ANTIMICROBIAL USE AND RESISTANCE: INTERSECTIONS OF COMPANION ANIMAL AND PUBLIC HEALTH

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Dedication

To my husband and parents. Without your unwavering faith and support, I would not have gone down this path, much less finished it. And to Oliver, my budding little scientist.

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ABSTRACT

ANTIMICROBIAL USE AND RESISTANCE: INTERSECTIONS OF COMPANION ANIMAL AND PUBLIC HEALTH

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A One Health approach, defined as an approach to health that considers the close connections between humans, animals, and the environment, is key to reducing the spread of antibiotic-resistant bacteria (ARB). Research on the reservoirs of ARB has focused mainly on human medical hospitals and the livestock industry. The potential health risks posed by dogs and cats as a reservoir for ARB has been largely overlooked, despite the intimate contact between pet owners and their pets.

The aim of this dissertation was to contribute to filling major scientific gaps on how companion animal veterinarians make decisions about antibiotics, the role that pets and residential locations play in human infections caused by ARB, and the ways in which ARB that affect human health may spread in veterinary hospitals. In the first study, we conducted in-depth interviews with veterinarians about how they make decisions on antibiotic use. We found that financial barriers are a significant driver behind antibiotic decision-making. Veterinarians perceived finances to affect issues including the use and selection of diagnostic tests that are used to guide antibiotic use, which antibiotics are stocked in practice pharmacies, and the use of inappropriate prescribing as an attempt to avoid economic euthanasia. In the second study, we identified geographic locations where high concentrations of children and dogs with ARB lived. We found that while residential location is a risk factor for ampicillin-resistant *Escherichia coli,* locations of higher and lower risk were different between children and dogs. Children living in more urban areas were at greater risk but living in the same area conferred a lower risk to dogs. In the third

study, we investigated risk factors associated with the acquisition of a *bla*$_{\text{NDM-5}}$ carbapenem resistant *E. coli* strain, as part of an outbreak investigation at a veterinary hospital. Using a case-control study design, we found that patients exposed to endotracheal intubation, surgery, and anesthesia were at greater risk. These studies will serve as a starting point for future research on the impact of ARB in companion animals and provide baseline data that will inform antibiotic stewardship interventions in veterinary medicine.

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CHAPTER 1: Introduction

Antimicrobial resistance is a rapidly growing public health concern. The Centers for Disease Control and Prevention estimate that each year 2.8 million people become infected with ARB, leading to 35,000 deaths.[1] Antimicrobial use is the single most important factor that drives resistance.[2–5] A reduction in antimicrobial use, particularly inappropriate use, is vitally important and is a major goal of national and international action plans.[6–9] These plans recognize that a One Health approach, encompassing human, animal, and environmental health, is critical to addressing the threat of antibiotic resistant bacteria. Efforts to address the threat of ARB have focused mainly on human medical hospitals and the livestock industry.[6,7,9,10] Despite the intimate contact between pet owners and their pets, and the shared antibiotic classes used in human and companion animal medicine, the potential health risks of ARB in dogs and cats have been largely overlooked.

Medically important antimicrobial resistant pathogens can be detected in pets, their environments, and the humans associated with their care. Methicillin resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* ribotype 027 have been isolated from veterinary hospitals.[11,12] *Salmonella spp.* and *Escherichia coli* resistant to multiple classes of antimicrobials have been isolated from fecal samples of healthy pet dogs.[13–15] A study of *E. coli* isolated from dogs at the Cornell University Animal Health Diagnostic Center between 2004 and 2011 showed that the prevalence of resistance to cephalosporins, fluoroquinolones, and tetracycline significantly increased.[16] Carbapenem resistant *Enterobacteriaceae* have been detected in cats and dogs across the world.[17–24] According to the American Pet Products Association national survey, over 67% of US households, own a pet.[25] As a result, the development of antimicrobial resistant bacteria in pets is not only a veterinary challenge, but may also pose a public health concern.

Other studies show the potential for transmission of ARB between humans and animals. In one study a multi-drug resistant *Klebsiella pneumoniae* strain resistant to tigecycline, an antibiotic of last resort in human medicine, was isolated from two unrelated canine urine samples.[26] The dogs had never been treated with tigecycline. This demonstrated the adaptation of human bacterial clones to animals, which could increase the spread of antimicrobial resistance. In another example, a collaborative study between the veterinary and medical schools at the University of Pennsylvania assessed MRSA carriage of pets in households with a MRSA-infected person. Of the 99 pets sampled, 11.5% were MRSA-positive. Among MRSA-positive pets, 54.5% harbored strains that were genetically concordant with the infected household members'.[27] Dog-to-human transmission has also been documented. Case studies have identified MRSA infection in companion animals and subsequent infection in their owners and veterinary workers that assisted with their care.[28] Between 2016 and 2018, an outbreak of multi-drug resistant *Campylobacter* attributed to contact with puppies from Petland stores affected at least 113 people in 17 states.[29] The outbreak brought the transmission of antibiotic resistant infection from pets to people into the national spotlight.[30,31] These examples highlight the need to better understand how antibiotic use and antibiotic resistance in companion animal medicine can affect human health. The presence of ARB in pets is both a veterinary and a public health concern.

Veterinary Antibiotic Prescribing

Companion animal veterinarians and human physicians often use antibiotics inappropriately. A recent study concluded that approximately 30% of all oral antibiotics prescribed in outpatient human clinics may have been inappropriate.[32] Most of the available data on antibiotic use in veterinary medicine are limited to single center studies of teaching hospitals or surveys conducted outside the United States, but a similar rate of inappropriate prescribing is likely. Prescribing practices of primary care veterinarians in the United Kingdom[33] and a survey of veterinarians in New Zealand[34] found that dogs treated for pyoderma were often prescribed a shorter course of antibiotics and at a lower dose than veterinary guidelines recommended. The

authors concluded that this could have contributed to the high rate of recurrent infection and isolation of antimicrobial resistant bacteria also found in those dogs. The New Zealand study also found that broad spectrum drugs that are considered critical to human health by the World Health Organization (such as fluoroquinolones and amoxicillin-clavulanic acid), were among the most frequently prescribed (11% and 48% of all canine cases of antibiotic prescribing respectively). However, despite prescribing broad-spectrum drugs, veterinarians only submitted samples for culture and sensitivity testing in 19% of cases. Research on companion animal antibiotic use conducted in the United States is more limited. One retrospective cross sectional study from Tufts Veterinary Teaching Hospital that analyzed a random sample of 678 dogs, found that despite defining suspected infection broadly (any wound, skin infection, evidence of pneumonia on radiographs, any diagnostic test indicating infection), over 38% of patients that were treated with antibiotics had no documented evidence of infection.[35] These examples highlight the opportunity to reduce antimicrobial resistance by improving inappropriate prescribing.

Complex social and behavioral processes underlie antibiotic prescribing by veterinarians and human physicians. To develop interventions to improve antibiotic prescribing behavior, a deeper understanding of the way companion animal veterinarians think about and use antibiotics is necessary. Few published studies have attempted to understand the attitudes and influences veterinarians experience when prescribing antibiotics.

To our knowledge, the largest study on veterinary antimicrobial decision-making was a survey of 3,004 veterinarians from 25 nations across Europe.[36] Antimicrobial susceptibility testing (AST) of bacteria was determined to be the most important factor which governed the selection of an antibiotic, yet the majority of veterinarians (54.1%) surveyed never used AST, or only used AST after an antimicrobial treatment failure. The next two top factors were risk of resistance and the veterinarians “own experience.” Although economic factors were rated as the least important in antibiotic choice, cost of therapy and testing were reported to be important barriers to judicious prescribing. Data on companion animal veterinary antimicrobial decision making in the US is

limited. A single survey of 71 veterinarians working for a single academic teaching hospital found that the only source of public health knowledge for most veterinarians was veterinary school. This highlights both a dependence on veterinary training to convey information about appropriate antibiotic use, and a lack of continuing education to provide updated information.[37] While peer-reviewed literature was ranked by respondents as the most important source of antimicrobial use information, only 12% of respondents listed it as their most commonly used source. Nearly 75% of veterinarians felt that at least one antibiotic class (most often carbapenems or vancomycin) should be restricted in companion animal medicine "for public health reasons." However there were no restrictions in place at this hospital, and carbapenem prescribing during the survey period (2.3 per 1000 accessions) was higher than a rate previously reported at another small animal veterinary teaching hospital (1.3 per 1000 accessions).[38] This highlights some of the areas where attitudes and practice may conflict—although veterinarians recognize the importance of antimicrobial resistance and see value in AST, formulary restrictions, and peer-reviewed antimicrobial use information, a gap appears to exist between this ideal and the realities of practice.

Qualitative studies are better suited to more deeply investigate veterinary perspectives on antimicrobial use and resistance and understand the reasons for some of these gaps. For example, respondents consistently listed "own experience" and personal preferences as top reasons for prescribing,[36,39,40] yet the what drives experience and preference are left unclear. Qualitative methodologies, like semi-structured interviewing allow for further probing about the meaning of vague phrases like these to develop new insights into veterinarians' decision-making.

A limited number of studies have used qualitative methodology to better understand antibiotic decision-making in companion animal veterinary medicine.[41–44] In one study by Mateus et al. (2014), semi-structured interviews were conducted with 21 veterinarians across seven first opinion companion animal practices in the UK.[41] In addition to more general questions about factors that influence antibiotic use, four hypothetical case scenarios were used to evaluate the veterinarian's knowledge of appropriate use. Many of the interviewees were unaware of the

existence of guidelines and recommendations for companion animal antimicrobial prescribing. This was reflected in the responses to the case scenarios presented. Almost half (9 of 21) of the interviewees falsely believed that feline lower urinary tract disease (a common condition in companion animal practice) was infectious in origin, and an additional three were aware that it was non-infectious but supported prophylactic antibiotic use, which is against published guidelines. A similar lack of knowledge and support of antimicrobial use against published guidelines was found in other case scenarios.

Researchers also found that many factors outside clinical evidence and scientific knowledge influenced the veterinarians' decisions. Their perception of efficacy, perception of client compliance and willingness to treat, short length of appointments, ease of antibiotic administration, and informal agreed upon protocols between vets at the practice were the main external drivers. Only the veterinarians that worked in practices in low- or mixed-income neighborhoods perceived cost of therapy to influence antimicrobial decision making. Again, they also found that the veterinarians' preference and experience were the most important internal drivers but did not report further questioning to better understand what specifically led to the development of this preference.

Another study of companion animal veterinary antibiotic decision making in the UK focused on behavioral aspects of prescribing while interviewing 16 veterinarians.[42] In contrast to Mateus et al's study, King and colleagues found that economic concerns played a key role in decision making. Specifically, although clients rarely demanded antibiotics, veterinarians in their study were concerned about maintaining client relationships to sustain their business and perceived that clients believed the cost of diagnostic testing to be too high. Other findings, like the tendency for veterinarians to prescribe "just in case" and prescribing based on habits or experience were similar to the findings of Mateus et al.

Human, Animal, and Environmental ARB

Understanding the barriers and facilitators of antimicrobial stewardship in veterinary medicine is crucial to reduce inappropriate use in that setting. However, reducing the risk of ARB causing infection in both humans and companion animals requires further investigation into how ARB spread through those populations. Spatial and temporal patterns of ARB both in the environment and as a source of disease may provide insight into how location affects risk of ARB infection in both humans and animals. Spatial variation in the background levels of antimicrobial resistance are influenced by a variety of factors, including agricultural runoff, wastewater treatment, and heavy metal concentrations in the soil.[45–48] Resistance of bacteria in river sediments to various antimicrobials are higher in areas used by humans compared to more pristine natural environments.[49] Although many environmental bacteria are non-pathogenic, there is increasing evidence that the environment is a reservoir for ARB and resistance genes that can act as a driver of clinically relevant disease in humans.[50–52] A 2016 Lancet review of the mechanisms and drivers of antimicrobial resistance identified a lack of understanding about how patient location and the built environment affect the transmission of ARB, especially outside the clinic, as a major knowledge gap. [53] In the urban environment, examples of dissemination hotspots for ARB include hospital and pharmaceutical waste, wastewater treatment plants,[54] and areas like dog parks where high concentrations of ARB in fecal samples have been found.[13] These hotspots may be "critical control points," which govern the selection, proliferation, and spread of resistant pathogens.[45] A greater understanding of how antimicrobial resistance transmission between human beings, animals, and the environment occurs in space and time is needed.[53,55]

In addition to environmental factors, animals can directly transmit microbial disease and contaminate the environment with ARB. Livestock and aquaculture industries[56,57] are sources of ARB, although their contribution to the emergence of clinically important pathogens is controversial.[58] Studies have identified a greater risk of carriage of various ARB in poultry workers than non-workers[59], increased macrolide resistance in the fecal microbiota of farmers who worked

with swine than non-farmers,[60] and that the level of animal contact and number of MRSA positive animals were associated with MRSA carriage in humans working on veal calf farms.[61] Case-control studies have concluded that living near swine operations[62] and livestock dense regions[63] are risk factors for MRSA carriage and livestock-associated MRSA respectively. While these studies were small scale and suffered from various biases[64], they provide some preliminary evidence that ARB in animals may affect humans living in close proximity. Whether or not a similar relationship exists between ARB in humans and their pets remains to be seen.

Children may serve as a particularly good population to study how ARB spread in a community, including environmental exposure and exposure to pets. Children and young children (<5 years of age) in particular are more likely than older individuals to participate in poor hygiene behaviors like not washing their hands when appropriate or allowing themselves to be licked on the face by dogs.[65] By studying the risk of ARB in children and pets, while tracking the environments in which the infections occur, we can better understand how ARB spread through humans, animals, and the environment.

Carbapenem-Resistant Enterobacteriaceae (CRE) and Companion Animals

While understanding antibiotic use decisions and the dynamics of community spread may help slow the spread of ARB, outbreaks of ARB already impact veterinary medicine. The ability to identify sources of transmission during outbreak is essential. In July 2018, a strain of *Escherichia coli*, that was subsequently shown to contain a blaNDM-5 gene, was isolated from a dog being treated at a tertiary veterinary hospital in Pennsylvania.[66] This isolate belonged to sequence type 167 (ST167) and contained additional antimicrobial resistance genes.[66] A retrospective review of hospital records documented an initial outbreak between July 11–August 3, 2018. In the study, seven CR-E. coli isolates were obtained from six affected animals .[67]

Reducing the spread of CRE is vital for both animal and human health. CRE are resistant to most antibiotic classes, including carbapenems. Due to this, the Centers for Disease

Control and Prevention (CDC) identify CRE as a public health threat. The CDC defines CRE as Enterobacteriaceae that are resistant to at least one of the carbapenem antibiotics.[68] Many produce carbapenemases, enzymes which inactivate not only carbapenems but other beta-lactam antibiotics. The most common carbapenemase is the *Klebsiella pneumoniae* carbapenemase (KPC). Other carbapenemases, including New Delhi Metallo-beta-lactamase (NDM), the type identified at the veterinary hospital, have historically been less common within the US. [68] Their spread is particularly concerning because they are resistant to newer antibiotics that were effective against KPC producing CRE.[68]

CRE have emerged as an important cause of human healthcare associated infections (HAI) and have become a major clinical and public health problem.[69] Control of infections caused by CRE in human health care-settings can be a challenge because the organisms colonize the gastrointestinal tract and can go undetected.[70] In human medicine, risk factors for CRE include admission to the ICU, mechanical ventilation, presence of indwelling devices, receipt of immunosuppressors, and prior antimicrobial exposure. [71–74] CRE are predominantly believed to be spread via healthcare worker's contaminated hands[75], although endoscopes have also been documented as a source of human transmission.[76] Human healthcare settings have mitigated the risks of CRE acquisition through patient isolation, contact colonization screening, bathing infected patients daily with chlorhexidine, limiting the use of invasive devices, shortening the duration of mechanical ventilation, improving environmental cleaning, improving hand hygiene rates and antibiotic stewardship.[77,78]

Reports of CRE in companion animals have been sporadic but have been documented around the world. In 2013, researchers in the US reported identification of NDM-1 encoding gene from 6 unrelated clinical *E. coli* isolates collected from dogs and cats in five states between 2008 and 2009.[17] A screening study in Germany identified six dogs from a single veterinary clinic with *E. coli* (n=3) or *Klebsiella pneumoniae* (n=5) isolates harboring the OXA-48 carbapenemase over a five month period.[18] As all dogs had been housed either in the intensive care unit or with another case, researchers concluded that transmission within the hospital was likely. Between

2015 and 2019, reports of individual or small numbers of companion animals with CRE have also been reported in Africa,[19] Asia,[23] Europe,[24] and again in a tertiary veterinary hospital in the US.[22] In 2018, a study from Finland reported confirmed case of transmission between dogs and humans after identifying NDM-5 *E. coli* from two dogs and one human residing in the same household.[21] While the direction of transmission (human to animal or animal to human) is not clear, many authors of these reports hypothesize that these cases spread primarily from humans to animals due to the larger CRE burden in humans, close genetic relationship between companion animal and human isolates, and the wider use of carbapenems in human medicine.[18,20,21,24]

In the US, the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 allows for "extralabel use" of carbapenems in companion animal medicine.[79] Data on the use of carbapenems in companion animal veterinary medicine are limited, but available data indicate low levels of use. A report from the Cummings School of Veterinary Medicine in Massachusetts identified 1 prescription of imipenem out of 435 encounters targeting infectious disease randomly sampled between 2008, and 2009.[35] In a report comparing opinions of veterinarians at the North Carolina State University veterinary teaching hospital to actual antibiotic use, carbapenems were prescribed for 2.3 cases per 1000 small animal patients between 2012 and 2014.[37] Although different use indicators make direct comparisons difficult, use of carbapenems in inpatients in hospitals across the US is estimated to be approximately 28 days of therapy per 1000 patient days,[80] which likely indicates wider carbapenem use in human than veterinary medicine.

Regardless of the source for CRE in companion animals, reducing its spread is important for both veterinary and public health. Therapeutic options for CRE infections are limited[68] in all patients, including animals. Although CRE are suspected to be predominantly transmitted from humans to animals,[21] companion animals have the potential to serve as reservoirs for CRE in the community.[81] Restricting the emergence and spread of CRE between companion animals is vital to limit the potential transfer of CRE between companion animals and humans. Identifying risk

factors for in hospital transmission will allow for better containment of future outbreaks, reducing CRE spread in companion animals, and protecting human health.

Overview of Included Studies:

Large knowledge gaps still exist around antibiotic use and antibiotic resistance in veterinary medicine and how it relates to public health.

Study 1 of this dissertation examined what influences the antimicrobial use and prescribing decision-making of companion animal veterinarians. A robust qualitative methodology was used to address gaps in knowledge left by previous limited studies of companion animal veterinarians. Most existing studies focus on European veterinarians trained under different education systems in societies where attitudes and policies about antimicrobial resistance reflect a greater public concern over antibiotic use than in the US. Similar to human physicians,[82] veterinarians practicing in different countries face differences in the factors that influence their prescribing decisions due to cultural, contextual, and behavioral differences.

The qualitative methodology used in Study 1 allowed us to uncover and more deeply probe new perceptions and influences on antibiotic use that emerged from our interviews, instead of rigidly adhering to a set of predetermined criteria. Prior studies suggest that there is a complex relationship between economic factors and antibiotic use in veterinary medicine. One study of companion animal veterinarians in the UK suggests that this relationship may be further modified by the socioeconomic status of the clients they serve. [41] For this reason, we were also interested in understanding how the decisions that companion animal veterinarians make concerning antibiotics are affected by the demographics of the clients they serve.

Study 2 of this dissertation examined the spatiotemporal relationship between ARBs infecting animals and children residing in the Philadelphia metropolitan area (PMA). Most studies that have investigated the transmission of ARB between humans and pets have been small studies that largely, though not completely,[11,12,83] ignore the influence of the environment or spatial location on ARB acquisition. To better understand the relationships between ARB in

people and pets and design interventions to improve public health, larger studies, and studies that consider environmental variation, are needed. Using AST results and patient residential address found in electronic medical records, hotspots of antimicrobial resistance among children in the greater Philadelphia region were mapped to uncover how residential location affects risk of ARB infection. The same method was applied to canine records, and spatiotemporal patterns of veterinary and human ARB was modeled using Generalized Additive Models to determine whether or not a relationship existed. Other studies have used spatiotemporal methods to compare animal and human disease.[84–86] This study was the first, to our knowledge, to do so for companion animal antimicrobial resistance. The findings from this study provide insight into the intersection of animal and human health in their shared environments relating to antibiotic resistance.

Study 3 of this dissertation investigated an outbreak of CRE in companion animals at the Veterinary Hospital of the University of Pennsylvania (VHUP). Between July 2018 and June 2019, 15 patients were identified as part of the first documented companion animal blaNDM-5 E. coli outbreak in the US. Unlike other reports[18] of outbreaks of NDM-5 in companion animals from a single veterinary hospital, the number of patients and access to hospitalization and microbiology reports provided data to identify modifiable risk factors for in-hospital transmission of CRE. VHUP partnered with the Philadelphia Department of Public Health to determine potential sources of in-hospital transmission, review infectious disease related protocols and procedures, and reduce the potential for both animal to animal and animal to human spread. As part of this outbreak investigation, a case control study was conducted. Each case was matched 1:2 to controls by length of hospitalization and species. Three main categories of exposure, exposure to services within the hospital, exposure to procedures thought to potentially be associated with CRE transmission, and exposure to medications including antibiotics that might put patients at risk, were assessed, and relevant findings from the review of infectious disease protocols were reported. This study adds to the sparse literature on CRE in companion animals and identifies

precautions veterinary hospitals can take to reduce CRE transmission between animals, reducing the potential of animal to human CRE transmission.

Location for all Studies, the Philadelphia Metropolitan Area

The Philadelphia Metropolitan Area (PMA) and the University of Pennsylvania offer a unique opportunity to examine veterinarians' perceptions of antimicrobial use, the spatial relationship between antimicrobial resistance in children and dogs, and risk factors for the acquisition of CRE in companion animals. The region includes urban, sub-urban and rural areas allowing for variation in clients served for the respondents in Study 1 and variation in population density in Study 2. Veterinarians working in diverse institutions including animal shelters, low cost clinics, general practice clinics, and specialty hospitals are in PMA, providing the opportunity to investigate veterinary perspectives on antibiotic use in a variety of settings. Multiple large medical hospitals, including the Children's Hospital of Philadelphia (CHOP), are located within a few blocks of the Veterinary Hospital of the University of Pennsylvania (VHUP), allowing for the comparison of pediatric and veterinary patients living in overlapping regions for Study 2. In addition to the main hospital, the CHOP network also includes primary care practices serving children living throughout the PMA. The physical locations and shared university affiliation of the veterinary and human hospitals provide a rare opportunity to connect veterinary and human medical data to gain a deeper understanding of antimicrobial resistance. VHUP sees over 30,000 companion animal patients annually and has an in-house microbiology lab, providing critical data on antimicrobial resistance for Studies 2 and 3. Collaboration between VHUP and the Philadelphia Public Health Department facilitated the outbreak investigation used for Study 3. The interconnectivity and willingness to collaborate between researchers across the PMA in veterinary medicine, human health, sociology, and public health was essential to this dissertation.

Study Data

For Study 1, in-depth, semi-structured interviews were conducted between March 2018 and April 2019 with companion-animal veterinarians working in the greater Philadelphia Metropolitan Area. Participants were chosen using a purposeful sampling approach,[87] in which veterinarians with a variable number of years in practice, working in different types of practices (e,g. general practice, specialty, animal shelter), and serving clients of varying socioeconomic status were recruited to ensure different practice contexts were included in our analysis. Interview participants were recruited through emails to individual veterinarians, list-servs and social media, in-person at continuing education events, and referrals from colleagues.

For Study 2, Electronic Health Record (EHR)-derived data were obtained from a pediatric care network including the CHOP tertiary care hospital and primary care practices located across the PMA. Patient level data extracted from the EHR included race (patient reported), gender, age, insurance type and geocoded residential addresses. Visit level data included visit date and visit type (office visit vs hospital encounter), encounter and "problem list" ICD-9/10 (*International Classification of Diseases*) codes. Information on hospitalization, chronic medical conditions, and antibiotic use were also collected for the 90 days prior to the date of culture.

Hospital records data of dogs encountered by VHUP were obtained from Hospital Information System (HIS). HIS was not a full EHR, but included patient demographic data (sex, age, breed), dates of admission, discharge, and procedures completed, residential location, and codes for procedures and medications used primarily for billing and record-keeping. A codebook was developed to identify all procedure codes from HIS indicating antibiotic use. These codes were further classified by class of antibiotic. Additional codes were created to identify patients receiving bacterial culture and antimicrobial susceptibility testing.

Inclusion criteria for children and dogs included receipt of an antimicrobial susceptibility test (AST) indicating *Escherichia coli* between January 1, 2013 and December 31, 2017. To reduce the effect of healthcare associated infections, only cultures taken during outpatient visits

or within the first 48 hours of hospitalization qualified for inclusion. Children also were required to be <18 years of age at the time of culture. Only the first qualifying culture per patient (whether child or dog) was included in the analysis.

Table 1.1 Variables to be derived from patient medical records

Humans	Dogs
Age	Age
Sex	Sex
Race	Breed
Ethnicity	Location
Location	Admission date
Admission date	Admission type
Admission type	Health care-associated infection
Insurance type	Antibiotic use: any (y/n)
Health care-associated infection	Antibiotic use: specific class (y/n)
Antibiotic use: any (y/n)	
Antibiotic use: specific class (y/n)	

For **Study 3**, VHUP data from HIS along with data from bacteria culture and antimicrobial susceptibility testing was used. The data exported from HIS included hospitalization information such as dates of admission and discharge, services utilized and codes for procedures and medications utilized with associated dates. Procedure codes in the dataset were grouped into categories based on type of procedure (ex: endotracheal intubation, catheterization) and medications received (ex: glucocorticoids, antibiotics). Results of testing from the in-house clinical microbiology laboratory were added to this dataset to assign case status.

A case was defined based on the criteria of the PDPH. Any animal patient from which a CRE was recovered between July 1, 2018 and June 30, 2019 was included. Only the first positive culture was used for statistical analysis. Controls consisted of patients who underwent bacterial

culture testing in the same time period and did not test positive for CRE. In order to control for length of exposure to hospitalization, each case was matched to two controls by number of days of hospitalization prior to culture. Cases were also matched on species.

Goals of the Dissertation

Detailed rationale, methods, and results of these three studies are included in Chapters 2-4. These studies fill gaps in companion animal veterinary literature on antibiotic decision making, how residential location affects ARB risk in children and dogs, and risk factors for hospital acquisition of CRE in companion animals. The results will be useful to veterinary professionals, policy makers, and other stakeholders interested in the ways in which companion animal medicine is relevant to public health.

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CHAPTER 2: Money Matters: How Companion Animal Veterinarians Perceive the Impact of Finances on Antibiotic Decision Making

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Abstract

Background: The overuse and misuse of antibiotics is a persistent problem in both human and veterinary medicine. While research has shown that complex social and behavioral factors drive inappropriate use in human medicine, less is known about these factors in companion animal medicine.

Objective: The objective of this study was to identify the perceptions that veterinarians practicing companion animal medicine hold about the drivers of antibiotic use.

Methods: Semi-structured qualitative interviews were conducted with veterinarians practicing companion animal medicine in a major metropolitan area in the Eastern United States (US). Respondents were sampled purposefully, and data were analyzed using a grounded theory approach.

Results: Interviews were conducted with 36 veterinarians from 19 practices. Veterinarians believed that their clients' willingness to pay for diagnostic testing or treatment interfered with their ability to make appropriate decisions about antibiotic use. Veterinarians who described their clients as predominantly lower income were more likely to withhold recommendations for costly diagnostic testing than those who described their client base as middle income or affluent. Concerns over antibiotic expiration and subsequent financial losses limited which antibiotics veterinarians stocked. Some veterinarians feared that restricting antibiotic use to appropriate uses could harm their business and lead to economic euthanasia of their patients.

Conclusions: Veterinarians perceive that financial factors are often key barriers to their ability to appropriately prescribe antibiotics. Interventions that address the financial aspects of prescribing have the potential to improve antibiotic decision-making in veterinary medicine.

Introduction

Inappropriate antibiotic prescribing is a persistent problem in human[1] and veterinary medicine[2–4] and is a major driver of antimicrobial-resistant (AMR) bacterial infections.[5] AMR bacterial infections cause over 35,000 human deaths in the United States per year.[6] Some AMR bacteria can pass between humans and pets. [7–9] To prevent the spread of AMR bacteria in general and between humans and pets, it is vital that antibiotic use be improved in both human and veterinary medicine. There is a paucity of research on antibiotic decision-making among veterinarians who treat companion animals such as dogs and cats. This knowledge could be used to create antibiotic stewardship programs targeted specifically at companion animal veterinarians.

Complex social and behavioral processes underlie antibiotic prescribing.[10–12] The dynamics of the relationship between the prescriber and the patient, seniority of the prescriber relative to their colleagues, and the time pressures prescribers experience within their work environments have been shown to affect prescribing decisions in human medicine.[13] In veterinary medicine, identified factors impacting antibiotic use decisions include the results of diagnostic testing, veterinary experience, client pressures, and the cost of diagnostic testing.[2–4,14,15] How these barriers function within the social and behavioral context of veterinary practice remains poorly understood. Most of the few studies on the social and behavioral influences on veterinary prescribing have taken place in Europe.[11,16,17] where training and antibiotic stewardship policies differ markedly from those in the US. Research conducted in the US and has focused primarily on the livestock industry.[18] Given the differences between food animal and companion animal veterinary medicine (particularly the population vs individual health focus), these existing studies are unlikely to represent the majority of US private-practice veterinarians — approximately 75%[19] — who work primarily with companion animals.

The goals of the qualitative study were to use a constructivist grounded theory approach to investigate how companion animal veterinarians perceived the factors that shape their antibiotic prescribing decisions. [20,21] In-depth interviews were conducted with companion animal

veterinarians, focused broadly on their experiences making decisions about antibiotic use in daily practice. In this report, we focus on the causes and consequences of financial barriers to appropriate antibiotic use in companion animal practice.

Methods

Study Design, Setting, and Participants

In-depth, semi-structured interviews were conducted between March 2018 and April 2019 with companion animal veterinarians working in the greater Philadelphia Metropolitan Area. Participants were chosen using a purposeful sampling approach,[22] in which veterinarians with a variable number of years in practice, working in different types of practices (i.e. general practice, specialty, animal shelter), and serving clients of variable socioeconomic status were recruited**.** The study was led by an investigator with a background in veterinary medicine (S.H.L.) in collaboration with a medical sociologist with extensive qualitative research experience (J.E.S.).

To recruit participants, we emailed individual veterinarians, used list-servs and social media, recruited veterinarians in person at continuing education events, and asked interview respondents to refer colleagues. Consent for the interview and audio recording was given verbally, as the only link between the respondent and the study would be the consent document, and the primary risk was a breach of confidentiality. The study protocol, interview guide, and consent processes were approved by the University of Pennsylvania Institutional Review Board.

Data Collection

A semi-structured interview guide was created prior to data collection. Pilot testing of the interview guide was conducted with two veterinary specialists and two general practitioners. Feedback was solicited around question comprehension, language used, and length, and the guide edited accordingly.[23] Interview questions were designed to elicit veterinarians' perceptions of antibiotic use and antibiotic resistance in companion animal medicine. Semi-structured interview methodology is intended to identify how research participants perceive the phenomenon

under study and describe it in their own terms.[24] Consistent with this approach, the interview guide did not define for respondents "appropriate" antibiotic use. As such, “appropriate” use in this study is defined by what the responding veterinarian believed they should prescribe under ideal conditions.

All interviews were conducted in person, typically in an empty examination room. All interviews were audio-recorded with permission, except one in which the respondent did not consent to audio recording and the interviewer took notes by hand. One author (S.H.L) conducted all interviews. Each respondent was asked the same set of general open-ended questions from the interview guide, with the interviewer asking follow up probing questions to elicit more depth, detail, and clarification when necessary.[23] The interviewer kept an analytic memo throughout the course of the study to capture emergent themes, notes on the adequacy of the interview guide, and her impressions of the interview. The research team monitored for thematic saturation to determine sample size adequacy via the use of these memos, a saturation matrix, and general discussion.[25]

Data Analysis

Audio files were professionally transcribed and uploaded into NVivo 12 for data management and coding. Interviews were coded by two authors (S.H.L. and S.L.) with experience in veterinary medicine and training in qualitative data analysis. A constructivist grounded theory approach was used. In brief, the two coders reviewed the interview transcripts in a process of initial coding where emergent themes were identified, noted, and defined in a codebook. In the second stage of focused coding, the coders reviewed all interview transcripts line by line to apply the codebook to the data. During focused coding, a portion (13/36) of the interviews, selected to include respondents from a variety of practice types, were double-coded. Intercoder reliability was evaluated using the coding comparison feature in NVivo12 to ensure consistent application of the codebook. The coders frequently met with each other and the study team to discuss code definition, emergent themes not captured in the codebook, and

disagreements - which were resolved by consensus. In the third phase of theoretical coding, S.H.L and J.E.S. performed more advanced analyses on the financial codes to create a conceptual framework.

Results

A total of 36 veterinarians employed in 19 practices were interviewed. Interviews ranged in length from 20-105 min (mean: 53 min). Respondents varied in gender, years of experience, practice setting, and perception of the socioeconomic status of their clientele (Table 1). Results are grouped into three main findings that describe how our respondents perceived the influence of financial factors on antibiotic decision-making. As is consistent with grounded-theory methodology, in which the goal is to achieve a nuanced understanding of a phenomenon rather than the distribution of themes in a population, we do not present counts of concepts.[26]

Table 2.1: Characteristics of Study Sample

Characteristic		**No. (%) of Participants N=36**
Gender		
	Female	26 (72)
	Male	10 (28)
Years of Practice		
	<6	14 (39)
	6-20	10 (28)
	>20	12 (33)
Primary Work Setting		
	General Practice	22 (61)
	Shelter Medicine	7 (19)
	Other Specialty	7 (19)
Reported SES of Client Base		
	High Income	14 (39)
	Mixed Income	9 (25)
	Low Income	6 (17)
	Shelter Medicine (Primarily Unowned Animals)	7 (19)

Table 2.2: Themes Identified

Theme	Illustrative Quotations
Client willingness to pay for diagnostic testing or treatment interferes with veterinarians' ability to make optimal decisions about antibiotic use	(1) "A lot of times I can't get a skin impression approved. Like, for some perspective, it's about $55 here for a skin impression. I'm not sure how that compares with other practices in the area. Sometimes that's a barrier, to get that approved. So, I'll typically go first for a cephalosporin first if there is a pretty bad pyoderma there. If that is not working...okay, if that's not working, yeah, then I'm pushing for a culture. A lot of the time, that's not an option." –*General Practitioner* (2) "I did not feel prepared coming out at all because school focuses a lot on having actual...knowing exactly what microbe you have and you do not have that in practice or shelter. And that's why here, we're focused around empiric first choices because our clientele don't have the money to do diagnostics, let alone culture and sensitivity. We're certainly not doing that in the shelter." –*Shelter Veterinarian* (3)"So he came back in. Dog's got a 107 temp, snot pouring out of it's face, and it won't eat. I looked at him and said, "I need x-rays on your dog." This was a circumstance where I didn't offer an estimate. In my opinion, he didn't have a choice. So the entire right middle lung lobe was completely consolidated with just sludge. It was a Saturday, and I said, "Here's your estimate for transtracheal wash. You can pick him up at 3:00." It was for like over $1,000. "Oh my god, I just need antibiotics." "Antibiotics are not working." "He needs antibiotics." "I do not know which one to use. I need more information." "–*General Practitioner* (4)"So our lab, the culture is a $104, and that is less expensive than a recheck exam to come into the office to see me, and I use that to...I say to people, "It is cheaper for you to just do the culture upfront, make sure we're choosing the right drug than for me to pull one out of thin air, fail, and then you have to come back to get the culture taken and pay another office visit. So let's save you a $117, which is the recheck office fee. And just culture right now, $104 bucks. We're done, hopefully. If the bug is susceptible to something safe and easy, then we win." " –*Specialist* (5)"Or, if you constantly get recurrent true urinary tract infections, like if you drop off urine and I'm still seeing bacteria, I might need to do a culture. And the culture is gonna be 120 bucks. Not doing it right now. Just so you know. Right? And I feel like if they hear it, and then it happens later, it is an easier pill to swallow. If they never hear it, and now you're saying, "I wanna spend 250 bucks," it's very much more difficult for them. "–*General Practitioner* (6)"We actually have more people who have insurance for their pets than I encountered previously at [a corporate hospital], which was kind of surprising to me because pet insurance is a completely different model from human insurance

	and it's been nice because it's been so liberating to be able to treat patients and have people go, "It's fine. Just do anything you need to."" –*General Practitioner* (7)"So most of the time, most practices I've worked for, depending on the test, most places will double or triple the cost of the lab because you have to think about, you have to get the sample. Like some people charge for like for urine test, they also charge for collecting the samples, cystocentesis, things like that. I tend to be kind of a sucker. I tend not, I don't wanna over, and not to overcharge people, you know what I mean? Like I try to make things reasonable because I think the tests are important." –*General Practitioner* (8)"So in relation to the cost, I think veterinarians, we are often afraid or feel bad asking clients to pay for certain procedures or tests, which in a way we should not. If you look at...if you walk into human doctors, I mean, you probably walk out with a $20 co-pay but if you look at your insurance fee that is outrageous for...No, it's not. I should say that it is much higher cost than what clients will pay at our visit. So in that sense maybe I shouldn't feel bad charging that price for culture sensitivity. So in a way things do...so if it's cheaper I may do more, but even if it's not cheaper, if I really change how I feel, I may do more culture sensitivity and then prescribe appropriate antibiotics." –*General Practitioner* (9)"Biggest barrier is cost. So, if I have something that is 140 pounds, and Irish Wolfhound that I cultured, pick a fluid, pick something, right, and it needs [marbofloxacin]. Cooka-freaking-ching. Right? It's not gonna...how... Right? And now I have to say, "I can fix this, but you are going to spend 200 bucks a week, for three weeks." You know? And I'm looking at someone who's tearing up, who doesn't have it. Like, and they will flat-out say, "I can't do it." And, you know, what do you say? "–*General Practitioner* (10)"I've learned to not judge. You know, I have the clients who come in looking like absolute white trash and look like they you know, would not spend 10 bucks on their animal and I'm worried. You know, if you just glanced at them, you'd be worried that they'd even be able to pay for the exam fee and they're the ones that you know will pay for that $200 of [enrofloxacin] without batting an eye. And so, I you know, really try not to judge, I try to you know, every single person, here's my top choice, here's what it's going to be. And then I also have the people who drive in in the super fancy cars, wearing the really fancy watch and carrying the expensive purse and they don't want to spend 20 bucks on their animal." –*General Practitioner* (11)"I try to give them a gold standard every time. I give them... I typically I'm the type of person that gives them option A, B, and C, and I say option A is gonna carry your best prognosis, gold standard, no question, this is what I do for my own pet. Doc, that's too much, all right, let's talk about B, and C. You know, what can we do? What's your budget today you know? What are you willing to do? Let's see if we can make it work. " –*General Practitioner*

	(12) “We don't like to use "gold standard of care," like that terminology is not really in vogue right now in our field, but that idea of, that best practices, everything that people would do, all the way down to like, you have literally no money. You have to stopgap to decide what's going on. And the goal is to use evidence-based decision-making and cost-benefit analysis to make a decision that is based in literature and decision-making, and not just because somebody else does it that way. So when we try to encourage good decision-making, that's kind of how we frame it.” –*Shelter Veterinarian* (13)“I will take that choice away from the client and find something else because they're gonna look at me and they're not gonna trust any treatment recommendations I make. All right? Because if I hand them for an antibiotic a $400 estimate, they're not gonna trust...they're not gonna come back to me, number one. Number two, they're not gonna trust the other recommendations I'm making, it's gonna create a huge barrier, so sometimes I make that decision depending on my interaction with them and choice.” –*General Practitioner*
Antibiotic selection is limited by fear of expiration and financial losses	(14) “As a practice owner I try to stock, you know, as small number of antibiotics as possible. If I don't do it, they expire. I lose money. So, you know, I always have to be conscious of when things expire, how much I used.” –*General Practitioner* (15) “You know, like amoxiclav, like, generic or brand name is so expensive. So, like, in my other practice, we have human, like, amoxiclav, because it's way more cost-effective. Similarly, that's why we don't carry [it] for dogs here, because it's so expensive, and you have to buy it in these big cartons, and if you don't go through it fast enough, it expires, and then you've lost money.” –*Shelter Veterinarian* (16) “The owner comes in and they wanna leave with the medication and they wanna be done with it. So, in most cases, I'm sure someone's gonna be like, "Can't you just give me something here?" I'm gonna try to [write an antibiotic prescription] but it takes me remembering it, it takes more time because I've got to go get a script and I have to do it rather than being like, "Okay, nurse, you've got it. Go get the meds and get them out of here," kind of a thing. So it's just a lot more effort and I'm not even sure that the owner's gonna, like, care.” –*General Practitioner* (17)“I can call amoxicillin in to a local pharmacy and it's often on, like, the $4 script list, and that is something that I will often do, especially in my wellness clinic days where I'm working with a low-cost, mainly, population and they're struggling to, you know, they want to do what's right, but need to be able to keep finances in mind. You know, calling in medications like amoxicillin, really cheap, $4 list. Great, awesome, let's do that. Same thing for TMS.” –*Shelter Veterinarian* (18)“We don't really use [enrofloxacin] that often. Number one, it's expensive, even the generic. And we don't carry the tablets for dogs. We will use ciprofloxacin in kind of in place of [enrofloxacin], which is not...of course, we know it's not as good, but it still does work for a lot of animals.” --*Shelter Veterinarian*

	(19)“Shelter medicine is very protocol-driven, and we kinda defer to, like, the academic institutions that run these shelter programs to kinda tell us, "These are the best antibiotics that you should be using and know your limitations. Know what you can treat in-house. Don't get yourself into a position where you're treating multiple drug-resistant anything," that those need to be handled in private practice because all the reasons why we might not do a culture and sensitivity because of money, because of time. Most places don't have even the equipment to run it, and there are so many other animals to think about.” –*Shelter Veterinarian*
Restricting antibiotic use to “appropriate use” carries financial risks	(20)“And I find, unless they have had this before and no one has either offered or done that diagnostic, they almost always say, "Yes" [to the test]. If they are a client who sees their GP and their GP is like... And they are like, "Well, all our other dogs this happened to, they just put them on the antibiotic and they're fine," then you usually don't get to do it. But if they haven't had that past experience, almost everyone will say, "Well, yeah, that makes sense. We should find out what it is and make sure we're treating it." And that's it. That's been my experience really.” –*Specialist* (21)“They'll be unhappy and then they'll go somewhere else and after about the fifth day, the next veterinarian will give them an antibiotic and the cat will get better because it was gonna get better anyway, but they think it's the antibiotic. So, it's kind of what's out there and then you don't wanna lose a client over digging your feet in and just saying, "No, you can't have it," because they get upset when the cat is not feeling well. And previously I used to think, "Well, it's not gonna hurt." Now we know it does, but I still do it.” –*General Practitioner* (22) “[The client] said, "I need doxycycline." "I'm not giving you doxycycline. I'm not giving you doxycycline without chest x-rays." So he left. He said, "Fine." Wrote a bad review. [My colleague] got trash-talked on Yelp, because social media now, people are... I have found clients are... Veterinarians are more likely to give clients what they want now so they don't get their name bashed on the internet.” –*General Practitioner* (23)“So, like, when something would go wrong and people would be angry and they wanted accountability for it, it would be, "Who has a license?" And that's me as the only person there who had a license. So there's a lot of times that I had, you know, issues, where I felt like that license was under scrutiny and stuff like that for bad things that happened. And, you know, I'm paying my student loans every month and, you know, I have $300,000 worth of debt that I have to pay back, and my means of paying that back is my license.” –*Shelter Veterinarian* (24) “Sometimes I'm like, "Well, would I rather have you pay for the culture and then not be able to afford your antibiotics, or would I rather give you empiric antibiotics and, you know, at least try something?” –*General Practitioner*

	(25)“It was appropriate, per guidelines, to not put it on[antibiotics], but again, maybe if we're wrong and the dog does progress to pneumonia, and they can't afford $3000 of hospitalization and treatment, that dog is dead. So I would rather just throw a week of doxy at it, whether it needed it or not, in the hopes that if it did, then it doesn't have to come back and die.” –*Specialist*

Finding 1: Client willingness to pay for diagnostic testing or treatment interferes with the ability of veterinarians to make appropriate antibiotic use decisions.

All veterinarians interviewed, including those that served mostly affluent clients, described taking measures to address concerns regarding the cost of diagnostic testing and patient treatment using antibiotics. Many of these measures centered on the ability of the veterinarian to convince the client to pay for an expensive diagnostic test or treatment. Veterinarians across all practice types reported that they often could not use diagnostic tests that would help them make appropriate antibiotic use decisions because clients refused to pay (Table 2, quotation 1). This issue was exacerbated in low-cost clinics or shelter environments where finances were further restricted (quotation 2).

Respondents described negotiations between themselves and clients where they would attempt to "sell" and persuade clients to "buy into" specific diagnostic tests and treatments. After multiple rounds of empiric antibiotic therapy, some veterinarians would refuse further treatment unless clients agreed to diagnostic testing (quotation 3). Respondents described using logical arguments to convince their clients of the cost-effectiveness of diagnostic tests (quotation 4). Some would spread out diagnostic tests and treatments over multiple appointments because this allowed them to give clients price estimates for their next visit so that they could prepare for the cost (quotation 5). Multiple specialists noted that clients were more likely to pay based on the recommendations of a specialist compared to those of a general practitioner.

Some veterinarians described measures taken at the practice level to improve their ability to perform diagnostic tests and improve antibiotic prescribing. Respondents from one practice, described as having an affluent or mixed-income client base, advocated heavily for pet insurance. At this practice, every examination room included a display recommending insurance plans, and veterinarians were encouraged to discuss pet insurance with each new client. Veterinarians at multiple practices felt that pet insurance allowed them to more frequently use diagnostic tests before prescribing antibiotics and alleviated the emotional labor of persuading clients to pay (quotation 6). Veterinarians also employed other strategies at the practice level to increase the

use of diagnostic testing to guide antibiotic prescribing. One specialist recounted her successful efforts advocating for a switch to a lower cost diagnostic testing laboratory which significantly reduced the cost of culture and sensitivity testing. She attributed the lower cost to an increase in the number of cultures performed at the practice. Other respondents in general and specialty practices described that their practices reduced the mark-up rate of some diagnostic testing — i.e. reducing their profit for those services — so that they could use these tests more often prior to prescribing an antibiotic (quotation 7).

Respondents largely expressed discomfort over making costly medical recommendations (quotation 8). Many empathized with their client's financial difficulties when costs of care were high (quotation 9). Given how often cost concerns occurred and the stress of negotiating treatment plans that were largely declined, many veterinarians described struggling with what level of care to offer clients. Veterinarians described being unable to determine a client's ability to pay by their appearance (quotation 10). This sentiment was reiterated across practice types, from those serving mostly affluent clients to low-income clinics.

Veterinarians responded to this discomfort and uncertainty around expensive diagnostic tests and antibiotic treatments in two distinct ways. Some veterinarians offered what they viewed as the "gold standard" every time (quotation 11), either alone or as one of multiple options. Other veterinarians discussed making a judgement about what costs would be too much for clients of their practice and limited what diagnostic tests or treatments they would offer accordingly. Some veterinarians described limiting what they offered clients a way of allocating limited financial resources (quotation 12). Others did not present certain diagnostic tests or treatments due to repeatedly "being shot down" when offering services to clients or because they believed offering an expensive estimate would break the clients' trust in their medical recommendations (quotation 13). Among veterinarians who reported that their client base was affluent or mixed-income, the "gold standard" strategy was more common, and among those serving low-income clients or working in animal shelters, offering recommendations based on their client base's perceived financial limits was more common.

Finding 2: Antibiotic selection is limited by fear of expiration and the resulting financial losses.

Most veterinarians in our study both prescribed and dispensed antibiotics at their practice. General-practice owners and veterinarians working in corporate-owned hospitals described stocking their in-practice pharmacies with as few antibiotics as was feasible out of concerns that stocking a multitude of antibiotics would lead to drug expiration and financial losses (quotation 14). Across all practice types, respondents discussed "price shopping" for antibiotics. Suppliers, formulations, and even pill sizes were considered when deciding which drugs were most cost-effective. Some specifically ordered human generic drugs because of reduced costs and the ability to buy in smaller quantities (quotation 15).

When the antibiotic a veterinarian determined was most appropriate was not stocked in their own pharmacy, some veterinarians described prescribing from what was in stock, even if that meant using second-line choices, while others wrote prescriptions to be filled at human pharmacies. Some respondents working in general practice described writing prescriptions to human pharmacies as a last resort because of time pressures and client expectations of leaving with antibiotics in-hand (quotation 16). Other respondents, particularly those working at animal-shelter community clinics aimed at serving low income clients, described liberally writing prescriptions to be filled at human pharmacies, unable to beat the costs of drugs on "the $4 script list" (quotation 17). Respondents also described replacing the more expensive veterinary drug enrofloxacin with the human antibiotic ciprofloxacin, especially in larger patients. Most of these veterinarians admitted that ciprofloxacin was not as effective as enrofloxacin (quotation 18) but felt it was their only option due to enrofloxacin's price.

Although shelter veterinarians also described the risk of antibiotic expiration as a reason to keep fewer antibiotics in stock, they largely chose to stock antibiotics they perceived as first-tier empiric choices (i.e. used in the absence of diagnostic testing) and to limit the conditions they would treat. Shelter veterinarians relied heavily on formal protocols to guide prescribing using a limited set of antibiotics (quotation 19). If animals at one large shelter could not be treated with

those antimicrobials, they would be prioritized for transfer to an animal rescue where they could receive more in-depth care. Although the capacity for care varied across shelters, many described having such a high number of animals per veterinarian on staff that examining every animal directly, let alone conducting diagnostic testing on individual animals, would not be financially feasible. Respondents described the protocols as standardizing treatment among multiple veterinary staff, ensuring that antibiotic choices were evidence-based, and allowing other shelter staff to treat animals and reduce the spread of disease when the shelter veterinarian was not available.

Finding 3: Restricting antibiotic use to "appropriate use" carries financial risks.

Veterinarians across all practice types perceived multiple risks related to antibiotic use and stewardship. Many of these centered on financial risks of not deferring to client demands for antibiotics. Some veterinarians perceived that clients who had previously been given antibiotics without diagnostic testing were much more likely to demand antibiotic treatment than others (quotation 20). Some respondents worried that if the demands of clients were not met, they would take their business elsewhere (quotation 21). Others described themselves or their colleagues getting "trash-talked" on review websites and social media by clients who demanded, but did not receive, antibiotics, thereby hurting their reputation and potentially their business (quotation 22). Multiple respondents also described fear of being sued by clients if they did not give into antibiotic demands, even if antibiotics were not medically warranted. Early-career veterinarians were concerned about paying their student loan debt, often hundreds of thousands of dollars (quotation 23), if they lost their licenses due to legal action taken by an unhappy client.

Some veterinarians were concerned that practicing good antibiotic stewardship could lead to economic euthanasia, where euthanasia is elected based primarily on the client's inability to pay. Veterinarians worried that if they pushed cost-constrained clients to pay for diagnostic testing, there would not be funds left to treat the patient (quotation 24). Other veterinarians worried that if they took a "wait and see" approach for suspected viral infections, they would

eventually need to euthanize some patients if their conditions worsened. One veterinarian recalled giving dogs antibiotics for suspected viral respiratory infections, going against the guidelines his practice uses, because he believed owners would not be able to pay for the treatment necessary to save their dogs' lives if he was wrong (quotation 25).

Discussion

Through a series of in-depth interviews with a diverse range of companion animal veterinarians, we examined how veterinarians perceived the influence of financial factors on antibiotic prescribing. Regardless of their perception of the economic status of the clients they served, veterinarians saw cost, including the cost of diagnostic testing and of certain antibiotics, as a major barrier to appropriate antibiotic use. Veterinarians discussed how clients' willingness to pay impacted their antibiotic decision-making, how financial factors affect the stocking of antibiotics in the practice pharmacy, and their perspectives on the potential financial risks of appropriate antibiotic use.

Other studies have found that cost is an important factor in veterinary antibiotic decision-making. A survey of European veterinarians found that although economic factors were rated as the least important factor in antibiotic choice, cost of therapy and testing were rated as important barriers to judicious prescribing.[2] Two surveys conducted in the United States found that 65%[3] and 84%[4] of participants reported that the cost of culture and susceptibility testing impeded the use of these tests. Despite veterinarians indicating that culture and susceptibility testing was important for antibiotic selection,[2] it may be used in as few as 12.4%[27] of visits where a highest priority critically important antibiotic is prescribed. Studies using qualitative techniques like those used in this report provide additional insight into how veterinarians address financial problems in antibiotic decision making (advocating for pet insurance, lowering prices, or not offering diagnostic testing) and other aspects of the problem that were not addressed in surveys (how fear of expiration and profit losses impact antibiotic pharmacy stocking decisions).

Qualitative studies of antibiotic decision-making in companion animal veterinary medicine are limited. One study in the United Kingdom,[11] found that only veterinarians working in practices described as located in low- or mixed-income socioeconomic areas perceived cost of therapy to be a barrier. In our study, all veterinarians reported experiencing barriers related to cost. Other studies from Europe found that veterinarians were concerned over financial losses to their practices if they did not give in to client demands for antibiotics[28] and that economic factors including the perception that clients were not willing to pay for diagnostic tests were key barriers to appropriate prescribing.[29] Most of the other findings in our study — such as the range of strategies explicitly aimed at addressing antibiotic-related cost concerns, the financial risks of stocking antibiotics in practice pharmacies, and concerns over economic euthanasia — were not described.

The pervasive presence of financial concerns in our study was striking. Although the interview guide for our study (Appendix) did not include direct questions that asked about the impact of finances on antibiotic use, it emerged as a central theme and was discussed by respondents repeatedly, regardless of practice setting. Various factors may account for the differences in our study compared those outside the US. Similar to human physicians,[30] veterinarians practicing in different countries likely face different barriers to appropriate prescribing due to cultural, contextual, and behavioral differences. European veterinarians are trained under different educational systems, in societies where attitudes and policies about antibiotic resistance may differ from those in the US.[31–33] We also interviewed veterinarians in a wide range of veterinary practice types, including shelter medicine, which was not specifically sampled in the other studies.

Veterinarians in our study believed they could not judge the financial resources of individual clients based on appearance. However, veterinarians who perceived their practice's clients to be predominantly affluent or predominantly low-income used different strategies to address this uncertainty. These two groups of veterinarians may respond differently to different antibiotic stewardship interventions or policies. Future research may identify strategies that are

effective with veterinarians that work with unowned animals, or clients across varied socioeconomic status.

In US studies of the factors that shape how physicians prescribe antibiotics for human patients, the cost of diagnostic testing and treatment for individual patients has not been found to be a primary influence on decision making.[34–36] The ubiquity and variety of insurance plans obscures the cost of care in human medical practice ,[37] as one of our respondents noted explicitly. Doctors in specialties where insurance coverage is less common, like dentistry,[38] may perceive similar financial barriers to appropriate antibiotic decision making as veterinarians. If so, this could have implications for the development of antibiotic stewardship strategies within those fields.

Many veterinarians in this study described a financial gap between practicing appropriate antibiotic use and what was possible within the constraints of their budgets. Research into interventions that help bridge this gap may be particularly helpful in improving antibiotic prescribing in veterinary medicine. For example, multiple veterinarians in this study believed that pet insurance improved their ability to conduct diagnostic testing and provide appropriate treatment. Another respondent believed that lowering the price of culture and susceptibility testing at her practice led to an increase in its use. Future quantitative studies could evaluate whether these practices are effective at improving veterinary antibiotic use.

Our study has several limitations. We cannot broadly generalize this purposeful sample to veterinarians in the US. However, this study covers veterinarians from diverse practice types and reached thematic saturation. Veterinarians may have withheld describing perspectives or behavior they believed would viewed negatively. To minimize this, the study and its interview questions were framed to understand experiences and perceptions, rather than to judge. Although we reached out to veterinarians through a variety of networks, veterinarians who chose to respond may have been more interested in antibiotic stewardship than those who did not. Despite these limitations, we are confident that the perceptions in this study have relevance to developing research and interventions for antibiotic stewardship in veterinary medicine.

Interviews with companion animal veterinarians, working in settings ranging from specialty practices serving largely affluent clients to animal shelters working with unowned animals, revealed that in all settings, respondents perceived financial factors to frequently impair their ability to prescribe antibiotics appropriately. Financial factors such as client willingness to pay and restricted budgets must be considered central to veterinary antibiotic stewardship interventions.

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CHAPTER 3: Mapping Ampicillin-Resistant *Escherichia Coli* Infections In Children And Dogs

Abstract

Background: Antimicrobial resistance is a rapidly growing public health concern. How antibiotic resistant bacteria spread through the environment between people and animals is poorly understood. Our objective was to determine if ampicillin-resistant *Escherichia coli* infections are spatially determined in children and dogs and assess the relationship between canine and human risk factors.

Methods: Data were obtained from a children's health care network and nearby tertiary veterinary hospital from patients receiving a bacterial culture with *E. coli* between January 1, 2013 and December 31, 2017 and residing in the Philadelphia Metropolitan Area. Variables assessed included residential location, patient characteristics, and antibiotic use and hospitalization prior to culture. Generalized additive models were used to determine the association between risk factors and ampicillin-resistant *E. coli* infection. Unadjusted models were compared between children and dogs. Two adjusted models were created for children, one incorporating a variable indicating the predicted probability of ampicillin-resistant *E. coli* infection in dogs at their residential location.

Results: 3,072 children and 279 dogs were included in the analysis. Children were at significantly increased risk of ampicillin-resistant *E. coli* infection if their residence was in the most urban parts of the region. Significantly lower areas of risk were located outside of the city in more rural and suburban regions to the northwest. The reverse pattern was seen in dogs, with an increased risk in more rural or suburban regions and a lower risk in the city. These patterns persisted in the adjusted model. After adjusting for all other variables, including residential location, children who were tested during a hospital encounter (OR=2.39, $p<0.001$) or had beta-lactam use in the 90 days prior to culture (OR=1.66, $p<0.001$) had a significantly increased risk. Children of a younger age (OR=0.97 per year, $p<0.001$) and black race (OR=1.26 compared to white race, $p=0.037$) had greater odds of ampicillin-resistant *E. coli.* The probability of ampicillin resistance in dogs at a child's location was not a significant predictor ($p = 0.068$).

Conclusion : Using a One Health study design that incorporated humans, animals, and the environment, we found that children with *E. coli* infections in urban areas had an increased risk of ampicillin-resistant infections than those residing in nearby suburban and rural areas. While residential location impacted risk in dogs, those living in the suburban and rural area were at greater risk and those in the urban area at lower risk. This highlights the importance of community and environmental factors on antibiotic resistance risk for animal and public health.

Introduction

The Centers for Disease Control and Prevention (CDC) estimates that 2.8 million people in the United States become infected with antimicrobial-resistant bacteria (ARB) annually, causing 35,000 deaths.[1] National[2] and global[3] action plans recognize that a multi-sectoral One Health approach, incorporating human, animal, and environmental health, is needed to combat antibiotic resistance. A critically important gap in knowledge is understanding how antibiotic resistance circulates between people, animals, and the environment.[3,4]

The relationship between children, dogs, and their shared environment provides an opportunity to better understand where ARB are concentrated and how they might spread. Animals can directly transmit microbial disease [5-7] and contaminate the environment with ARB. [8] Children are more likely than older individuals to participate in poor hygiene behaviors such as not washing their hands when appropriate or allowing animals to lick their faces.[9] This may put children at increased risk of contracting ARB from their community than adults, including environmental exposure and exposure to pets. Identifying locations with disproportionate ARB burden in children and dogs may allow us to better understand how ARB circulate in these groups.

Our objective was to determine if cases of ARB infections in children are spatially and temporally dependent and to compare spatial and temporal patterns of ARB in children and dogs in the Philadelphia metropolitan area (PMA). For this purpose, we selected ampicillin-resistant *Escherichia coli,* a common bacterial pathogen in both children and dogs in our study populations. We hypothesized that residential location would be a significant risk factor for ampicillin-resistant *E. coli* infection after controlling for known demographic and clinical risk factors.

Methods

Data:

Electronic Health Record (EHR)-derived data were obtained from a pediatric care network including a tertiary care hospital and primary care practices located across southeastern Pennsylvania and New Jersey. Patient-level data extracted from the EHR included race and ethnicity (patient reported), gender, age, insurance type, and geocoded residential addresses. Visit-level data included visit date, visit type (office visit vs hospital encounter), encounter, and "problem list" ICD-9/10 (*International Classification of Diseases*) codes. Information on hospitalizations, chronic medical conditions, and antibiotic use were also collected for the 90 days prior to the date of culture.

Hospital records data of dogs visiting a nearby tertiary veterinary hospital were obtained from the veterinary hospital's hospital information system. This system was not a full EHR, but included patient demographic data (including sex, age, and breed), residential location, and codes for procedures and medications used primarily for billing.

Inclusion criteria for children and dogs included receipt of a bacterial culture indicating *Escherichia coli* between January 1, 2013 and December 31, 2017. Only patients with community onset episodes, that is with cultures taken during outpatient visits or within the first 48 hours of hospitalization, qualified for inclusion. Children were required to be <18 years of age at the time of culture. Only the first qualifying culture per patient (whether child or dog) was included in the analysis.

Unadjusted Spatial Analyses:

Generalized additive models (GAM) were used in both the unadjusted and adjusted spatial analyses. Unadjusted spatial GAMs were generated for both children and dogs for comparison. As some areas were more densely populated or include people who are more likely

to seek medical care at study centers, the geographic distribution of patients included in the study sample was not spatially homogenous. To control for this violation of the complete spatial randomness assumption, we compared the distribution of cases of ampicillin-resistant *E. coli* in relation to cases of ampicillin-susceptible *E. coli*.

Residential location was modeled using a bivariate nonparametric smooth of longitude and latitude of the geocoded address to develop unadjusted models separately for children and dogs. The loess smoothing methodology, which adjusts the span size used for smoothing based on local population density, was employed for all spatial smooth terms. The number of neighboring points used in the loess smoothing was determined by minimizing the Akaike's Information Criterion (AIC).

For each GAM, 999 permutations randomly reassigning subjects (retaining all covariates) to specific residences was used to assess a global test of significance for parameters of the spatial smooth.[10] When this global test was significant ($p<0.05$), we performed a local test to determine geographic locations with statistically higher or lower odds of being a case. The GAM generated log-odds at each point on the spatial grid. Any points ranked in the top or bottom 2.5% of the permutation distributions were labeled as “hot spots” or “cold spots” respectively.[10,11]

Unadjusted Analyses:

The unadjusted relationships between a variety of potential risk factors, including antibiotic use and case status of each patient, were assessed with logistic regression. Natural cubic splines were used to assess the relationship between time and risk of ampicillin-resistant *E. coli*. Infections in children or dogs with two or more days of hospitalization in the previous 90 days or IV chemotherapy administration or hemodialysis within 30 days of culture were labeled healthcare-associated infections (HAIs).[12] Complex chronic conditions were identified using ICD-9/10 codes.[13,14] The unadjusted spatial model for dogs was used to predict the probability of

ampicillin-resistant *E. coli* at each child's residential location. This dog predictor variable was tested for its association with ampicillin-resistant *E. coli* infections in children.

Adjusted GAM Analysis:

After unadjusted analysis, two adjusted models were created for children. The adjusted GAMs for children took the form

$$logit[p(x,y,z)] = \gamma^{*}z + S(x,y)$$

where $logit[p(x,y,z)]$ was the log-odds of being a case at latitude and longitude coordinates (x, y) for a child with covariate vector z (including the spline basis functions for time), and $S(x,y)$ was a bivariate smooth of latitude and longitude that represented the spatial variation. In the first model, only variables from the pediatric EHR data were included. In the second model, the dog predictor variable was also included, and the analysis was restricted to children living within the boundaries of the dog model. Global and local tests of significance for the spatial smooth terms were performed in the same manner as for the unadjusted models.

Results:

Overall, 3,072 children and 279 dogs met inclusion criteria for the study. Of the children, 1,096 (35.7%) had an *E. coli* infection resistant to ampicillin. Of the dogs, 104 (37.3%) had an *E. coli* infection resistant to ampicillin. The characteristics of the children in the study are included in Table 3.1.

Table 3.1: Characteristics of children included in the study

Factor		**Cases, n=1,096**	**Controls, n=1,976**
Age (mean (SD))		5.73 (5.9)	7.34 (6.0)
Sex (n (%)):			
	Female	954 (87.0)	1817 (92.0)
	Male	142 (13.0)	159 (8.1)
Race (n(%)):			
	White	313 (28.6)	836 (42.3)
	Black	551 (50.3)	774 (39.2)
	Asian	58 (5.3)	79 (4.0)
	Multiple Races	23 (2.1)	41 (2.1)
	Other	151(13.8)	246 (12.5)
Ethnicity (n (%)):			
	Not Hispanic or Latino	961 (87.7)	1814 (91.8)
	Hispanic or Latino	133 (12.1)	158 (8.0)
	Refused or Unknown	2 (0.18)	4 (0.20)
Payor Category (n (%)):			
	Private	367 (33.5)	919 (46.5)
	Medicaid	649 (59.2)	959 (48.5)
	Missing	80 (7.3)	98 (5.0)
Visit Type (n (%)):			
	Office Visit	264 (24.1)	1056 (53.4)
	Hospital Encounter	794 (72.5)	871 (44.1)
	Other	38 (3.5)	49 (2.5)
Beta Lactam Use (n (%))		109 (10.0)	155 (7.8)
Healthcare Associated Infection (n (%))		376 (34.31)	403 (20.39)
Complex Chronic Condition (n (%))		236 (21.53)	385 (19.48)

Unadjusted Spatial Analysis:

In the unadjusted spatial analysis, the presence of ampicillin-resistant *E. coli* among children who had an *E. coli* positive culture was significantly affected by their residential location. Children living in more urban parts of the PMA, particularly along the Schuylkill River, had a significantly higher risk of infection with ampicillin-resistant *E. coli* than children in other parts of the PMA (Figure 1, p=0.002). Children with residences to the north and the west of the city had a significantly lower risk of infection with ampicillin-resistant *E. coli*.

Residential addresses for dogs meeting inclusion criteria covered a smaller geographic region than those for children, resulting in a smaller area of analysis. As in children, residential location was a significant risk factor for ampicillin-resistant *E. coli* infection in the dogs (Figure 1, p=0.027). However, these hot and cold spots differed in dogs and children. Dogs had a significantly increased risk of ampicillin-resistant *E. coli* infection in suburban and rural locations, whereas children had a significantly decreased risk; and dogs had a significantly decreased risk in an area that overlapped with the hotspot in children.

A. Children

B. Dogs

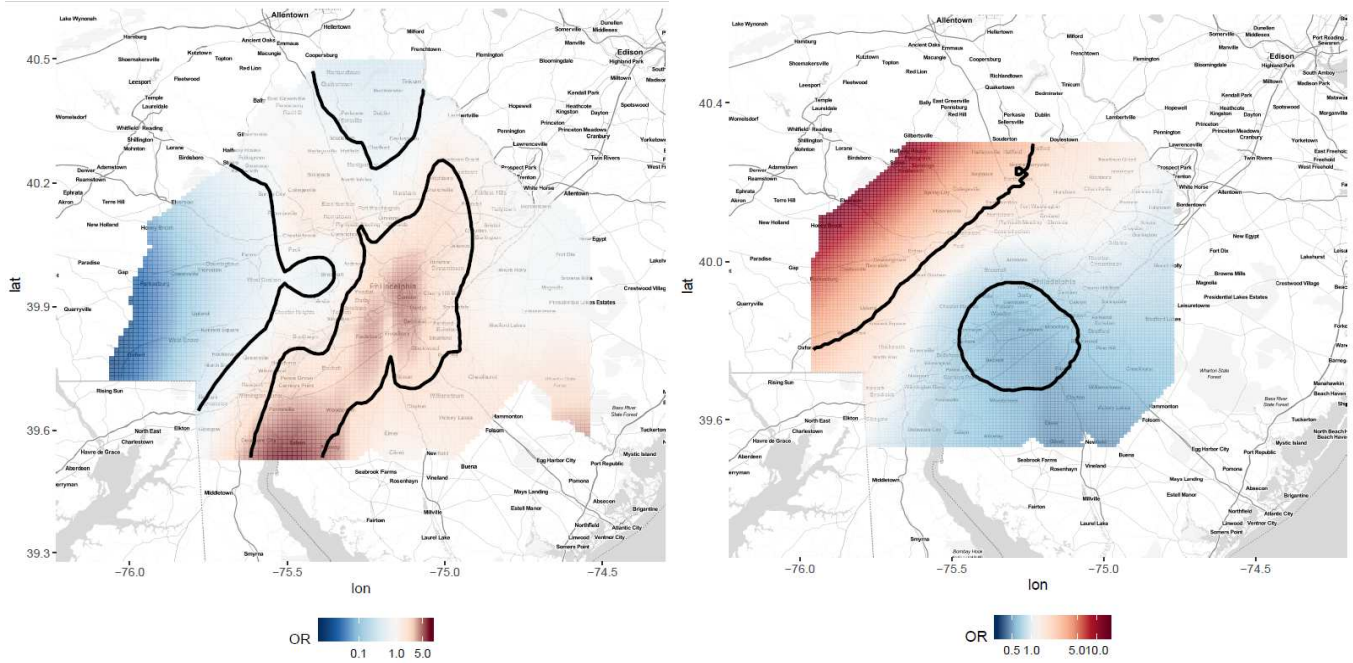

Figure 3.1: Unadjusted risk of ampicillin-resistant E. coli infections in children and dogs in the Philadelphia Metropolitan Area. (A) Odds of ampicillin-resistant vs ampicillin-susceptible E. coli infection based on residential location for children ($p<0.002$). (B) Odds of ampicillin-resistant vs ampicillin-susceptible E. coli infection based on residential location for dogs ($p<0.027$). Note: The area of analysis for dogs is smaller due to the smaller distribution of residential location for dogs.

Unadjusted Temporal Analysis:

In children, the risk of infection with ampicillin-resistant *E. coli* changed significantly throughout the time period (Figure 2). This included a decreasing trend in the proportion of ampicillin-resistant *E. coli* infection through mid-2014, followed by an increasing trend through the end of the study period. In dogs, the proportion of ampicillin resistant *E. coli* infections remained stable over time.

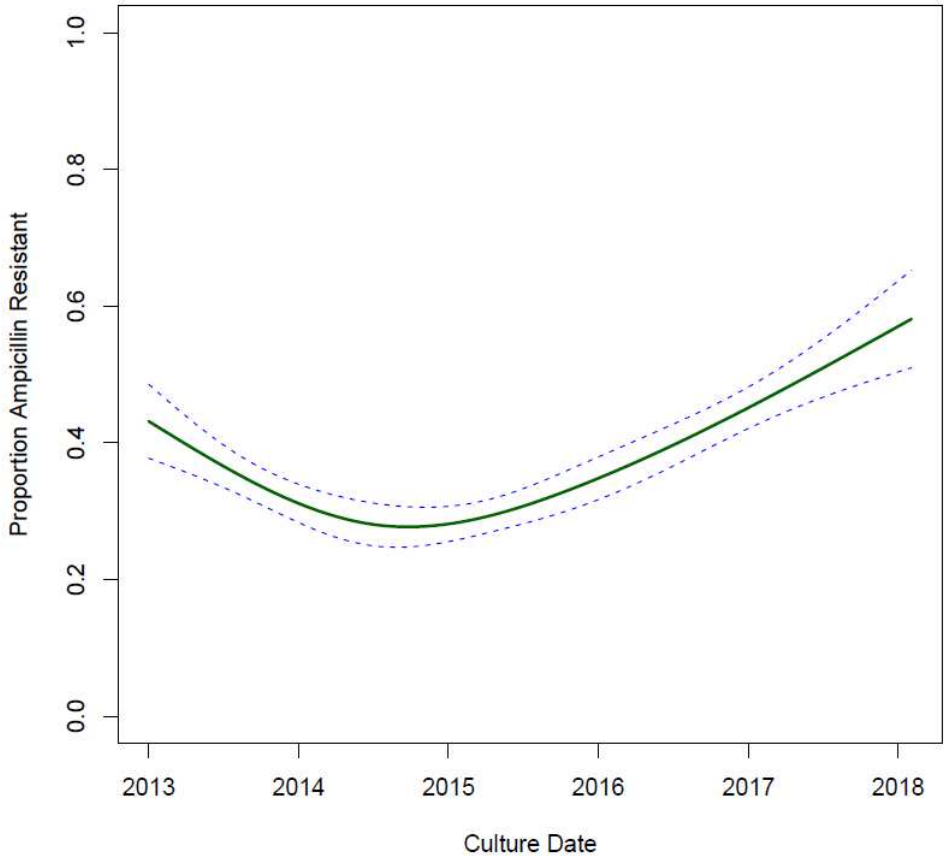

Figure 3.2: Proportion of ampicillin-resistant *E. coli* infections in children over time.

Table 3.2: Unadjusted Risk Factors for Ampicillin-Resistant *Escherichia coli* Infection in Children

Factor		**Odds Ratio**	**95% Confidence Interval**	**p Value**
Age (per year)		0.96	0.94-0.97	<0.001
Sex:				
	Female	ref		
	Male	1.70	1.33-2.16	<0.001
Race:				
	White	ref		
	Black	1.90	1.36-2.82	<0.001
	Asian	1.96	1.60-2.25	<0.001
	Multiple Races	1.50	0.88-2.54	0.13
	Other	1.63	1.28-2.09	<0.001
Ethnicity:				
	Not Hispanic or Latino	ref		
	Hispanic or Latino	1.59	1.25-2.03	<0.001
Payor Category:				
	Private	ref		
	Medicaid	1.69	1.45-1.98	<0.001
Visit Type:				
	Office Visit	ref		
	Hospital Encounter	3.65	3.09-4.30	<0.001
Beta Lactam Use		1.29	1.00-1.68	0.047
Healthcare Associated Infection		2.04	1.72-2.41	<0.001
Complex Chronic Condition		1.13	0.95-1.36	0.18
Predicted canine probability of ampicillin-resistance at child's residential location (per 1% change)		0.97	0.96-0.98	<0.001

Other Unadjusted Risk Factors:

In the unadjusted analysis, younger age (OR=0.96 per year p=0.001) and male sex (OR=1.7, p<0.001) were associated with higher risk of ampicillin-resistant *E. coli* infection among all children with E. coli infections (Table 2). Black children (OR=1.90, p<0.001), Asian children (OR=1.96, p<0.001), and Hispanic or Latino children (OR=1.59, p<0.001) were at significantly greater risk. Children with Medicaid as a payor had odds of ampicillin-resistant *E. coli* infection that were a 1.69 times greater than those with private insurance (p<0.001).

Factors related to the visit and the child's previous medical history also contributed to ampicillin-resistant *E. coli* infection risk. Children who had bacterial cultures taken as part of a hospital encounter (within 48 hours of hospitalization) had infections with a higher odds of ampicillin resistance (OR=3.65, p<0.001) than those in office visits. Children who had an HAI had an increased risk of an infection with ampicillin resistance (OR=2.04, p<0.001). Children with complex chronic conditions did not have a significant change in risk. Use of beta-lactam antibiotics in the 90 days prior to culture was associated with ampicillin-resistant *E. coli* (OR=1.29, p=0.047). The predicted probability of ampicillin-resistant *E. coli* in dogs at the child's residential location was associated with a lower risk (OR=0.97 for a 1% increase in probability, p<0.001) for ampicillin-resistant *E. coli*.

Dogs with HAIs (OR=1.84, p=0.042) and dogs that were exposed to beta-lactams in the 90 days prior to culture (OR=1.93, p=0.027) were more likely to have an ampicillin-resistant *E. coli* infection in the unadjusted canine analysis. Because the canine data derived from a single tertiary care veterinary hospital, all dog cultures were taken as part of a hospital encounter. No other variables investigated, including age, sex, or breed, were associated with ampicillin-resistant *E. coli* infection (supplemental table 1).

Adjusted Mapping Analysis:

In the adjusted analysis, a child's residential location was significantly associated with his or her risk of having an ampicillin-resistant *E. coli* infection. In both the adjusted analysis excluding the canine data (n=3072, p<0.001) and the adjusted analysis including the dog predictor variable (n=2968, p<0.001), the global statistic was significant. In the local analysis for both, one area of increased risk was centered around the city, while an area of decreased risk was centered to the west of the region (Figure 3). Although the maps were similar, the model without canine data showed a greater increase in odds of ampicillin-resistant *E. coli* infection due to spatial location than the model incorporating the dog predictor.

Adjusted Analysis: Other Variables

In the adjusted analysis without the dog predictor variable, children of a younger age (OR=0.97 per year, p<0.001) and black race (OR=1.26, p=0.037) had greater odds of ampicillin-resistant *E. coli* (Table 3). Children who had samples taken for culture as part of a hospital encounter (OR=2.39, p<0.001) or had beta-lactam use in the 90 days prior to culture (OR=1.66, p<0.001) also had a significantly increased risk after adjusting for all other variables, including residential location. Time was a significant risk factor in the adjusted analysis (p<0.001).

The addition of the canine predictor to the adjusted model did not substantially change the associations between the risk factors and ampicillin-resistant *E. coli* (Table 3). The dog predictor was not a significant risk factor for ampicillin-resistant *E. coli* for children in the adjusted model.

A. Child Data Only

B. Child Data and Dog Prediction Variable

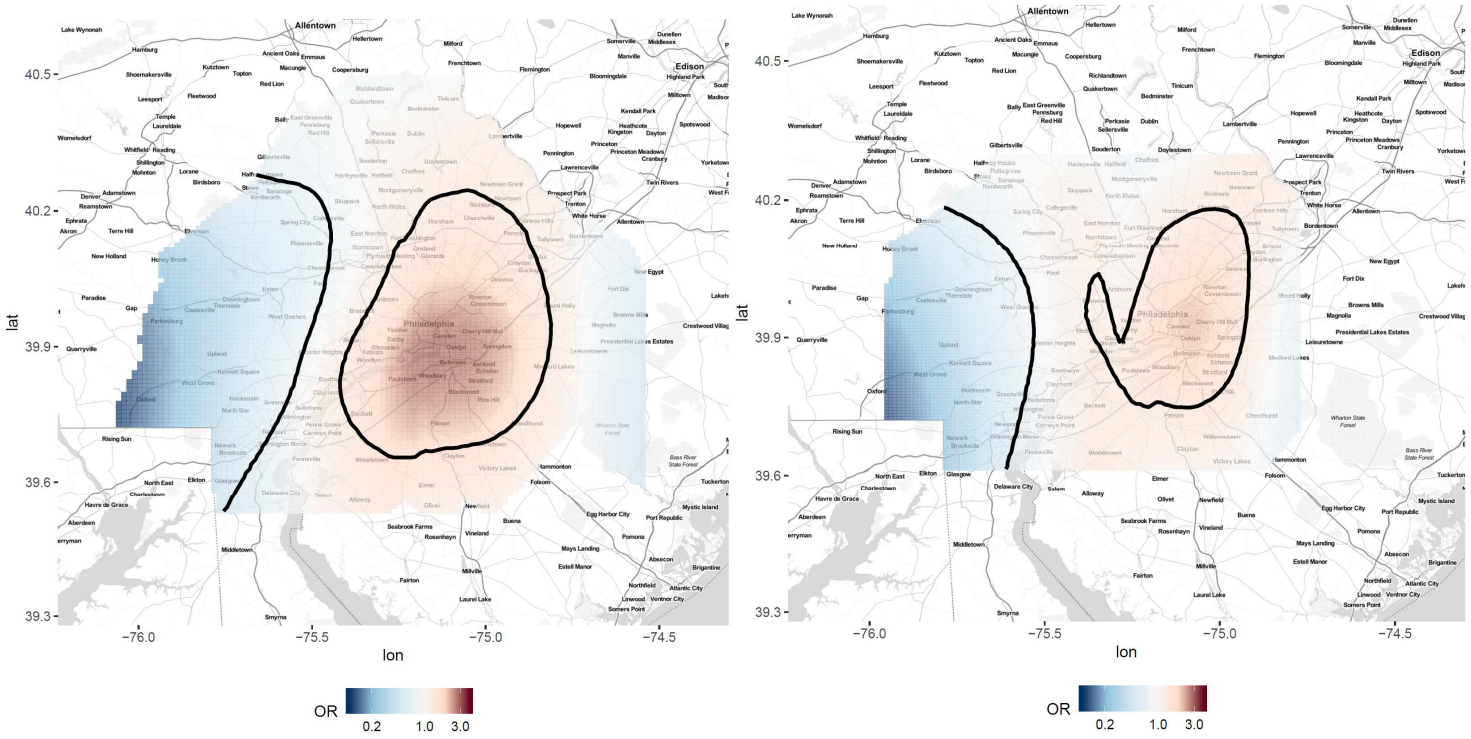

Figure 3.3: Adjusted risk of ampicillin-resistant E. coli infections in children in the Philadelphia Metropolitan Area. (A) Odds of ampicillin-resistant vs ampicillin-susceptible E. coli infection by location from an adjusted model including data from pediatric EHR (global statistic: p<0.001). (B) Odds of ampicillin-resistant vs ampicillin-susceptible E. coli infection by location from an adjusted model including data from pediatric EHR and including a variable derived from the predicted probability of ampicillin-resistant E. coli infection in dogs at that location (global statistic: p<0.001).

Table 3.3: Adjusted Risk Factors for Ampicillin-Resistant *Escherichia coli* Infection in Children

		Adjusted Model: Human Data Only (n=3072)			**Adjusted Model with Dog Predictor (n=2968)**		
Factor		**Odds Ratio**	**95% Confidence Interval**	**p Value**	**Odds Ratio**	**95% Confidence Interval**	**p Value**
Age (per year)		0.97	0.96-0.99	<0.001	0.97	0.96-0.99	<0.001
Sex:							
	Female	ref		ref			
	Male	1.22	0.92-1.61	0.16	1.26	0.95-1.66	0.11
Race:							
	White	ref					
	Black	1.26	1.01-1.56	0.037	1.41	1.13-1.75	0.002
	Asian	1.22	0.81-1.83	0.34	1.22	0.81-1.84	0.34
	Multiple Races	0.96	0.53-1.75	0.90	0.55	0.30-1.01	0.84
	Other	1.12	0.81-1.56	0.49	1.18	0.85-1.65	0.31
Ethnicity:							
	Not Hispanic or Latino	ref					
	Hispanic or Latino	1.41	1.00-1.98	0.051	1.36	0.96-1.92	0.084
Payor Category:							
	Private	ref					
	Medicaid	1.14	0.94-1.38	0.20	1.13	0.93-1.37	0.23
Visit Type							
	Office Visit	ref					
	Hospital Encounter	2.39	1.96-2.91	<0.001	2.32	1.90-2.83	<0.001
Beta Lactam Use		1.66	1.23-2.24	<0.001	1.69	1.24-2.29	<0.001

Healthcare Associated Infection	1.11	0.90-1.37	0.32	1.09	0.89-1.34	0.41
Complex Chronic Condition	1.21	0.98-1.49	0.077	1.15	0.93-1.43	0.20
Predicted canine probability of ampicillin-resistance at child's residential location (per 1% change)	N/A	N/A	N/A	0.99	0.97-1.00	0.068

Discussion:

In this study we used a One Health approach to demonstrate that residential location was a risk factor for ampicillin resistance in pediatric *E. coli* infections, with an urban location at higher risk and a western sub-urban and rural area at significantly lower risk. This risk persisted even when controlling for known risk factors of antibiotic resistance, including patient characteristics, recent hospitalizations, and antibiotic use. Younger children, black children, children presenting at a hospital, and children with recent beta-lactam use were at significantly greater risk of ampicillin resistant *E. coli* infections. Although ampicillin resistance of *E. coli* infections in dogs was also associated with residential location, dogs were at greater risk in the western, suburban and rural area and at a lower risk in the urban environment.

Other studies have shown urban and rural differences in antibiotic resistance that may play a role in our study. Among people with similar diets and antibiotic use levels, those living in urban areas have been found to have an overall decrease in microbial diversity. [15] This is associated with an increase in the proportion of *Escherichia* and *Shigella* bacteria and an increase in antibiotic resistance genes. Environmental factors may explain some of these differences. Dissemination hotspots for antibiotic resistance genes include hospital and pharmaceutical waste and wastewater treatment plants.[16] These hotspots may be "critical control points" that govern the selection, proliferation, and spread of resistant pathogens. Children in the urban areas at greater risk in our study may have increased exposure to these areas.

Residential location and its effect on the risk of community-onset antibiotic-resistant infections may play a role in explaining why some groups of people with lower rates of antibiotic use are at greater risk of antibiotic-resistant infections. Other studies from Philadelphia have shown that although black children are prescribed fewer antibiotics and fewer broad-spectrum antibiotics than white children,[17,18] black children are at greater risk of antibiotic-resistant infections.[19] In the unadjusted analysis all non-white racial groups (with the exception of multiracial children) were at higher risk of ampicillin-resistant *E. coli* than white children. The Philadelphia metropolitan area is highly segregated, both racially and economically.[21,22] Conditions in these segregated regions affecting the exposure to antibiotic-resistant bacteria in the environment may contribute to disparities in acquisition of ampicillin-resistant *E. coli* in our study. Accessibility to healthcare facilities may also play a role. In the city of Philadelphia between 2008 and 2016, a persistent disparity in access to pediatric primary care was demonstrated in predominantly non-Hispanic Black neighborhoods. [23] Although it is beyond the scope of our study to determine what specific factors account for the increased risk for children in urban vs suburban and rural communities, this would be an interesting area for further analysis.

While the residential environment may impact ampicillin resistance among pediatric *E. coli* infections, the pattern of these infections is not similar in infections among dogs. The general pattern seen in children was reversed in dogs, with dogs having a higher risk in the suburban and rural western area and lower risk in the center of the city. One explanation may be a difference in the underlying populations of clients visiting the tertiary veterinary hospital and the parents of the children in the pediatric care network. The pediatric care network is socioeconomically diverse, with 52% of the children in this study having insurance coverage through Medicaid. Although no socioeconomic indicators were available for canine patients, the tertiary veterinary hospital is likely to have a wealthier overall clientele who can afford high-quality care for their pets. The socioeconomic status of clients may impact risk of antibiotic-resistant infection in all household members, including dogs in urban vs sub-urban and rural environments. Dogs and children also

may have different sources of environmental exposure to antibiotic resistant bacteria, which could affect which environments pose the greatest risk.

Our study has several limitations. Residential location may not be the most significant location to assess spatial risk. Other locations, such as schools or childcare centers, may have a greater impact on risk. However, the hotspots and coldspots found in our study are large enough to cover large areas of the cities or towns where children and dogs reside, likely including these additional areas of risk. In addition, we specifically studied the risk of ampicillin resistance among children and dogs with *E. coli* infections. By using patients with *E. coli* infections susceptible to ampicillin as controls, our antibiotic use data is biased towards showing a greater association between beta-lactam use and ampicillin resistance. Antibiotic use, however, was not the focus of this study. By limiting the control group to ampicillin-susceptible *E. coli* infections rather than all children in the network, we were able to isolate locations where antibiotic resistance, rather than *E. coli* infections, were concentrated. Identification of specific antibiotic resistance genes or bacterial strains was beyond the scope of this study. Future studies to sample the environment, children, and pets in these hot and cold spots may also help determine why the human and dog hotspots were so distinctly different and how ARB circulate through humans, animals, and the environment.

Conclusion:

Using a One Health study design that incorporated humans, animals, and the environment, we found that children with *E. coli* infections in urban areas were at increased risk of ampicillin-resistant infections than those residing in a nearby suburban and rural areas, after adjusting for patient factors and medical factors, including antibiotic use. While residential location impacted risk in dogs, those living in the suburban and rural area were at greater risk and those in

the urban area at lower risk. This highlights the importance of community and environmental factors on antibiotic resistance risk for animal and public health.

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Supplementary Materials

Supplemental Table 3.1: Characteristics of dogs included in study

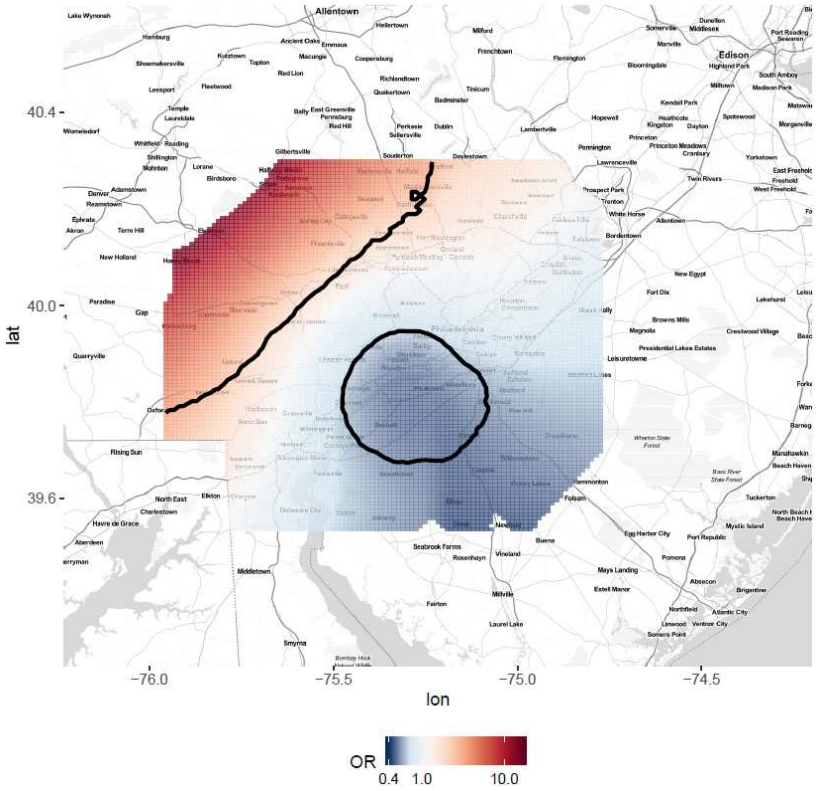
Factor	**Cases (n=104)**	**Controls (n=175)**
Age, mean (SD)	8.5 (4.1)	8.2 (4.0)
Male Sex, n (%)	41 (39.4)	60 (34.3)
Purebred, n (%)	79 (76.0)	131 (74.9)
Beta Lactam Use, n (%)	29 (27.9)	30 (17.1)
Healthcare Associated Infection, n (%)	28 (26.9)	29 (16.6)

Supplemental Table 3.2: Unadjusted Risk Factors for Ampicillin-Resistant *Escherichia coli* Infection in Dogs

Factor	**Odds Ratio**	**95% Confidence Interval**	**p Value**
Age (per year)	1.02	0.96-1.08	0.59
Male Sex	1.24	0.75-2.06	0.39
Purebred	1.06	0.61-1.88	0.84
Beta Lactam Use	1.87	1.04-3.35	0.035
Healthcare Associated Infection	1.85	1.03-3.35	0.040
Time	N/A	N/A	0.60

Supplemental Table 3.3: Adjusted Risk Factors for Ampicillin-Resistant *Escherichia coli* Infection in Dogs

Factor	**Odds Ratio**	**95% Confidence Interval**	**p Value**
Age (per year)	1.00	0.94-1.07	0.92
Male Sex	1.34	0.79-2.28	0.28
Purebred	0.97	0.53-1.77	0.91
Beta Lactam Use	1.42	0.67-3.00	0.35
Healthcare Associated Infection	1.74	0.82-3.68	0.15
Time	N/A	N/A	0.68



Supplemental Figure 3.1: Adjusted risk of ampicillin-resistant E. coli infections in dogs in the Philadelphia Metropolitan Area dogs in the Philadelphia Metropolitan Area. The p-value for the global spatial effect on ampicillin resistant *E.* coli in dogs is 0.013.

CHAPTER 4: Risk Factors for the Acquisition of a blaNDM-5 Carbapenem-Resistant *Escherichia coli* in a Veterinary Hospital

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Abstract

Carbapenem-resistant *Enterobacteriaceae* (CRE) are an urgent antibiotic resistant threat. Only sporadic reports of CRE in companion animals have been reported. Our objective was to identify risk factors associated with the acquisition of a *bla*$_{NDM-5}$ CR-*E. coli* strain as part of an outbreak investigation at a tertiary veterinary hospital in the United States. A matched case-control study was conducted among companion animals admitted during July 1, 2018 through June 30, 2019. The 15 identified *bla*$_{NDM-5}$ CR-*E. coli* cases were matched 1:2 with controls (culture negative for *bla*$_{NDM-5}$ CR-*E. coli*) based on species and number of days of hospitalization prior to bacterial culture sample collection. The association between exposure to various procedures and hospital services and the acquisition of *bla*$_{NDM-5}$ CR-*E. coli* was assessed through conditional logistic regression. Case patients had significantly higher odds of exposure to the anesthesia service (odds ratio [OR]=12.8, p = 0.017), the surgical service (OR=4.0, p =0.046), and to endotracheal intubation (OR=10.0, p = 0.03). Veterinary hospitals should be aware of the potential for transmission of CRE via anesthetic and surgical procedures, especially those that require the placement of endotracheal tubes.

Introduction

The emergence of carbapenem resistant *Enterobacteriaceae* (CRE) in companion animal veterinary medicine was inevitable. CRE are regarded by the Centers for Disease Control and Prevention as an urgent public health threat because not only are they carbapenem-resistant, they are also resistant to most other antibiotic classes. To date there have been only a few sporadic reports of CRE from companion animals.[1–6]

Carbapenem drugs are critically important antimicrobials that are generally reserved for the treatment of infections caused by multidrug-resistant Gram negative bacteria.[7] CRE have emerged as an important cause of human healthcare associated infections and have become a major clinical and public health problem.[7] Control of infections caused by CRE in human health care-settings can be a challenge because the organisms colonize the gastrointestinal tract and can go undetected.[1]

In July 2018, a strain of *Escherichia coli*, that was subsequently shown to contain a New Delhi metallo-β-lactamase, $bla_{\text{NDM-5}}$ gene, was isolated from a dog being treated at a tertiary veterinary hospital in Pennsylvania.[8] This isolate belonged to sequence type 167 (ST167) and contained additional antimicrobial resistance genes. A case report has since documented an outbreak of $bla_{\text{NDM-5}}$-*E. coli* (ST 167) in companion animals in the United States.[9]

Since April 2018, the Philadelphia Board of Health has required the reporting of infection or colonization with CRE to the Philadelphia Department of Public Health (PDPH). A case was broadly defined as a culture yielding a bacterium in the family *Enterobacteriaceae* that is documented to produce a carbapenemase by means of a laboratory test. In May 2019, the microbiology laboratory at the veterinary hospital contacted PDPH to report the cases when the $bla_{\text{NDM-5}}$ gene mechanism was confirmed. The veterinary hospital worked with PDPH on an outbreak investigation to determine potential sources of in-hospital transmission, review infectious disease related protocols and procedures, and reduce the potential for both animal to animal and animal to human spread.

As part of the outbreak investigation, a case-control study was conducted to identify potential sources of *bla*$_{NDM-5}$ CR-*E. coli*. The goal was to identify modifiable risk factors for in-hospital transmission of *bla*$_{NDM-5}$ CR-*E. coli*. Effort focused on three main categories of exposure: exposure to services within the hospital, exposure to procedures thought to be associated with *bla*$_{NDM-5}$ CR-*E. coli* transmission, and exposure to medications including antibiotics that might put patients at risk.

Materials and Methods:

Dataset: The data used in these analyses were collected in the course of clinical activities and assessed retrospectively as part of an outbreak investigation. All data were collected from an electronic Hospital Information System (HIS) that is primarily used for tracking procedures and billing. The data exported included dates of admission and discharge, services utilized, and codes for procedures and medications utilized with associated dates. Procedure codes in the dataset were grouped into categories based on type of procedure (ex: endotracheal intubation, catheterization) and medications received (ex: glucocorticoids, antibiotics). Procedures or services in the hospital information system occurring after the date of the procedure code for bacterial culture were excluded from analysis. Results of testing from the in-house clinical microbiology laboratory were added to this dataset to assign case status. A broad list of potential exposures were evaluated, and only those that were sufficiently common among patients were included in analysis (see Supplemental Table 1).

Case Definition: A case was defined based on the criteria of the PDPH. For inclusion purposes, laboratory record review identified any animal patient from which a CRE was recovered between July 1, 2018 and June 30, 2019. Organisms in the family *Enterobacteriaceae* that showed phenotypic resistance to imipenem based on Clinical and Laboratory Standards Institute (CLSI) interpretive guidelines[10] were recovered from cryopreservation. These organisms were

tested for the production of a carbapenemase using the modified carbapenem inactivation method (mCIM).[11]

Only the first positive culture from each animal was used for statistical analysis. Controls consisted of patients that had an aerobic bacterial culture submitted to the clinical microbiology lab during the study period and did not test positive for *bla*$_{NDM-5}$ CR-*E. coli*. In order to control for length of exposure to hospitalization, each case was matched to two controls by species and number of days of hospitalization prior to culture.

Statistical Analyses: Data extracted from HIS were cleaned using R (3.5.1). Exact matching of cases to controls based on species and days of hospitalization prior to culture was performed using the program Optmach (R Software Package). Unadjusted analysis was performed using conditional logistic regression in Stata (14.2). A 2-sided α level of 0.05 was used to determine statistical significance.

Outbreak Investigation: As part of the outbreak investigation, the PDPH reviewed the hospital Infection Prevention Policy and Procedure Manual. All standard operating procedures (SOP) were reviewed with emphasis on the following areas: hand hygiene, environmental cleaning and disinfection and medical device reprocessing. Semi-critical devices were defined as devices that come into contact with but do not typically penetrate mucosal surfaces. If deficiencies were found a corrective plan was put in place.

Results:

A total of 15 patients were identified as cases between July 1, 2018 and June 30, 2019. *bla*$_{NDM-5}$ CR-*E. coli* was isolated from all patients. Included in these case patients were 14 dogs and one cat. Each case patient was successfully matched by species and length of stay prior to culture, to two controls, resulting in a total of 30 controls.

Case status was significantly associated with exposure to the anesthesia service (OR=12.8, p=0.017) and the surgery service (OR=4.0, p=0.046; Table 1). Other services showed no significant difference in odds. *bla*$_{NDM-5}$ CR-*E. coli* case patients were also more likely to be exposed to endotracheal intubation (OR=10.0, p=0.03) than control patients. Other procedures

showed no significant difference between cases and controls. Exposure to various medications including glucocorticoids, and any antibiotics prior to culture showed no significant difference between groups.

Table 4.1: Comparisons of Clinical Exposures of CR-*E. coli* Case and Control Patients

		Cases n=15	**Controls n=30**	**Odds Ratio**	**95% Confidence Interval**	**p Value**
Services n (%)						
	Anesthesia	11 (73.3)	8 (26.7)	12.79	1.59-102.90	0.017*
	Surgery	8 (53.3)	6 (20.0)	4.0	1.03-15.60	0.046*
	Intensive Care Unit	7 (46.7)	4 (13.3)	6.97	0.81-60.20	0.076
	Cardiology	4 (26.7)	3 (10.0)	5.26	0.55-50.02	0.15
	Radiology	11 (73.3)	19 (63.3)	1.52	0.42-5.57	0.53
	Emergency	9 (60.0)	19 (63.3)	0.74	0.11-4.90	0.75
	Internal Medicine	4 (26.7)	10 (33.3)	0.76	0.21-2.74	0.67
	Dermatology	1 (6.7)	1 (3.3)	2	0.13-31.98	0.62
Procedures n (%)						
	Endotracheal Intubation	11 (73.3)	10 (33.3)	10	1.23-81.47	0.03*
	Intravenous Catheterization	6 (40.0)	9 (30.0)	1.88	0.39-8.92	0.42
	Insertion of Medical Device	11 (73.3)	15 (50.0)	3.7	0.72-18.97	0.12
	CT Scan	3 (20.0)	3 (10.0)	2.38	0.38-14.97	0.36
Medications n (%)						
	Glucocorticoids	6 (40.0)	5 (16.7)	3.14	0.76-13.00	0.12
	Antibiotic Use	11 (73.3)	19 (63.3)	2.17	0.36-12.94	0.4

Review of the medical device reprocessing protocols by the PDPH revealed that there was no standard approach for reprocessing of endotracheal tubes between patients. A written SOP was available, but the review identified deficiencies during an audit of device reprocessing. There was an observed lack of consensus among staff regarding the standard soaking time, concentration of disinfectant to be used or standard pre-cleaning approaches. An unofficial practice of discarding tubes from patients with suspected respiratory infections was in place but, in general, endotracheal tubes were disinfected and re-used. It was also determined that the disinfection product being used at the time of the review (Cetylcide II, Cetylite, Pennsauken, NJ) was for hard-surface disinfection and not for high-level disinfection. It was subsequently determined that only new, sterilized endotracheal tubes would be used in the facility. The new policy was implemented 50 days following discharge of the 15th patient to be identified.

Discussion:

In response to an outbreak of *bla*$_{NDM-5}$ CR-*E. coli* in companion animals, this study investigated potential risk factors for in-hospital acquisition. While CRE in companion animals have been documented across the world (North America[6], Europe[2,5], Asia[3], Africa[4], and Australia[12]), these reports are sporadic and generally included only a few animals. The outbreak of *bla*$_{NDM-5}$ CR-*E. coli* in companion animals described here was large enough to identify potential risk factors for transmission in the veterinary setting. After adjusting for species and length of stay prior to testing through matching, exposure to the anesthesia service, surgery service, and endotracheal intubation were significantly associated with the isolation of *bla*$_{NDM-5}$ CR-*E. coli*. A review of the hospital Infection Prevention Policy and Procedure Manual and associated SOP's discovered inappropriate reprocessing of endotracheal tubes.

Exposure to the anesthesia service, surgery service and endotracheal intubation were not only statistically significant, but clinically important. Case patients had more than 10 times higher odds of being exposed to the anesthesia service and endotracheal intubation than controls. Anesthesia, endotracheal intubation, and surgery are linked (though they do not completely overlap), pointing to a potential exposure to *bla*$_{NDM-5}$ CR-*E. coli* during the preparation

for anesthesia. In human medicine, risk factors for infection or colonization with CRE include admission to the Intensive Care Unit (ICU), mechanical ventilation, presence of indwelling devices, receipt of immunosuppressive drugs, and prior antimicrobial exposure. [13–16] CRE are predominantly believed to be spread via healthcare worker's contaminated hands[17], although endoscopes have notably been documented as a source of human transmission.[18]

One key difference between veterinary and human healthcare settings is the common practice of reusing endotracheal tubes in veterinary medicine.[19] A duodenoscope, a medical device that is commonly reprocessed when used in human medicine, was implicated in the spread of an NDM-producing *E. coli* in a tertiary care human hospital in northeastern Illinois. [18] In that study, case status was significantly associated with a history of exposure to the duodenoscope. Although no lapses of duodenoscope reprocessing occurred, after the hospital changed its reprocessing procedures from automated high-level disinfection with ortho-phthalaldehyde to gas sterilization with ethylene oxide, no additional case patients were found. The authors concluded that the duodenoscope was a likely source of transmission. The results from our case control analysis and the finding that endotracheal tubes were being inappropriately reprocessed, supports the potential for CRE to move between animal patients during endotracheal intubation with reprocessed endotracheal tubes.

Notably some risk factors for CRE transmission in human hospitals were not found to be significant risk factors in our study. Admission to the ICU, insertion of a medical device, and receipt of glucocorticoids were not associated with CRE, despite being risk factors in human medicine. Antibiotic use was also not found to be significantly associated with CRE acquisition. This may be due to low power from the number of patients in this outbreak, differences in companion animals and humans or differences in practices in veterinary and human medicine. Exposure to the ICU had a high odds ratio (6.97) and a low but not significant p value (0.076), indicating that this may be a risk factor, but this study may be too underpowered to detect it.

The small size of this outbreak limited the power of the study. Matching and conditional logistic regression also were used to increase the study's ability to detect risk factors for *bla*$_{\text{NDM-5}}$

CR-*E. coli* infection and colonization.[20] If more patients were available, additional risk factors in this analysis may have been determined. However, even with a small sample size, the associations between the anesthesia and surgery services and endotracheal intubation with *bla*$_{NDM-5}$ CR-*E. coli* were strong and supported by the outbreak investigation's review of infection prevention protocols. Misclassification of exposures or CRE infection or colonization status may also occur. Restricting controls to patients with bacterial culture results was used to reduce misclassification bias. This study is also specific to exposures during an individual hospitalization that affect the risk of isolation of *bla*$_{NDM-5}$ CR-*E. coli* and does not include risks related to medical care outside the tertiary hospital admission, the impact of concurrent diseases, or community exposure. It was not within the scope of the study to assess the association between exposures prior to hospitalization and CRE.

Human healthcare settings have mitigated the risks of CRE acquisition through patient isolation, contact colonization screening, limiting the use of invasive devices, improving environmental cleaning and hand hygiene, and antibiotic stewardship.[21] Our findings, and the human medical literature, suggest that veterinary hospitals should consult qualified infection control professionals and review specific infection control procedures associated with instrument re-use and reprocessing. Specifically, veterinarians should not re-use or reprocess endotracheal tubes against manufacturer's instructions.

Reducing the spread of CRE is vital for both animal and human health. Multidrug resistant bacteria like CRE are implicated in increasing length of hospitalization, severity of disease, and cost of care for veterinary patients.[22,23] CRE can colonize the gastrointestinal tract and remain undetected serving as a potential source of community spread.[24,25] Although CRE are still rare in veterinary medicine, evidence from human medicine points to the potential for the prevalence of these highly drug resistant organisms to increase quickly. A study of community hospitals in the Southeastern United States recorded an over fivefold increase in the detection of CRE among human patients between 2008-2012.[26] As CRE become more prevalent in

companion animals, veterinary medicine must be prepared to take additional precautions to ensure the health of companion animals, staff, and pet owners.

Conclusion:

In this outbreak, hospital risk factors for *bla*$_{\text{NDM-5}}$ CR-*E. coli* acquisition included exposure to the anesthesia service, surgical service, and endotracheal intubation. The device reprocessing policy was changed, and only new endotracheal tubes are now used. It is our expectation that the improved infection control practices will lead to a reduction in the number of *bla*$_{\text{NDM-5}}$ CR-*E. coli* positive animals identified at our hospital. To reduce the spread of CRE in companion animals and humans, veterinarians should strengthen infection control procedures, specifically regarding the reprocessing of endotracheal tubes.

Supplementary Materials

Supplementary Table 4.1: Exposures Investigated

		Cases n=15	Controls n=30	Inclusion
Services n (%)				
	Anesthesia	11 (73.3)	8 (26.7)	Included
	Surgery	8 (53.3)	6 (20.0)	Included
	Intensive Care Unit	7 (46.7)	4 (13.3)	Included
	Cardiology	4 (26.7)	3 (10.0)	Included
	Radiology	11 (73.3)	19 (63.3)	Included
	Emergency	9 (60.0)	19 (63.3)	Included
	Internal Medicine	4 (26.7)	10 (33.3)	Included
	Dermatology	1 (6.7)	1 (3.3)	Included
Procedures n (%)				
	Endotracheal Intubation	11 (73.3)	10 (33.3)	Included
	Intravenous Catheterization	6 (40.0)	9 (30.0)	Included
	Insertion of Medical Device	11 (73.3)	15 (50.0)	Included
	CT Scan	3 (20.0)	3 (10.0)	Included
	MRI	1 (6.7)	0 (0)	Excluded
	Endoscopy	1 (6.7)	0 (0)	Excluded
	Biopsy	2 (13.3)	0 (0)	Excluded
Medications n (%)				
	Glucocorticoids	6 (40.0)	5 (16.7)	Included
	Anti-neoplastic Medications	0 (0)	0 (0)	Excluded
	Antibiotic Use	11 (73.3)	19 (63.3)	Included

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CHAPTER 5: Conclusion

A One Health approach, considering humans, animals, and the environment is key to reducing the spread of antibiotic resistance and preserving antibiotics for the future. Antibiotic use and resistance in companion animal medicine is only one component of the problem, and likely has less overall impact on public health than what occurs in human healthcare and farms. However, despite the close connections between people and their pets, companion animal medicine is relatively understudied compared to other industries which use antibiotics.

The aim of this dissertation was to contribute to filling major gaps in the literature around how companion animal veterinarians make decisions about antibiotics, the role that pets and residential location play in human antibiotic resistance, and ways in which ARB critical to human health may spread in veterinary hospitals. In doing so, we discovered barriers veterinary antibiotic stewardship programs may need to overcome, developed novel methods for understanding the connections between resistance in humans and animals, and identified procedures associated with the spread of CRE in veterinary hospitals. More work is needed to understand how to overcome these barriers to better antibiotic decision making, reduce the spread of antibiotic resistant bacteria infections in pets, the environment, in people, and effectively reduce the spread of multi-drug resistant ARB in veterinary hospitals. The studies contained in this dissertation provide a starting point for a wide range of future work.

In study 1, we interviewed 36 companion animal veterinarians from a range of practice types, serving clients of different socioeconomic status to understand how they made decisions about antibiotics. We found that regardless of their practice type or how they viewed the clients they served; money played a key role in decisions surrounding antibiotic use.

Veterinarians believed that a client's ability or willingness to pay for diagnostic testing interfered with their ability to make informed choices about antibiotic use. Veterinarians reported

that due to client finances, they were frequently unable to perform diagnostic testing on patients when they believed it was medically important. Some veterinarians, predominantly those serving what they perceived to be affluent communities, always offered clients "gold standard" diagnostic testing and treatment plans. Other veterinarians, predominantly those serving what they perceived to be lower or mixed income communities, reported restricting what diagnostic testing and treatments they offered, not wanting to present clients with a large bill. Finances also impacted how veterinarians stocked antibiotics. Many veterinarians described stocking a limited inventory of antibiotics out of concerns that if their inventory was too broad, antibiotics would expire before they could be used, leading to financial losses. Some veterinarians working in animal shelters described limiting their pharmacy to first line choices and limiting what types of infections they would treat. Veterinarians in our study also feared financial consequences for "appropriate" use of antibiotics. As described elsewhere[1,2] this included fear of losing business if not giving into client demands for antibiotics without diagnostic testing. However, we also found veterinarians concerned about economic euthanasia if diagnostic testing left little money for treatment or if a wait and see approach led to a severe infection.

The findings of study 1 indicate that financial matters are often key barriers to US companion animal veterinarian's ability to make judicious antibiotic use decisions. This study adds a US perspective to the limited research, often conducted in European countries, on how veterinarians make antibiotic decisions. Our findings provide more detail than previous studies into the intricate ways in which finances impact and affect antibiotic use, which may be useful for designing antibiotic stewardship interventions. For example, the inability to perform key diagnostic tests is an antibiotic stewardship problem that has been identified elsewhere,[3,4] however this study also adds strategies respondents report using to address this problem. Veterinarians at multiple practices reported that pet insurance allows them to make decisions around antibiotic use from a medical perspective, without being impeded by client finances. Other veterinarians reported finding ways to reduce the cost of diagnostic testing, again allowing them to more easily perform tests they considered medically necessary. While a qualitative study does

not allow us to determine the efficacy of these strategies, only how our respondents perceived them, future studies may determine if interventions to increase pet insurance coverage or decrease the cost of diagnostic testing improve decision making around antibiotic use.

In study 2, we determined that residential location was significantly associated with ampicillin-resistant *E. coli* infections in children in the Philadelphia Metropolitan Area even after controlling for patient characteristics and antibiotic use. Residential location was also significantly associated with ampicillin-resistant *E. coli* infections in dogs. However, while children had a higher risk in the most urban part of the PMA, this was where the risk for dogs was the lowest. Results also indicated that younger age, black race, sample collection during the first 48 hours of hospitalization (vs as an outpatient), having a healthcare associated infection, and previous beta-lactam use was associated with ampicillin resistance in the adjusted model including residential location.

The Philadelphia metropolitan area is highly segregated, both racially and economically.[5,6] Conditions in these segregated regions affecting the exposure to antibiotic resistant bacteria in the environment may contribute to disparities in acquisition of ampicillin resistant *E. coli* in our study. Dissemination hotspots for antibiotic resistance genes include hospital and pharmaceutical waste and wastewater treatment plants.[7] These hotspots may be "critical control points," which govern the selection, proliferation, and spread of resistant pathogens. Children in the urban areas at greater risk in our study may have increased exposure to these critical control points. In contrast, ampicillin-resistance among *E. coli* infections in children was not associated with canine infections after adjusting for other variables.

To understand what factors of the urban environment put children at greater risk, future prospective studies may sample children, dogs, and the environment in the hot and cold spots identified in this study. This sampling may allow for more specific characterization of bacterial samples that allow for a more detailed understanding of the circulation of bacteria and antibiotic resistance genes in children, dogs, and their environments. Adding variables to the model

indicating potential environmental exposures like proximity to wastewater treatment plants, may also help shed light on the means through which residential location affects ARB risk. One limitation was the use of a tertiary care hospital for identifying dogs with ampicillin-resistant *E. coli* infections as the client population and dogs were likely not generalizable to clients and dogs within the PMA. Larger studies investigating how residential location affects ARB risk in dogs using a general practice network or broader diagnostic laboratory data might help determine if the dog pattern of lower risk in urban locations and higher risk in suburban/rural locations holds true.

In study 3 we investigated an outbreak of blaNDM-5 *E. coli* in 15 companion animal patients at the Veterinary Hospital of the University of Pennsylvania occurring between July 2018 and June 2019. Working with the Philadelphia Department of Public Health (PDPH), we conducted a case-control analysis of hospitalization risk factors for the acquisition of the CRE and an investigation of hospital protocols to evaluate potential sources of in hospital transmission. After matching the 15 cases to controls based on length of hospitalization and species, we found that exposure to the anesthesia service, exposure to the surgical service, and exposure to endotracheal intubation were all significantly associated with CRE infection. Review of the medical device reprocessing protocols by the PDPH after the 15 patient outbreak revealed that there was no standard approach for reprocessing of endotracheal tubes between patients. Endotracheal tubes were typically disinfected and reused between patients, but the product used was for hard-surface disinfection and not for high-level disinfection. A policy of using only new, sterilized endotracheal tubes was implemented.

CRE infections in animals have been sporadically reported since 2013,[8] including documentation of transmission between animals and people.[9] While CRE are currently rare in companion animals, our outbreak demonstrates its ability to spread and potential source as a public health threat. Veterinarians must be prepared to institute infectious disease protocols to reduce the spread of CRE and other pathogens with the potential for animal to human transfer. We identified the anesthesia-surgery process and specifically endotracheal tubes as a potential

source of CRE transfer. Although some practices in veterinary medicine, such as reusing endotracheal tubes may have been practiced for years, emerging threats to animals and public health, like CRE, will require improvement of infectious disease policies in veterinary hospitals. Future studies uncovering additional critical points in infection control in veterinary medicine are needed as well as intervention trials testing the efficacy of infection control measures. In addition, while the outbreak investigation provided sufficient evidence to change the endotracheal tube reuse policy at VHUP while it was affected by the outbreak, additional studies are necessary to determine if this was effective at reducing CRE transmission in our hospital and in other settings.

These studies are a starting point for better understanding the impact that companion animal medicine has on antibiotic use and stewardship. While none offer definitive interventions to improve antibiotic stewardship, they shed light on some key factors that can influence future research. Financial matters play a key role in antibiotic use decisions in veterinarians and should be considered when designing research on antibiotic decision making or interventions to reduce inappropriate use. The local environment in which a child or dog lives impacts their risk for antibiotic resistant bacterial infections, but potentially in different ways. Understanding what drives these urban/rural differences may be key to designing ways to reduce community spread of ARB. A critical moment for potential transmission of CRE in veterinary hospitals may occur during the preparation for anesthesia and surgery, specifically endotracheal intubation. It is important to determine how to prevent within hospital CRE transmission and what other interventions can reduce ARB transmission between animals. This may reduce the potential of pets to serve as reservoirs for ARB of human medical importance. Antibiotic resistance is a public health threat and veterinarians and veterinary researchers have an important role to play in combating its spread.

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APPENDIX:

Interview Guide for Study 2

Warm Up

1) What is your job title?
2) Tell me a little about your (practice/shelter/institution)?
3) How would you describe the clientele you serve?
4) Tell me a little bit about your job. What does a typical day look like?

Section 1: Decision Making About Antibiotics

5) Think of the last time you prescribed antibiotics to an animal. Walk me through the process of deciding to prescribe, prescribing, and dispensing the drug.
6) How do you decide whether to prescribe an antibiotic? Which antibiotic to prescribe?
7) Can you talk about a time when the decision was difficult? What made the decision difficult? How did you decide?
8) In addition to clinical factors already discussed, can you think of any additional factors that you need to take into account?
9) How do you talk to clients about your diagnostic and treatment plan?
10) How do you view your own antibiotic prescribing levels and patterns in relation to others?
11) Do you think your antibiotic prescribing practices have changed over time? How?

Section 2: Perceptions of Antibiotics and Antibiotic Resistance

12) How do you get new information about antibiotics?
13) Do you feel like there is a need to improve the use of antibiotics in companion animal veterinary medicine? Please elaborate.
14) What do you think the barriers are to using antibiotics appropriately? How do those barriers get in the way?
15) Do you feel like improving the use of antibiotics is an important goal at your (practice/shelter/institution)? Please elaborate.

16) How do you think veterinary medicine fits into the overall issue of antibiotic resistance?

17) What could be done to improve antibiotic use in veterinary medicine?

Demographic questions:

18) What year did you graduate from veterinary school?

19) Did you do an internship or residency?

20) How long have you been working at this current practice?