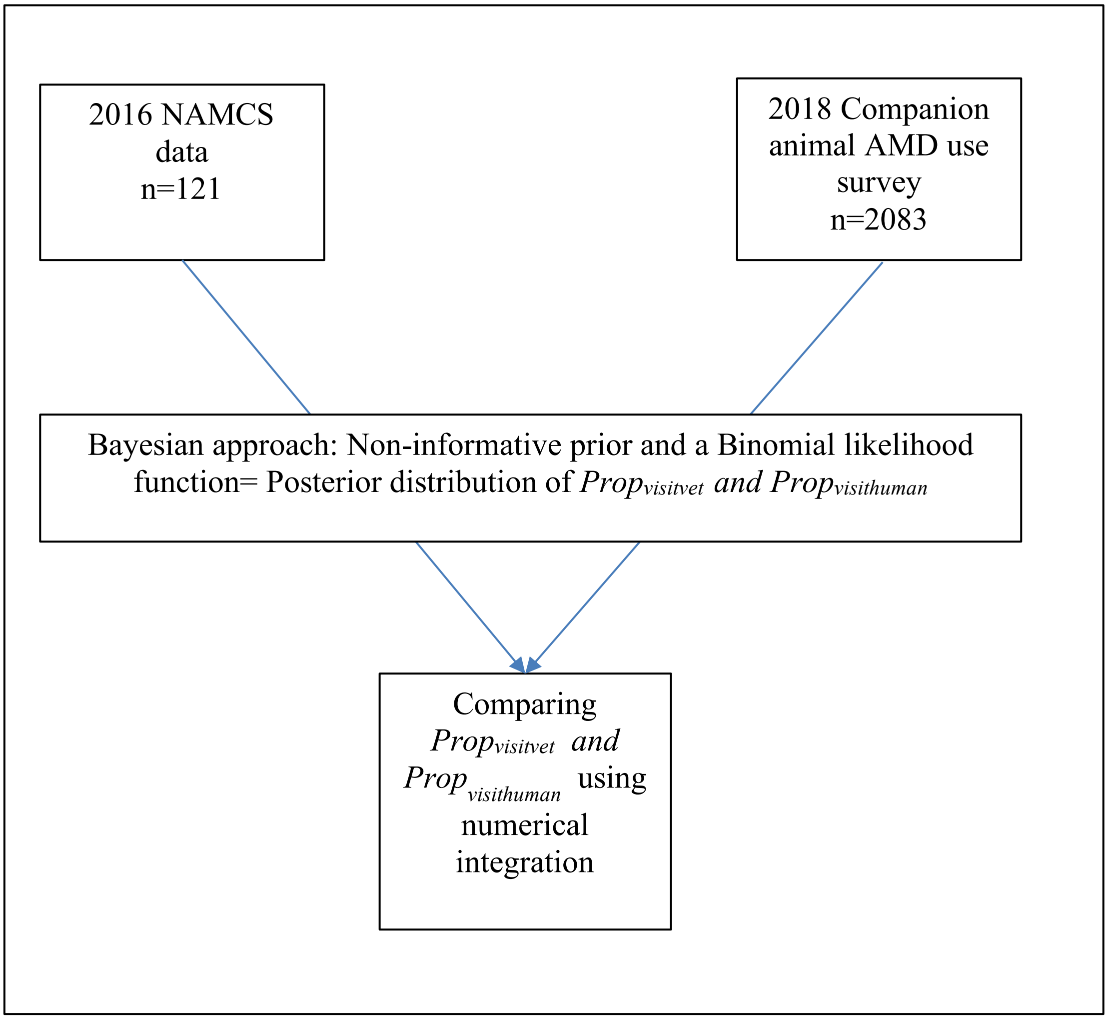

Figure 5.1: An outline of the data sources, analyses and outcomes for Aim 3

Data from the Aim 1 cross-sectional survey was used to estimate $Prop_{vet}$ for cases of feline viral upper respiratory disease. Per the ISCAID guidelines, if a veterinarian elected to give antibiotics to the cat with upper respiratory symptoms in the hypothetical scenario, it was considered an inappropriately prescribed AMD. As there is no previous knowledge in regard to proportion of feline upper respiratory veterinary visits that resulted in an AMD prescription, a non-informative prior, which allows for a diffuse, vague prior distribution density, was employed. As the survey tool relied on self-report of AMD prescription practices, it was assumed the survey tool did not have 100% sensitivity or specificity. In this context, a survey response that indicated what the participant actually recommended in clinical practice was considered a true positive while a response that was contra to what was done in the clinic was considered a false positive. A test sensitivity distribution of 80% was incorporated into the model, while the specificity was determined to be 97%. The sensitivity and specificity were determined by comparing a sample of respondent survey responses and comparing them to prescription diary data that recorded what was actually done in practice. As the outcome of the dataset was AMD prescription (yes/no), a binomial distribution was fit to the data to model the likelihood, which was informed by the survey data. The parameters of the binomial distribution used to fit the data included "s" successes and "p" trials, where "s" represented $Visit_{AMDvet}$ and "p" represented $Visit_{totalvet}$. The prior distribution and likelihood were multiplied together, resulting in a posterior distribution. The posterior distribution was sampled 10,000 times, with replacement, which resulted in a posterior sample distribution of proportions. The posterior sample distribution described the statistical uncertainty in $Prop_{visit}$ estimates.

$Prop_{visithuman}$ was estimated using the 2016 NAMCS dataset following a similar protocol that was used for the veterinary outcome. The dataset was created by identifying patient visit records that contained an ICD-10 code for an upper respiratory condition that typically does not require antibiotics (table 5.1). Existing AMD use guidelines for upper respiratory disease symptoms provided justification for which ICD-10 codes to include[243,244]. The dataset was also restricted to visits that included at least one of the ten ICD-10 codes that typically do not require AMDs[243]. Patient visit records were excluded if they indicated an AMD was prescribed for a non-upper respiratory illness condition, such as a urinary tract infection. This step is unique from the veterinary analysis as the hypothetical scenario represented a single young, otherwise healthy cat with no other comorbid conditions. Visit records were then screened using free-text analysis for the mention of an AMD, and if the record mentioned an AMD for a respiratory visit, it was considered an inappropriate AMD. A similar approach that was utilized for the veterinary dataset was employed to the resultant NAMCS data. Like the assessment of uncertainty in the veterinary dataset, the non-informative prior represented all possible values to evaluate the proportion of visits that inappropriately received an AMD. Also like the veterinary analysis, the data was fit to a binomial distribution, which was informed by patient visit data. The resultant likelihood and the non-informative prior were multiplied together, resulting in a posterior distribution. The posterior distribution was sampled 10,000 times with replacement, which resulted in a posterior sample distribution of proportions.

Table 5.1: ICD-10 codes that typically do not require AMDs captured in the human outpatient dataset

ICD-10 code	Description
J069	Acute upper respiratory infection
J209	Acute pharyngitis
J00	Rhinitis
J040	Laryngitis
J111	Influenza
J310	Chronic rhinitis
J311	Chronic nasopharyngitis
J312	Chronic pharyngitis

The resulting posterior sample distributions from both healthcare systems were compared using numerical integration, which resulted in a level of confidence that one system had a higher proportion of upper respiratory visits ending with an AMD prescription than the other. In this analysis, a healthcare system was considered to prescribe more AMDs if it had a higher $Prop_{visit}$. There were assumptions made when making this comparison, including the two healthcare systems approaching viral upper respiratory conditions similarly and upper respiratory illness affecting humans and cats in a similar manner. The difference in $Prop_{visit}$ for each healthcare system was expressed as a percentage difference in the mean posterior sample proportions for each system. R statistical software was used for all analyses.

Results

From the Small Animal Veterinary Antibiotic survey, 2,083 responses were used in determining a prevalence estimate of veterinarians who prescribed AMDs in cases of feline viral upper respiratory disease. In the original dataset, 576 hypothetical visits resulted in an AMD recommendation for a cat experiencing upper respiratory disease symptoms (576/2083, 27.6%). After determining a posterior distribution, a mean of 32.5% (SD=0.01) of visits resulted in AMD prescriptions. Similarly, from the human visit dataset, 28.1% (34/121) prescribed AMDs for a diagnosis of a viral upper respiratory condition. A mean of 29.3% (SD=0.04) of visits resulted in inappropriate AMD prescriptions. Figure 5.2 shows the distribution of the $Prop_{visit}$ that resulted for each healthcare system after random samples were drawn from the resulting posterior distribution

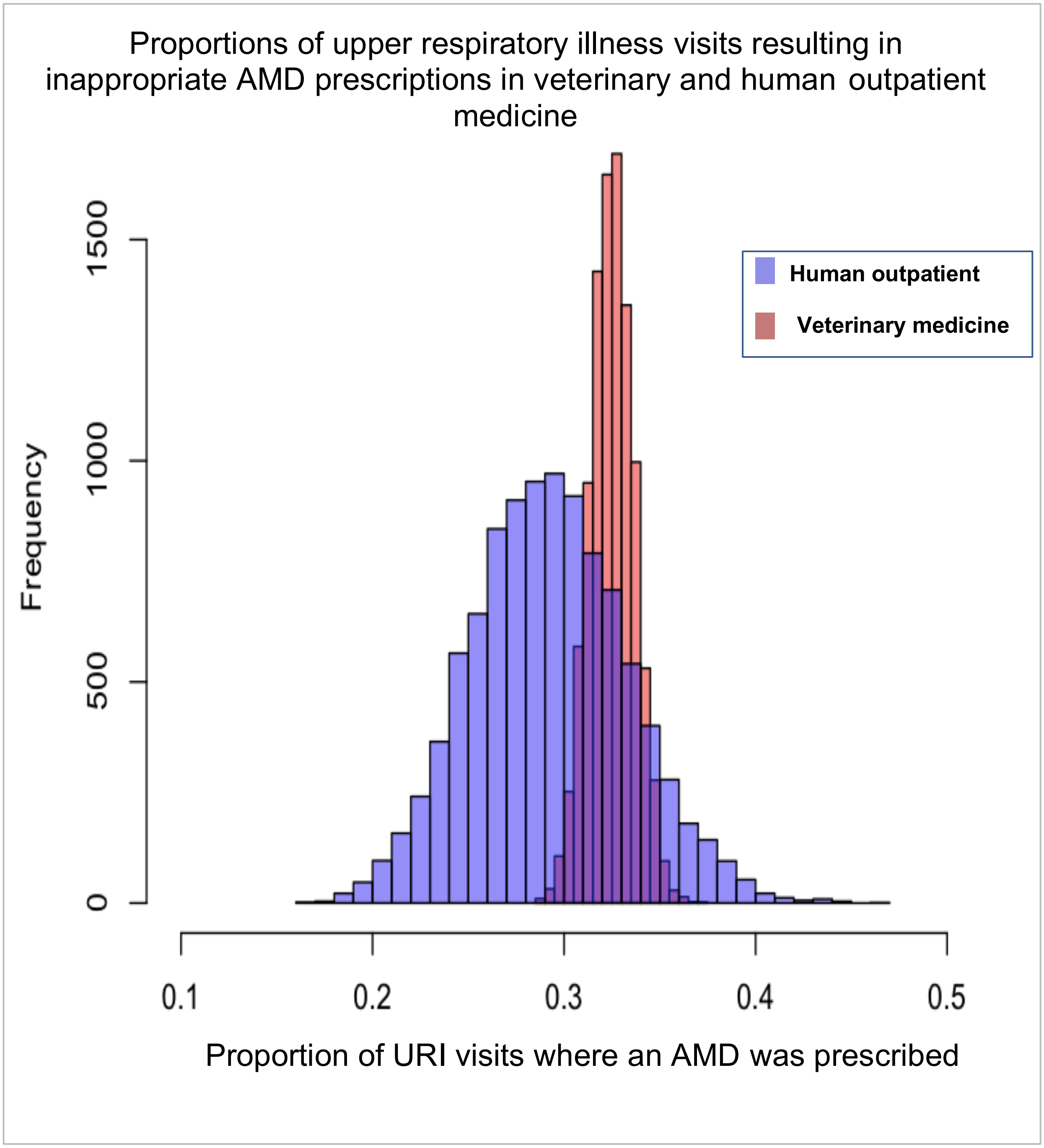

Figure 5.2: Posterior sample distributions of $Prop_{visithuman}$ and $Prop_{visitvet}$

Physicians prescribed AMDs inappropriately less often than their veterinarian counterparts in times of suspect viral upper respiratory conditions. There is a 78.1% confidence that veterinarians had a 9.8% higher mean $Prop_{visit}$ than human outpatient physicians when comparing treatment for a viral upper respiratory illness.

Discussion

By utilizing existing datasets, estimates of $Prop_{visit}$ indicate that there is room for improvement for both veterinary and outpatient human medicine. Comparison of the two estimates indicates that there is a 78.1% confidence that veterinarians prescribe more AMDs for a suspect viral upper respiratory condition in cats than outpatient human physicians prescribe for humans with non-bacterial upper respiratory conditions. This type of assessment has not been previously attempted, and results can inform different aspects of a complex intervention development to improve AMD use in companion animal medicine.

While quantifying uncertainty and accounting for survey tool sensitivity and specificity, it was estimated that approximately one-third of feline upper respiratory visits in the nationally representative dataset of veterinarian survey responses from the Aim 1 resulted in an inappropriate AMD prescription. A nationally representative cross-sectional estimate of inappropriate veterinary AMD prescription rates has not been published in the United States. A handful of studies, which have previously been discussed, have described veterinary AMD prescription practices but samples are usually restricted to specific regions, institutions and companies. Furthermore, no consistent AMD use measure has been established. While there have not been published estimates of proportions of visits that resulted in AMD prescriptions in the United States, the data to compute them in other countries likely exists. In the United Kingdom, a veterinary disease surveillance network has been established and collects medical record data, including disease and prescription information, from veterinary practices voluntarily[245]. Methods described in this aim could be adapted to estimate proportions of various disease condition visits in Europe that receive AMDs. While this aim only covers one specific disease condition for a single species, the data from these surveillance networks could inform estimates for many disease conditions in multiple species. While it may seem more accurate to judge inappropriate AMD prescriptions on a patient visit level, it can be argued that it is more appropriate to measure inappropriate prescribing on a provider level. But until a nationwide veterinary surveillance network or complex survey study is available, provider level estimates would likely come under scrutiny. What makes measuring prevalence of inappropriate AMD prescribing on a provider level significant is that the measure relies on more available veterinarian census counts, whereas precise counts of canine and feline patients do not exist, at least at the precision level of human census data. Ultimately, as there are currently no other studies that explore inappropriate AMD prescribing in terms of a national prevalence measure, this aim acts as a model for determining such a measure by outlining what data sources are required to accurately determine a provider level AMD use prevalence. As discussed in upcoming sections, the study design has certain limitations. However, from a methodology aspect, this aim can identify limitations to this type of analysis, which will improve future study design and data collection.

Perhaps one the biggest advantages to this type of measure is that nationwide trends could be assessed over time. Typically, AMS guidelines come from national professional organizations and AMD use trends could prove valuable in their assessment of the effectiveness of such guidance. For example, $Prop_{visitvet}$ calculated in the current aim could serve as a baseline for an AMS program targeted at reducing AMD prescriptions for cats with upper respiratory symptoms. As the survey tool employed in the Aim 1 is easily distributed and requires little effort to complete, it can be repeated to help define how AMDs are being used over time. In the context of complex interventions, these methods provide a way to evaluate AMS programs.

Compared to veterinarians, human outpatient physicians prescribe fewer AMDs for cases of suspect viral upper respiratory disease. At a glance, $Prop_{visitvet}$ and $Prop_{visithuman}$ appear similar between human and veterinary providers. However, when determining which system follows AMS guidelines more closely, (i.e., which one has less frequent inappropriate prescriptions), results indicated that, on average, fewer human outpatient upper respiratory visits result in AMDs when compared to their veterinary counterparts. Although this technique indicates a lower proportion of inappropriate prescribing in human healthcare, the margin is estimated to only be approximately 10% less than in veterinary medicine. The comparison of the two systems contributes to the complex intervention cycle in two ways: 1) informing possible AMS interventions in companions animal medicine and 2) relating human and veterinary AMD prescribing for a common disease presentation.

A comparison of nationwide datasets revealed a higher proportion of feline upper respiratory visits receive AMDs than human outpatient visits. While there are inherent limitations when utilizing the available datasets, the difference in mean proportions of visits that received an AMD indicates that there may be AMS interventions or programs utilized in human medicine that could be applied to veterinary medicine. In principle, the cause and presentation of upper respiratory conditions is similar in humans and people. Regardless of the specific etiology, in most instances, these cases do not require the use of AMDs for either veterinary or human patients. As outlined previously, external influences on the AMD prescription decision-making process between the two healthcare systems are also very similar. With causes, presentations and influences being similar between the two systems, the question as to why the human setting sees a lower proportion of visits being prescribed an AMD remains. It is possible that there are interventions on the human side that are effective in reducing the rate of AMD prescribing for upper respiratory cases. If this is truly the case, then there is a real possibility that these interventions can be adapted and applied to veterinary medicine, thereby reducing the proportion of upper respiratory visits that result in an AMD prescription. This is relevant in the complex intervention framework as it suggests human interventions should be evaluated for their potential to be adapted to companion animal medicine. Besides potentially informing a veterinary specific intervention, the comparison of the two systems also draws attention to the need to include AMD use in companion animal medicine in the conversion of overall AMD use among healthcare professions.

Much of the current literature does not consider AMD use in companion animal medicine when defining how inappropriate AMD use accelerates AMR. By comparing human outpatient and companion animal settings, a systematic comparison is provided, which brings attention to the contribution of inappropriate AMD use in dogs and cats to the public health threat of AMR. Through recognition of the contribution of companion animal medicine AMD use, more attention and resources may be designated to further understand and intervene on the problem. The expansion of understanding AMD use in companion animal medicine, of how it relates to public health and of how interventions can improve the practice of prescribing can all be augmented through the increased recognition brought on by comparing current practices to human medicine.

Limitations and Strengths

Limitations

Aim 3 has several limitations, both in the estimation of the proportion of feline and human URI visits that resulted in AMD prescriptions and in the comparison of proportions between human and veterinary medicine. However, beyond the primary goal of comparing the two healthcare systems, a secondary goal of this aim was to illustrate a method for comparing two prescribing distributions in an effort to promote better veterinary data collection systems and collaboration among veterinarians, researchers and public health officials. In the absence of nationwide veterinary surveillance data, the number of visits where veterinarians who inappropriately prescribe AMDs to cats with upper respiratory illness can only be estimated by the data gathered in Aim 1. While this data, to date, represents the most comprehensive dataset available, it has limitations and estimates that are born from it should be interpreted carefully. As touched on in Chapter 3, the scenarios are hypothetical and do not represent all of the factors that affect the AMD decision-making process. The data also assumes that survey participants also prescribe AMDs for URI cats if they recommended the medications for the cat in the survey scenario. Practicing veterinarians see this type of case many times a year, and, in all likelihood, as each clinical URI case has different characteristics, the decision whether or not to prescribe AMDs likely varies from case to case. Therefore, a better approach would be to survey multiple real patient feline URI visits, much like it was done in the NAMCS sampling methods.

Comparing $Prop_{visitvet}$ and $Prop_{visithuman}$ using the current datasets has several limitations. Foremost, human and veterinary medicine are very different healthcare systems, clearly based on the species being treated. When computing the proportion of visits that received an inappropriate AMD prescription for acute viral upper respiratory disease in humans, real clinic data gathered from sampled physicians was used. As the data reflected what was included in a patient's medical record, it can be assumed that the sensitivity and specificity of measuring inappropriate AMD prescriptions for upper respiratory illness were close to 100%. When calculating this same measure for surveyed veterinarians, data from a cross-sectional hypothetical survey was used. This data collecting method is open to misclassification of practitioners, as it did not reflect real-life clinical cases. Therefore, the measure likely has a sensitivity and specificity of less than 100%. To avoid the problem of adequate sensitivity and specificity, computed values determined by a comparison of survey responses and actual medical records were incorporated into the model. However, the sample used to calculate sensitivity and specificity was small and may not represent the true sensitivity and specificity of the survey tool.

Strengths

The strengths of this aim include the novel objective of the study and the analytic methods used to produce results while accounting for parameter uncertainty, Additionally, the establishment of a population-based measure that can be expanded by continued study in veterinary medicine while providing a method for tracking use over time was also significant.

While the aim is comparing $Prop_{visitvet}$ and $Prop_{visithuman}$ between the two different healthcare systems, the premise of the study has the opportunity to open up a wider conversation surrounding AMD use and One Health. As previously discussed, by comparing these measures from human and veterinary medicine, there exists the potential to increase awareness that AMR is a One Health issue and all sources of AMD use should be looked at together. Additionally, it should be viewed that prescribing among healthcare professions is connected despite treating different types of patients, or species. The unification of healthcare professionals on the issue of AMR secondary to AMD use will help to concentrate efforts on how to best mitigate it. The cross-profession communication can help foster research and intervention ideas as well as interdisciplinary efforts to reduce the burden of AMR on society.

When determining, and, subsequently, comparing a population-based measure of inappropriate AMD use in veterinary medicine for feline viral upper respiratory disease, methods that are scarcely used in companion animal research were employed. The use of such methods not only ensures a more rigorous approach, but also provides an example of how such methods can be used in veterinary research, especially as more data becomes available from future studies. Future projects can expand on what was done in this assessment of AMD use not only by merely using advanced epidemiologic methods to advance the understanding of the research question, but also by extensively exploring the limitations of these methods given the data. By addressing the limitations that were discovered in this study design, future studies can employ strategies to avoid them during the study design phase. In that way, this aim is as much of a methodology aim as it is one estimating a measure of occurrence.

The results of this aim establish a population-based measure that has not yet been estimated in veterinary medicine. The development of an estimate of $Prop_{visit}$ can be useful when investigating trends over time. The idea of tracking AMD use in companion animal medicine has recently drawn the attention of the Federal Drug Administration (FDA), which recently released a five-year plan that included monitoring AMD use in companion animal medicine. Accurately estimating AMD use in companion animal medicine is part of the FDA 5-year plan meant to curtail mis- and overuse of AMDs in veterinary medicine. It may not be feasible to establish a nationwide veterinary surveillance system in the United States, and therefore, it may be necessary to rely on a representative sampling scheme that delivers an easy-to-complete, low-burden data collection tool when measuring and tracking AMD use in companion animals.

Applying a Bayesian approach, like in this aim, can help explain uncertainty surrounding the measure and can be used to continually update the measure of occurrence by incorporating prior knowledge into the most recently collected data.

CHAPTER VI

SUMMARY AND CONCLUSIONS

Summary and conclusions

AMR is a significant global public health threat partially driven by the excessive use of AMDs in humans, animals and agriculture. The application of AMDs in small animal medicine is thought to contribute to the problem. By considering key stakeholders, an understanding of AMD use in dogs and cats has been established through the results of the previously described aims, which can inform a framework for effective complex intervention development. Through a better understanding of the process from the perspective of all stakeholders, improvements to how AMDs are used in small animal medicine can be made through developing, piloting, evaluating and implementing effective complex interventions. The findings from the previously described aims combine to impact public health and veterinary medicine through the use of a complex intervention by: 1) contributing to important knowledge gaps within the AMD prescription process 2) allowing results to inform potentially useful interventions by defining content, delivery and timing needs of targeted groups and 3) offering tools to evaluate the performance of a piloted complex intervention prior to implementation.

Contribution to knowledge of veterinary AMD prescription practices

Prior to exploring the questions posed by these aims, relatively little was known about the AMD prescription decision-making process in the United States on a nationwide level. While more research is needed to fully define the AMD prescription process in companion animal medicine, findings from the research performed in this dissertation provide an encompassing explanation of the phenomenon. By exploring previous studies, hypotheses were developed with the intention of building on previous results to address the relative dearth of information surrounding AMD use in companion animal medicine. By collecting a large number of responses from companion animal veterinarians, evidence has objectively pointed to the widespread injudicious use of AMDs in dogs and cats. Aims one and three both address the measurement aspect of AMD use and identify areas for potential improvement in prescribing. Veterinarians are over-recommending AMDs for common clinical scenarios that do not require the medications. This initial measurement of over-prescription provides evidence that AMDs are being used excessively for feline URI and urinary tract symptoms, canine diarrhea and canine dental procedures. While the number of these cases that are receiving AMDs unnecessarily is alarming, there should also be a sense of opportunity that inappropriate AMD use and be successfully reduced use through targeted complex interventions.

A mixed methods approach in assessing pet owner attitudes and perceptions of AMD use in pets also provided key stakeholder information that did not exist in the United States prior to the execution of aim 2. In defining these attitudes and perceptions, attention can be turned to how the pet owner contributes to excessive use and what can be potentially be done to intervene. While the results of these aims do not completely bridge stated knowledge gaps, they do help to contribute to the overall understanding of a very complex medical, social and behavioral phenomenon. Interventions cannot be expected to be effective if they do not address the root causes of the problem or consider all groups whose behavior the intervention is attempting to correct. Therefore, aims 1 and 2 are paramount in the beginning stages of development of a complex intervention.

Findings illustrate that intrinsic and extrinsic factors combine with objective medical data to inform the decision of whether or not to prescribe AMDs. Additionally, results applied an established theory of behavior (i.e., TPB) to explain what influences pet owner's compliance with administering AMDs as directed. Results support the theory that established personal values overcome the influence of objective science, suggesting that interventions must be presented in such a way that parallels a particular audience's values set in order to achieve judicious AMD use[246]. Through exploring veterinarian and pet owner perceptions and attitudes in regard to AMD use in companion animal medicine, it is clear that consideration of the social and behavioral aspects of both veterinarians and owners is needed in order to reduce inappropriate AMD use in veterinary medicine[246]. While results of the previously discussed aims starts to touch the surface of the social and behavioral aspects of AMD use in companion animals, further research in the framework of behavior change theory is ultimately needed to refine the direction of a complex intervention.

Inform interventions by defining content, delivery and timing needs of targeted groups

Not only does having a better understanding of AMD prescription practices fill critical knowledge gaps, but it also identifies points throughout the process that are amendable to intervention and kickstarts the conversation of which types of interventions might be most effective. While the previously described aims did not focus on developing specific interventions, results can inform the content, delivery and timing of potential interventions, both by identifying critical needs and by suggesting that there may be existing intervention frameworks already employed in human medicine.

Findings of how veterinarians prescribe AMDs, how pet owners perceive AMD use in their animals and how veterinary prescribing compares to human prescribing can be translated into clinical interventional content. Findings from aims 1 and 2 suggest there is promise of improving AMD use in companion animals through the use, application and translation of clinical AMD use guidelines. In aim 1, there is was positive significant association between veterinarian knowledge of AMD use guidelines and appropriate AMD recommendations. Aim 2 demonstrated that owners appreciate clear communication of veterinary reasoning. In the context of client-centered veterinary care, applying validated AMD use guidelines satisfies many requirements for improved AMS. From the veterinarian perspective, AMD use guidelines allow the veterinarian to practice medicine in an objective manner, without fearing the influence of a non-informed pet owner. From a pet owner perspective, this type of intervention will inform pet owners of the options that are best for their animal and include them in the decision-making process. Ultimately, beyond these two immediate stakeholders, there will be an overall societal benefit from this mutually beneficial type of intervention in that inappropriate use of AMDs will be reduced, thereby decelerating the rate of AMR development.

Delivery of an effective AMD use complex intervention is as important as the actual content of the intervention. An aspect of complex interventions is that they can target multiple groups of stakeholders. In this case, both veterinary and pet owner behavior would be expected to change with the intervention. However, as results from aims 1 and 2 suggest, the vehicle for content delivery will likely need to be tailored by grouping. As guidelines are not regulations and thus not upheld through enforceable actions, external motivation to change prescribing habits in veterinary medicine is lacking. Part of the solution of improving AMD use in veterinary medicine is to persuade veterinarians to not recommend AMDs in cases where they are not warranted. By having an awareness of how the veterinary profession prescribes AMDs, practitioners will likely be more aware of their individual practices. Giving veterinarians something to compare their practices to has the potential to improve prescribing. As shown in human medicine, a possible method for accomplishing this may be to employ a peer benchmark to promote internal motivation to improve practices[247]. When individual's practices were presented to them in the context of their colleagues, prescribers improved their subpar prescribing in an effort to not lag behind[247]. While these efforts may seem to undermine the expertise of practitioners, they have resulted in improved prescribing through self-motivation to not be "below average"[247]. In veterinary medicine, researching specific ways to track and compare provider AMD prescription patterns needs to be done as part of a complex intervention discovery. Also, ways to distill down key points of AMD use guidelines and AMS principles to make them more digestible for busy veterinarians and more amenable to translated to pet owners needs to be explored.

By not taking into account the needs of pet owners when addressing AMD use in companion animal medicine, a complex intervention would likely fail. Understanding what pet owners think about AMDs and AMR is vital to creating ways to overcome the barriers these influences pose. By building on the knowledge of how AMDs are prescribed, focus can be put toward removing non-medical barriers to judicious AMD use. As discovered from the utilization of mixed methods in aim 2, pet owners have no more than a basic understanding of why AMDs are prescribed in veterinary medicine. Furthermore, owners generally trust their veterinarian when it comes to deciding whether an AMD is needed or not but would also like to be involved in the decision-making process. Owners see veterinarians as the experts when it comes to knowing when AMDs are needed. However, it is likely that interventions aimed at improving owners' AMD compliance behaviors will need to be delivered in an informative, yet understandable, manner. Rather than just relying on veterinary expertise and varying communication abilities. A resource that is consistent and that owners can referred back may satisfy the need to be educated on appropriate AMD use and still be involved in the decision-making of their pet's treatments.

If the content and delivery system for a complex intervention are appropriate for the diverse group of stakeholders, but the timing it off, the effect will likely be muted. Not only with a complex intervention that is meant for pet owners and veterinarians need to target different content and delivery needs, but also will also likely need to be administered at different times.

Evaluation tools

In addition to filling knowledge gaps, the previously discussed aims offer methods that can easily be applied to the evaluation component of complex interventions. the easy-to-administer cross-sectional survey tool from aim one also provides a method for which AMD trends can be tracked over time. The tool is relatively easy and cheap to distribute among veterinarians and the disease conditions used in the scenarios are likely going to continue to be common clinical presentations. With continued success of re-administering the survey tool, new condition, such as kennel cough in dogs, could be added to the tool, especially as new consensus guidelines emerge. In much the same way that use for common disease scenarios can be estimated from aim one survey data, prevalence measures, like the one in aim three can also be estimated from a nationwide tracking system or cross-sectional survey tool. Prevalence measures would also be able to detect trends in use from year to year. A distinct advantage a nationwide tracking system would have over the cross-sectional survey in terms of estimating prevalence is that it could determine the patient prevalence of AMD prescribing, much like what can be calculated from the NAMCS survey tool. Calculating an AMD prescription rate for specific species and disease conditions would, however, depend on how the accuracy of pet census estimates, which historically possess higher variation than human census figures.

Conclusions

All AMD use drives the development of AMR, but it is the inappropriate use of AMDs that is of public health concern. AMDs are a frequently mis- and overused in companion animal medicine and a well-informed, effective intervention to curb inappropriate use is needed. The three aims of this dissertation drew a number of conclusions that can be used in the development of a complex intervention:

1) Evidence indicates veterinarians frequently prescribe AMDs for common clinical conditions that do not have a bacterial cause.

2) Veterinarians with an awareness of AMD guidelines are more likely to withhold AMDs in conditions where they are not indicated when compared to those with no awareness of such guidelines.

3) Pet owners also play an important role in the way AMDs are used in veterinary medicine and exhibit varying levels of compliance behavior that can be explained through the Theory of Planned Behavior and a mixed method approach.

4) Given existing data sources, prevalence of AMD use by provider can be estimated and has a variety of applications.

5) When compared to human medicine, AMDs are, on average, prescribed more for upper respiratory diseases of viral origin in veterinary medicine.

These referenced conclusions can inform the iterative process of a complex intervention cycle by addressing knowledge gaps, suggesting key aspects of the content, delivery and timing of the intervention and offering evaluation tools that can be used throughout the different phases of complex intervention development, piloting, evaluation and implementation. An effective complex intervention requires many actors and contributions across institutions. This dissertation not only strives to answer previously underexplored issues, but also aims to be a step in the overall process of improving AMD use in companion animal medicine. The hope is that this work will encourage others to build on what has already been done and to engage all stakeholders in the effort to mitigate AMR development secondary to inappropriate AMD use in companion animal medicine.

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