ABSTRACT

JOLLEY, ASHLAN LEE. Characterizing Antimicrobial Use in Companion Animals across North Carolina from 2019-2020. (Under the direction of Dr. Cristina Lanzas).

Antimicrobial Resistance (AMR) undermines the medical advancements introduced by antimicrobial drugs and threatens their future effectiveness. To slow the spread of resistance development in bacteria, One Health-based interventions must be applied. These can be aided through collection and analysis of use data from all species consuming antimicrobials. While human AMU is well-characterized in the United States (U.S.), use in animals has historically only been described in food animals. Research regarding companion animal AMU is lacking in the US despite the existence of nearly 140 million pet dogs and cats in 2018. With such a substantial population in a position to potentially receive veterinary care—and therefore antimicrobials—efforts must be undertaken to quantify AMU in this sector. In this dissertation, we aim to establish the foundation for an automated data collection framework for companion animal AMU in the U.S.

Challenges in collecting companion animal AMU data are discussed in Chapter 1. Here, we describe barriers identified in the field regarding access to large and diverse data and the extraction and transformation of these data into analyzable formats. Opportunities exist in natural language processing (NLP), a computer science technique capable of understanding and relaying human language, for automated collection of large-scale data that can be used to infer national estimates of AMU in companion animals. These results can then be used to compare prescribing across species for a holistic analysis of overall use.

In chapter 2, we pilot our data collection techniques within a tertiary veterinary referral hospital while investigating the impacts of the COVID-19 pandemic on antimicrobial prescribing. This global crisis severely affected human and veterinary medicine alike, through

highly modified operations and staffing shortages. Using ordinal logistic regression, changes in the prescribing of medically-important antimicrobials during the pandemic were explored. Results suggested that changes were service-specific, with increased use of more important drugs in the internal medicine, dermatology, and surgery specialties, and decreased use in cardiology. Negative binomial regression also showed that overall prescribing per week was decreased for dogs, while prescribing per patient visit increased for highly important drugs.

In the third chapter of this work, we obtained AMU data from electronic medical records for almost 400 primary care and emergency veterinary clinics in North Carolina (NC) through a partnership with IDEXX Laboratories Inc. NLP was used to extract instances of antimicrobial prescribing for dogs and cats. The state of NC was divided into 6 areas based on region—The Mountains, Piedmont, and Coastal Plain—and urbanicity—Rural or Urban, with records assigned to their originating strata. Social vulnerability was assessed for each area to investigate the potential effects of socioeconomic and demographic factors on prescribing. Negative binomial regression demonstrated that prescribing of beta-lactam combination, fluoroquinolone, and 3rd-generation cephalosporins was increased for female dogs, while prescribing of 1st-generation cephalosporins was decreased for all dogs in mountain and urban areas. Prescribing of fluoroquinolones was also decreased in female cats.

Through these studies, we have leveraged NLP to establish the foundation for the first automated framework collecting companion animal AMU in the U.S. We have also demonstrated that prescribing trends in these species can be influenced by region, urbanization, and patient sex.

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Characterizing Antimicrobial Use in Companion Animals across North Carolina from 2019-2020

by
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DEDICATION

I would like to dedicate this work to my family, friends, and mentors.

To my family, thank you for instilling in me a drive and work ethic early on. You taught me to explore my interests with passion and dedication. You have always been proud of me, and made me believe I could accomplish anything.

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BIOGRAPHY

Ashlan Lee Jolley was born in Sumter, South Carolina in 1997. Here she was homeschooled, allowing her to advance her education to the point of skipping a grade when she later entered public school. Her family soon moved to Camden County near the northeast coast of North Carolina, where she lived until she graduated high school in 2015.

Her desire to become a veterinarian led her to attend NC State University for her undergraduate education. During this time, she engaged in her first research experience under Dr. Sid Thakur that opened the door for her future career as a veterinary epidemiologist. She graduated summa cum laude for her BS in Biochemistry, BS Biological Sciences, and Microbiology minor in 2019.

That fall, she entered veterinary school at NC State with a focus in Epidemiology and Global Health. After her first year, she sought out additional research experience in the Veterinary Scholars Program. She began working under Dr. Cristina Lanzas, who would become her PI and mentor upon her entrance into the combined DVM-PhD program in 2021. Her dissertation research focused on characterizing antimicrobial use in companion animals.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: One Health Data Science Challenges in Generating Antimicrobial Use Data for Companion Animals

Abstract

Antimicrobial Resistance (AMR) is an important modern One Health challenge, and effective stewardship from all sectors is needed to preserve existing antimicrobials' efficacy. Accurate antimicrobial use (AMU) tracking is critical to assess stewardship, but is lacking in certain veterinary domains. For example, collecting accurate AMU data poses unique challenges in companion animal medicine due to lack of standardized coding in patient information management systems (PIMS). This review combines literature and research experience extracting companion animal AMU data to highlight the challenges with collecting, processing, integrating and comparing AMU data from multiple sources. Acquisition of reliable and consistent data from this sector will allow for the development of One Health-minded intervention strategies that can help slow the evolution of resistance in bacterial pathogens.

Keywords

One Health, Antimicrobial Use, Data Science, Companion Animals

Introduction

The National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) in the United States brings a One Health perspective to its objectives by recognizing that antimicrobial resistance (AMR) emerges in all domains where antimicrobial drugs are used [Federal (2020)]. Evidence-based policies and practices are encouraged to reduce antimicrobial use and the spread

of resistant pathogens in the One Health spectrum. The collection of antimicrobial use data is critical to evaluate the impact of national-level efforts to decrease use, assess the relationships between antimicrobial use and resistance, and guide the improvement of antimicrobial stewardship practices.

Efforts have been made to quantify antimicrobial use in food animals. In the United States, the Food and Drug Administration (FDA) requires pharmaceutical companies to report the total amounts of antimicrobial drugs sold for use in agriculture. The United States Department of Agriculture (USDA) and the FDA support on-farm collection of antimicrobial use [FDA F (2024), USDA (2024)]. These efforts have been essential in determining the baseline of antimicrobial use in food animals. However, companion animals have a gap in information on antimicrobial use. Gathering such data in companion animals is critical to understanding the emergence of antimicrobial resistance in these species. Increased resistance bacteria can reduce the therapeutic success of such drugs in companion animals and may also increase the potential for resistance transfer from companion animals to humans [European B (2015), Joosten (2020), Marco-Fuertes (2022)].

Although the interface between companion animals and humans has received less attention than that of livestock to humans, several factors suggest that the risk of transfer of zoonotic-resistant pathogens from such sources is non-negligible. First, a large population of pets live in close relationships with their owners. In 2020, 45% of US households owned pet dogs, and 26% owned pet cats [AVMA (n.d.)]. Second, antimicrobials classified as highly important and critically important for humans are commonly used in companion animal medicine; global events

such as the COVID-19 pandemic have further impacted these trends [Jolley (2023)]. There are also few approved products (i.e., with defined dosage regimens) for cats and dogs, and a limited number of professional guidelines defining recommended use for specific indications.

According to recent studies, veterinarians felt influenced by factors external to stewardship principles–product stocking costs, pressure from clients, and consequences of not providing drugs–in their decisions to prescribe antimicrobials [Lavigne (2021), Cazer (2023)]. In fact, many owners reported asking for an antimicrobial prescription during a visit; preference was even shown for drugs that were of greater importance to human medicine [Stein (2021), Stein (2022), Cazer (2023)]. Such reports support the necessity of considering a more holistic, representative sample of veterinary AMU–specifically, companion animals–to generate a more comprehensive understanding of antimicrobial prescriptions. Consolidation and adoption of electronic medical record systems in veterinary medicine provide an opportunity to collect AMU data from a large sample of patients electronically. This can be achieved by extracting information from medical software used in practices with advanced data science techniques.

The most common type of medical software used in veterinary practices is the patient information management systems (PIMS). The primary purpose of PIMS is to automate various administrative and clinical veterinary practice tasks for clinical staff to document patient care; these include tracking client and patient information, inventory, invoicing, billing, and client communication. While PIMS can be a source of valuable AMU data, there are several challenges in extracting AMU data from them. Veterinarians have no standardized medical coding, thus, data relevant to antimicrobial prescriptions is present in a rich but unstructured form in the

PIMS. To extract meaningful AMU data from such systems, various data science techniques are needed to identify data relevant to AMU within the PIMS, and then integrate the data coming from different PIMS components .

In this review, we identify some of the knowledge and data gaps in companion animal AMU, share our experiences with extracting companion animal AMU from PIMS, and review challenges and opportunities in integrating and standardizing AMU data across One Health domains.

Extracting and Reporting of Human AMU

Surveillance of AMU is one of the foundations of successful antimicrobial stewardship programs. In human healthcare, both inpatient and outpatient use are monitored. Inpatient settings are diverse, and include hospitals, acute care centers, nursing homes, and long-term care facilities. Outpatient settings include primary care, specialty, or emergency clinics [St. George (2021)]. Data on AMU from these two setting types are acquired from a variety of sources, including insurance claims, proprietary vendors, administrative databases, and Medicare/Medicaid centers [CDC (2024), TAFTAR (2019), Gouin (2022)]. Organizations such as the Centers for Disease Control and Prevention (CDC) in the United States collect such data from a variety of these sources to generate periodic assessments of AMU and opportunities to improve stewardship [CDC (2024)].

Collection of prescription, patient, and service data frequently requires integration of data from multiple data streams. Patients' medical records are a common and reliable source for

prescription and patient data. Information about administered and prescribed pharmaceuticals is required to be recorded in a patient's medical notes. The most direct method of harvesting data from medical records is manual review of either electronic or paper records. However, this approach is rarely suitable for surveillance as it is time consuming, inconsistent, and requires direct access to records or de-identification. Adoption of Electronic Medical Records (EMR) in human medicine has been assisted by the 2009 HITECH act and insurance providers, with almost 90% of physicians using them in some capacity [Office (2017), CDC A (2023), IEEE (2017)].

Patient-level information may include demographic information (sex, age, weight, race, etc.), diagnoses, and clinical service or ward. Weight in particular is useful for determining prescribed dosage, which may vary substantially in pediatric patients. The prescription's indicated diagnosis identifies the targeted tissue and impacts prescribing recommendations in some cases. Indications may be collected via medical coding or mined from unstructured medical records and notes. Collected data may include census, admissions, or total number of beds; this provides valuable "denominator data" that represents how many opportunities physicians have to prescribe antimicrobials and allows the estimation of more comparable prescribing rates.

Current Status of Companion Animal AMU

Antimicrobial use in companion animals is difficult to define; there are few approved products (i.e., with defined dosage regimens) for cats and dogs and a limited number of professional guidelines that define recommended use for certain indications. As described in the Animal Medical Drug Use Clarification Act of 1994 (AMDUCA), veterinarians are permitted to use

drugs, including antimicrobials, in an extralabel fashion, meaning in an animal outside of the approved labeling (e.g., species, indication, dosage, frequency, route) [FDA B (1994)]. The need for this legislation arose from the limited number of approved drugs in animal species and the lack of incentive for pharmaceutical companies to invest time and money into the FDA drug approval process for new animal drugs. Barriers to newly approved drugs include expectations of a small market share due to the indication or number of animals and the existence of drugs approved for use in humans decades prior (e.g., cefazolin, doxycycline) [FDA D (2024)]. Despite this, AMDUCA does not give unlimited prescribing authority; veterinarians must have a valid veterinary-client relationship, and the use must be for the animal's health, not for production. For these reasons, it is not uncommon for veterinarians to prescribe a generic drug approved for humans to cats and dogs in addition to products labeled for these species.

Professional organizations that support the preservation of the effectiveness of antimicrobial drugs have published policies and guidelines on judicious use and antimicrobial stewardship (AMS). These documents both give general guidelines on use as well as make more specific recommendations for when antimicrobial drugs are or are not indicated; they do not however specify dosage regimens (i.e., dose, frequency, duration, route of administration) [AVMA A (2024), AVMA B (n.d.), AVMA C (2024), AVMA D (2024), Bellows (2019), Frey (2022), Weese (2015)]. In contrast, guidelines do exist that specify antimicrobial drug and dosage regimens for common indications, including those by the International Society for Companion Animal Infectious Disease (ISCAID) for respiratory, skin, and urinary tract disease [Hiler (2014), Lappin (2017), Weese (2019)].

Despite the presence of such policies and guidelines, only 60% of veterinarians in a recent study were aware of guidelines, and 83% of those reported using them sometimes or often [Taylor (2022)]. There is some evidence that individuals are increasingly using guidelines to change usage patterns, such as decreasing the duration of antimicrobial therapy for sporadic bacterial cystitis [Weese (2021)]. Regardless, there are gaps in guidelines for some diseases (e.g., acute diarrhea), and veterinarians must rely on research publications for this information, which, while helpful, is not available to most veterinarians outside of academia [Pilla (2020), Nixon (2019), Schmalberg (2019)]. Further work is underway to meet these gaps or update older guidelines. These efforts are labor-intensive and time-consuming, though, and continued efforts to disseminate available information are ongoing.

Characterization of veterinary AMU in the United States is less advanced than in northwestern Europe and Australia. For example, several of these countries have already established networks or authoritative bodies for monitoring AMU in animals: Australia (i.e., NCAS), The European Union (i.e., ESVAC), The United Kingdom (i.e., SAVSNET, VetCompass), Denmark (i.e., DANMAP, VETSTAT), etc. [NCAS (2020), European (n.d.), University (n.d.), Royal (2022), Hi-Tier (2021), ANSES (n.d.), Statens (n.d.), Danish (n.d.), AACTING (n.d.), Wageningen (n.d.), SVA (2020)]. However, many of these programs do not focus on companion animals and utilize a variety of metrics ranging from sales data to dosage information to quantify use. Initial attempts have been made to replicate such frameworks within the US, like the University of Minnesota's CAVSNET (Companion Animal Veterinary Surveillance Network) modeled after SAVSNET [College (2023)]. Likewise, our team at NC State has established the framework for automated collection of companion animal AMU piloted at the College of Veterinary Medicine [Jolley

(2023), FDA G (2024)]. Previous studies leveraging such systems have shown them to be reliable sources of information [Hur (2019), Hur (2020)].

Collection of Companion Animal AMU

Data regarding AMU prescriptions in PIMS may include the antimicrobial drug name, formulation, dosage instructions, and indication of use. A critical challenge in extracting these data is that they may be recorded in different parts of the PIMS. For example, information on drug dose and duration may be located in the billing lines and/or prescription tables, but information on indication may appear only on the medical record or client communication notes. Atypical instances of antimicrobial prescribing–for example, perioperatively in surgeries–also represent a source of AMU that may be listed separately. Additionally, different names, including abbreviations and typos, may be used for a given antimicrobial drug. Thus, a carefully curated ontology and natural language processing are needed to extract the data meaningfully.

An Ontology of antimicrobial drugs is critical for identifying antimicrobial prescription records from PIMS. It should begin by selecting pharmaceuticals of interest, and should include genetic and trade names. While the listings for products will vary widely between clinics, these records are likely to include either the name of the generic pharmaceutical, licensed trade names, or unlicensed trade names used under AMDUCA. Antimicrobials that appear in CLSI M100 or that are classified as important, highly important, or critically important to human health (FDA GFI 152 appendix A) should be identified [FDA C (2023)]. Combination pharmaceutical products such as amoxicillin/clavulanic acid should be included in the ontology as both the combination and the individual compounds.

Oral, injectable, and topical formulations represent the most common routes of antimicrobial administration in companion animals. Some less common administration routes, such as intra-articular injections and antimicrobial-infused methyl methacrylate beads, are intended to act locally but are more invasive than topical administrations. Commonly used drugs are often listed using numerous trade names. For example, amoxicillin and clavulanate may be listed under Clavamox, Amoxiclav, Augmentin, Amoclan, Clavulin, Betacillin, Umbrellin, or Clavaseptin. Pharmaceutical products licensed for veterinary use by the FDA are listed in the Approved Animal Drug Products, colloquially known as “The Green Book” [FDA D (2024)]. Trade names of products licensed for human use included in the FDA’s Approved Drug Products with Therapeutic Equivalence Evaluations, or “Orange Book”" should also be included due to extralabel use [FDA E (2024)].

Ultimately, a method for data collection must be established to report and analyze use. Companies such as IDEXX Laboratories Inc.–the industry partner for our research team at NC State–compile AMU data from veterinary clinics within their networks to provide repositories of prescription records. Natural Language Processing (NLP) can then extract antimicrobial prescriptions from these data. NLP is a computer science technique that harnesses artificial intelligence to learn patterns in human language [Geeks (2024), Coursera (2024)]. In the health sciences, NLP can be trained to recognize keywords from EMR and clinical notes [Abellan (2024)]. This can be applied to AMU data as well, by identifying antimicrobial prescriptions of interest and aggregating them into usable databases.

In the absence of any external mandates or funding, penetration of EMR into veterinary medicine has been much slower–around 80% based on a study in Massachusetts–than in human medicine [IEEE (2017), Krone (2016)]. Further, inconsistencies from such a lack of standardization in EMR can make defining prescribing highly complex; records can represent single or repeated visits from patients, entries can be original prescriptions or refills, patients seen at multiple locations can register as separate cases, etc. Quantifying AMU is equally challenging (e.g., comparing an injectable dose vs. an oral course), especially if diagnosis or administration instructions (i.e., frequency, duration, and dose) are not available. Once these descriptive processes have been optimized, however, NLP can serve as continuous automated sources of data collection.

Comparisons Across One Health Spectrum

Integrated analysis across the One Health spectrum is necessary to compare and understand where antimicrobials are used and whether policies and interventions are effective.

The primary barriers to comparing AMU across species are the diversity of data sources characterizing use, and the absence of standardized metrics for use across domains. The two most popular metrics of AMU in humans–Defined Daily Dose (DDD) and Days of Therapy (DOT)–are more challenging to obtain in animals, as no common metric exists in companion animal medicine. This leads veterinary researchers and practitioners to create a multitude of diverse methods for tracking use. Although most of these metrics are based on similar theories to those found in people (e.g., there are numerous versions of an animal/veterinary defined daily dose created to mimic the human DDD), there is no standardization across the board [Schrag (2020)]. This makes quantifying comparisons of AMU between veterinary studies challenging

even without adding human data into the mix. Moreover, international variations in preferred metrics complicate these issues even further in both human and veterinary medicine.

One popular recurring metric in veterinary medicine is that of biomass, defined as "the total mass of an animal species, determined by multiplying that species' population by their average weights in a given year" [FDA (2023)]. This method has already been proposed by the FDA for estimating the sales of antimicrobial drugs in food-producing animals [(FDA A (n.d.)]. In contrast to people where dosage is based on a particular age group (i.e., adult or pediatric) that assumes an average weight for its category, veterinary drugs are traditionally prescribed according to the animal's specific weight range. While patient signalment factors such as species, age, and breed are also considerations in veterinary prescribing, the mass of the animal is the ultimate denominator for oral systemic agents. This fundamental difference in the human and veterinary use metrics highlights the need for a viable comparison method between the species.

The first step in achieving cross-species analysis is gathering accurate estimates of use for companion animals to compare to available human data. This can be accomplished by combining locally-collected companion animal use data with nationwide statistics regarding number of animals and practice counts. National estimates for AMU in companion animals could then be generated; this would represent the first look at total use for dogs and cats in the U.S. Using caseload data from practices or regions of interest, data could also be normalized for comparison across the country. Similarly, comparisons across species could be achieved by applying one of the previously mentioned human metrics (e.g., DDD) to companion animal data based on

accompanying signalment information (i.e., weight). Such normalizations would open the door for future One Health-based analyses of national AMU in humans and animals alike.

Conclusions

Companion animals represent a large population of animals in the U.S. for which reporting of AMU has not been established. As companion animals have the potential to serve as zoonotic reservoirs for bacterial pathogens, unmonitored use of antimicrobials represents a risk to human and public health. Substantial challenges exist in collecting AMU data in veterinary medicine due to lack of standardization in recordkeeping techniques combined with absences of reporting mandates and financial support. Data science techniques such as NLP can be harnessed to extract prescribing information from companion animal EMR and produce usable datasets for analysis. These data can then be normalized by caseload to produce national estimates of AMU in companion animals. Data can also be compared to use in humans, for a One Health-based analysis of overall AMU in the U.S. Insights from such research can be used to inform more effective holistic approaches to reducing further development of AMR affecting all species.

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CHAPTER 2: Impacts of the COVID-19 Pandemic on Antimicrobial Use in Companion Animals in an Academic Veterinary Hospital in North Carolina

Jolley, A., Love, W., Frey, E., & Lanzas, C. (2023). Impacts of the COVID-19 pandemic on antimicrobial use in companion animals in an academic veterinary hospital in North Carolina. Zoonoses and Public Health, 70(5), 393–402. https://doi.org/10.1111/ZPH.13040

Abstract

Antimicrobial resistance (AMR) in bacterial pathogens reduces the effectiveness of these drugs in both human and veterinary medicine, making judicious antimicrobial use (AMU) an important strategy for its control. The COVID-19 pandemic modified operations in both human and veterinary healthcare delivery, potentially impacting AMU. The goal of this research is to quantify how antimicrobial drug prescribing practices for companion animals in an academic veterinary hospital changed during the pandemic. A retrospective study was performed using prescribing data for dogs and cats collected from the NC State College of Veterinary Medicine (NCSU-CVM) pharmacy, which included prescriptions from both the specialty referral hospital and primary care services. Records (n= 31,769) for 34 antimicrobial drugs from 2019-2020—before and during the pandemic-related measures at the NCSU-CVM—were compared. The prescribed antimicrobials' importance were categorized using the FDA's Guidance for Industry (GFI #152) Appendix A, classifying drugs according to medical importance in humans. A proportional odds model was used to estimate the probability of more important antimicrobials being administered in patients seen during the pandemic versus before (i.e., Critically Important vs. Highly Important vs. Important). Rates of AMU per week and per patient visit were also compared. During the pandemic, cumulative antimicrobials prescribed per week were significantly decreased in most services for dogs. Weekly rates for Highly Important antimicrobials were also significantly lower in dogs. For Important and Critically Important

antimicrobials, rates per week were significantly decreased in various services overall. Rates of antimicrobial administration per patient visit were significantly increased for Highly Important drugs. Patients in the internal medicine, dermatology, and surgery services received significantly more important antimicrobials during the pandemic than before, while cardiology patients received significantly less. These results suggest that the pandemic significantly impacted prescribing practices of antimicrobials for companion animals in this study.

Keywords

Antimicrobial resistance (AMR), antimicrobial use (AMU), companion animals, COVID-19, pandemic

Impacts

- Changes in antimicrobial use in an academic veterinary hospital during the pandemic varied by service: internal medicine, dermatology, and surgery used significantly more antimicrobials of higher importance during the pandemic, while cardiology used significantly fewer.
- Antimicrobial prescribing per week was largely reduced in dogs during the pandemic. Rates of Important and Critically Important drugs prescribed per patient visit were reduced during the pandemic, while Highly Important drug rates increased.
- Overall, cats tended to receive fewer antimicrobials than dogs. However, cats received more antimicrobials of higher importance than dogs.

Introduction

This study aims to characterize changes in antimicrobial use (AMU) in companion animals at an academic veterinary hospital during the first year of the novel coronavirus pandemic. AMU is often considered to be a primary driver of antimicrobial resistance (AMR). Antimicrobial-resistant infections are responsible for over 35,000 human deaths per year in the United States, with worldwide mortality estimated at 1.3 million in 2019 [CDC (2019), Murray (2022)]. Morbidity and economic burdens from resistant infections are also high, prompting the World Health Organization (WHO) to consider AMR among the top 10 greatest challenges for the international public health community [WHO (2021)]. Some of these antimicrobial resistance threats are also of concern in cats and dogs, including extended spectrum β-lactamase (EBSL) Enterobacterales, methicillin-resistant *Staphylococcus* spp., and *Pseudomonas aeruginosa* [AVMA (2020)]. Since antimicrobial drugs exert selection pressure on bacterial populations, AMU may impact the prevalence and severity of AMR pathogens. Significant global health challenges such as the COVID-19 pandemic can create opportunities for changes in AMU [CDC (2022), Seneghini (2022)].

In human healthcare settings, AMU per patient was reported to have increased during the pandemic, but total use of antimicrobials decreased; these changes were the result of increased use of antimicrobials for COVID-19 patients combined with a decrease in total patient admissions [Dieringer (2021), Khan (2021), Winders (2021)]. Outpatient AMU decreased concurrently with visits for respiratory symptoms early in the pandemic [Buehrle (2020), King (2021)]. Both veterinary and human medical facilities were subject to extended periods of highly modified operations (i.e., limited hospital capacity, reduced personnel, medical equipment

shortages) as a result of supply chain disruptions and state/federal health-related mandates such as social distancing [AVMA A (2020), Cheeyandira (2020) FDA (2022)]. These disruptions included limited appointment slots, reduced client-clinician interactions, and staffing shortages [Bollig (2022), CDC A (2022), Powell (2022)]. All these events have created the opportunity for changes in veterinary AMU, which could have potential downstream consequences for AMR [Bollig (2022)].

This study aimed to identify effects of COVID-19 pandemic-related changes on antimicrobial prescribing in companion animals at an academic veterinary hospital in North Carolina. Various metrics were used to compare trends of antimicrobial prescribing for canine and feline patients from the NC State College of Veterinary Medicine (NCSU-CVM) before and during the pandemic. The dataset includes patients from the veterinary hospital's specialty and primary care services who were prescribed an antimicrobial within the study period of January 1, 2019–December 31, 2020. Antimicrobials were ranked according to the FDA's classification (Appendix A–GFI #251, 2003) for human medical importance, and used to quantify risk of changes in prescribing as a result of the pandemic. Rates of change in AMU per week and per patient visit were also analyzed for each category. Due to substantial global impacts observed in human outpatient medical care and AMU as a result of the pandemic, we hypothesized that AMU in veterinary hospitals would follow similar trends: decrease in overall frequency of use, but increase in per-patient use.

Materials & Methods

2.1 Prescription Data

Data collected from the NCSU-CVM pharmacy included prescriptions for dogs and cats made during the study period: 01/01/2019 to 12/31/2020. On 03/16/2020, the NCSU-CVM moved to emergency and urgent-only services in response to COVID-19 related executive orders in North Carolina [State (2020)]. To most accurately reflect this location-specific implementation, the pre-pandemic period in this study ranged from 01/01/2019 to 03/15/2020 (14.5 months), and the pandemic period ranged from 03/16/2020-12/31/2020 (9.5 months). Data regarding prescriptions made after 12/31/2020 were not available at the time. As this study's primary objective was to identify changes in AMU due to pandemic-related effects, prescriptions were chosen as the most appropriate metric for quantifying use. Prescription data in this study included oral and injectable antibacterial drugs administered in the NCSU-CVM hospital or dispensed through its pharmacy, and did not include prescriptions written by an NCSU clinician but filled by an external source (e.g., commercial pharmacy). Non-antibacterial drugs (e.g., antifungals, antivirals, antiparasitic) were excluded. The NCSU-CVM pharmacy serves both specialty and primary care services within the hospital; specialty services include cardiology, dentistry, dermatology, emergency and critical care (ECC), internal medicine, neurology, oncology, ophthalmology, surgery, and theriogenology.

Each prescription included in this study was assigned a service based on either the admitting clinical service (93.1%), or the signing clinician if no admitting service was listed (6.9%). Records not assignable to a service or associated clinician (e.g., rotating interns whose schedule could not be reliably tied to a particular hospital service) were omitted from the study. Admission

data for the NCSU-CVM were collected to approximate the number of animals seen at the hospital throughout the study period, aggregated by date, species, and service. Data were derived using patient invoices, which represented individual hospital admissions regardless of the duration of stay. Available admission data represented patients entering the hospital but did not discriminate outpatient from inpatient visits—patients that left the hospital the same day versus patients hospitalized for continuous care over multiple days. Hence, these data represented the total number of patients seen at the NCSU-CVM over the course of the study period, not the number of patients in the hospital on any given day. As information regarding readmissions and refills was not available, such entries could not be differentiated from initial visits or prescriptions within these data.

The prescription dataset included covariates ranging from patient-specific factors like species, breed, and birthdate, to drug administration information such as dose, frequency, and duration. Of these, the covariates considered for model inclusion were patient age (years), patient sex (male, female), patient weight (lbs.), patient species (cat, dog) and assigned clinical service. Age was calculated using birth date and date of drug administration for each entry. Sex was classified as either male or female regardless of reproductive status (i.e., intact vs. neutered). Prescribed antimicrobials were classified based on the FDA Guidance for Industry (GFI) #152 Appendix A for ranking drugs with increasing significance to human medicine: Important (I), Highly Important (H), and Critically Important (C) [FDA (2003)]. During the study period, no restrictions were placed on antimicrobial prescribing by the NCSU-CVM pharmacy.

2.2 Statistical Analyses

Three sets of regression models were fit to describe the changes in antimicrobial use before and during the pandemic. The first set of regression models were negative binomial models to estimate the weekly rate of antimicrobial prescriptions (Eq. 1) [Hilbe (2011), Schober (2021)]. One model was fit for each of the three categories of importance, as well as a fourth model that combined all categories; these models described how the pandemic and other covariates impacted weekly prescribing rates. The number of prescriptions y_i for the respective model during the i^{th} week was modeled as the outcome of a baseline weekly rate β_0, a linear combination of the selected covariates P (hospital service, species, and pandemic timing), and a residual term e_i. In these negative binomial models, the rate ratio of exposure for the covariate p is estimated as $e^{\beta p}$. These time-normalized models were used to estimate the hospital's overall antibiotic use, without accounting for hospital caseload changes that occurred during the pandemic.

$$ln(y_i) = \beta_0 + \sum_{p \in P}^{p} X_{ip}\beta_p + e_i \qquad \textbf{Eq. 1}$$

To account for the reduced caseload during the pandemic, a second set of negative binomial regression models were fit that accounted for patient admissions. These caseload-normalized models estimated the hospital's per-patient rate of antimicrobial prescribing, in contrast to the time-normalized models that estimated the hospital's weekly rate of prescribing. The structure of the caseload-normalized models was similar to the time-normalized models with the addition of an offset term determined by the weekly hospital admissions n_i (Eq. 2). Hospital admission data were stratified by service and species. A separate caseload-normalized model was fit for each of

the three levels of antimicrobial importance and a fourth was fit for all antimicrobials combined, as was done in the time-normalized models.

$$ln(y_i) = \beta_0 + \sum_{p \in P}^{p} X_{ip}\beta_p + ln(n_i) + e_i \qquad \textbf{Eq. 2}$$

Finally, a proportional odds model was fit to estimate how the profile of prescribed antimicrobials shifted during the pandemic. A mixed ordinal logistic regression model consisting of two equations was fit (Eq. 3) [Berridge (2011)]. As some patients received multiple antimicrobial prescriptions during the study periods, a random effect b_j was included to account for the correlation between multiple records from each unique patient *j*. This proportional odds model described the frequency of the importance categories relative to each other, and the model's exponentiated coefficients β_p estimated the odds ratio of the exposure being associated with an increased importance (e.g., the odds of increasing from I to H and from H to C). Note, log odds ratio is fixed between the two increases, I to H and H to C. A single proportional odds model was fit.

$$Logit\left(Pr(y_{ij} > I)\right) = \alpha_{H|I} + \sum_{p \in P}^{p} X_{ijp}\beta_p + b_j + e_i$$

$$Logit\left(Pr(y_{ij} > H)\right) = \alpha_{C|H} + \sum_{p \in P}^{p} X_{ijp}\beta_p + b_j + e_i \qquad \textbf{Eq. 3}$$

An all-possible-regression approach was used to select which covariates to include in each model for fit. Model fit was assessed using Akaike information criterion (AIC) [Akaike (1974), Hilbe (2011)]. Covariates not included for fit in each model were assessed as confounders using a

change-in-estimate method; covariates that changed the coefficient by 10% or more were considered confounders and included in the model. Comparisons were considered significant given $\alpha = 0.05$. All analyses were performed using R (v4.1.0). Cumulative link mixed models were fit using the *ordinal* package (v2019.12-20). Negative binomial models were fit using the *MASS* package (v7.3-55).

Results

3.1 Characteristics Of Prescribing Data

The pharmacy data initially contained 34,403 antimicrobial prescriptions representing 58 different antimicrobial agents, which included multiple formulations of the same active ingredient (i.e., tablet, suspension, injectable). Of these, prescriptions that were non-systemic (e.g., topical, ophthalmic, otic), non-antibacterial (e.g., antifungals, antivirals, antiparasitic), or made for species other than cats and dogs were excluded from the study (n= 2,634). The remaining 31,769 records represented 34 distinct antimicrobial drugs from 16 classes with the majority ranked as Highly or Critically Important (Table 2.1). Of note, the Important category of antimicrobials in this study consisted of only two drugs—cefazolin and cephalexin. The ratio of rank prescribing for I:H:C was roughly 1:2:1 in both pre-pandemic and pandemic periods. The number of antimicrobial prescriptions made during the pandemic period (9.5 months) was roughly 51% of the amount prescribed in the pre-pandemic period (14.5 months) (Table 2.2).

Table 2.1. Antimicrobial drugs (n=34) prescribed at NC State Veterinary Hospital (01/01/2019-12/31/2020) ranked according to FDA Guidance For Industry (GFI) #152 Appendix A.

Antimicrobial Class	Included Antimicrobial	Rank†	Number of Prescriptions
Aminoglycoside	Amikacin	H	59

Table 2.1 (Continued)

	Gentamicin	H	39
	Neomycin	H	335
Ansamycin	Rifampin	H	60
B-Lactamase	Amoxicillin/Clavulanic Acid	H	3657
	Ampicillin/Sulbactam	H	3053
	Piperacillin/Tazobactam	H	645
Carbapenem	Meropenem	H	421
Cephem	Cefazolin	I	4912
	Cephalexin	I	1897
	Cefovecin	C	257
	Cefpodoxime	C	598
	Ceftiofur	C	1
Folate Pathway Inhibitor	Sulfadimethoxine	C	14
	Trimethoprim/Sulfa	C	120
Fosfomycin	Fosfomycin	C	2
Glycopeptide	Vancomycin	H	80
Lincosamide	Clindamycin	H	1626
Macrolide	Azithromycin	C	352
	Erythromycin	C	1
	Tylosin	C	292
Nitroimidazole	Metronidazole	H	2353
Oxazolidinone	Linezolid	H	399
Penicillin	Amoxicillin	H	147
	Ampicillin	H	216

Table 2.1 (Continued)

	Penicillin	H	1
Phenicol	Chloramphenicol	H	86
Quinolone	Ciprofloxacin	C	537
	Enrofloxacin	C	3451
	Levofloxacin	C	198
	Marbofloxacin	C	1031
	Pradofloxacin	C	680
Tetracycline	Doxycycline	H	4005
	Minocycline	H	244

†GFI 152 Appendix A Rank: I=Important, H=Highly Important, and C=Critically Important.

Table 2.2. Proportion of antimicrobial drug prescriptions at the NC State Veterinary Hospital (01/01/2019-12/31/2020) according to FDA Guidance For Industry (GFI) #152 Appendix A rank by time period: pre-pandemic (01/01/2019-03/15/2020) and pandemic (03/16/2020-12/31/2020).

Rank†	Pre-Pandemic	Pandemic	**Total**
I	4621 (22.0%)	2188 (20.3%)	**6809**
H	11583 (55.2%)	5843 (54.1%)	**17426**
C	4766 (22.7%)	2768 (25.6%)	**7534**
Total	**20970 (100%)***	**10799 (100%)***	**31769**

†GFI 152 Appendix A Rank: I=Important, H=Highly Important, and C=Critically Important.
*The lengths of the pre-pandemic (14.5 months) and pandemic (9.5 months) periods, as well as the number of antimicrobials prescribed in each period (see above) are not equivalent.

A total of 52,252 admissions occurred over the study period representing 11 clinical services. The internal medicine, ECC, and oncology services consistently admitted the most patients (Figure 2.1). Likewise, internal medicine and surgery consistently prescribed the highest number of antimicrobials throughout the study (Figure 2.2) (Table 2.3). Patient signalment data

accompanying pharmacy records indicated that the majority of animals prescribed antimicrobials were under 10 years of age and less than 50 pounds. A marginally higher proportion of male patients were also seen, with species largely predominated by dogs (Table 2.3).

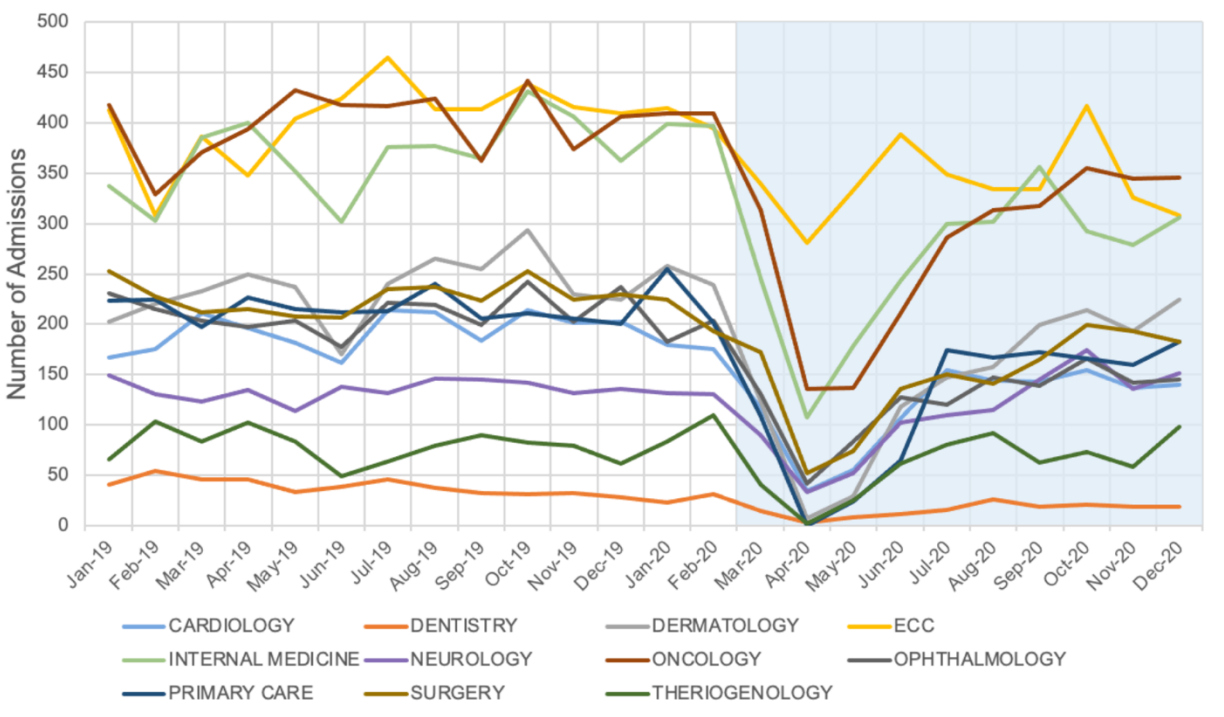

Figure 2.1. Monthly patient admissions at NC State Veterinary Hospital, 01/01/2019-12/31/2020 by service. Blue shaded region indicates the pandemic period (03/16/2020-12/31/2020). ECC (Emergency and Critical Care).

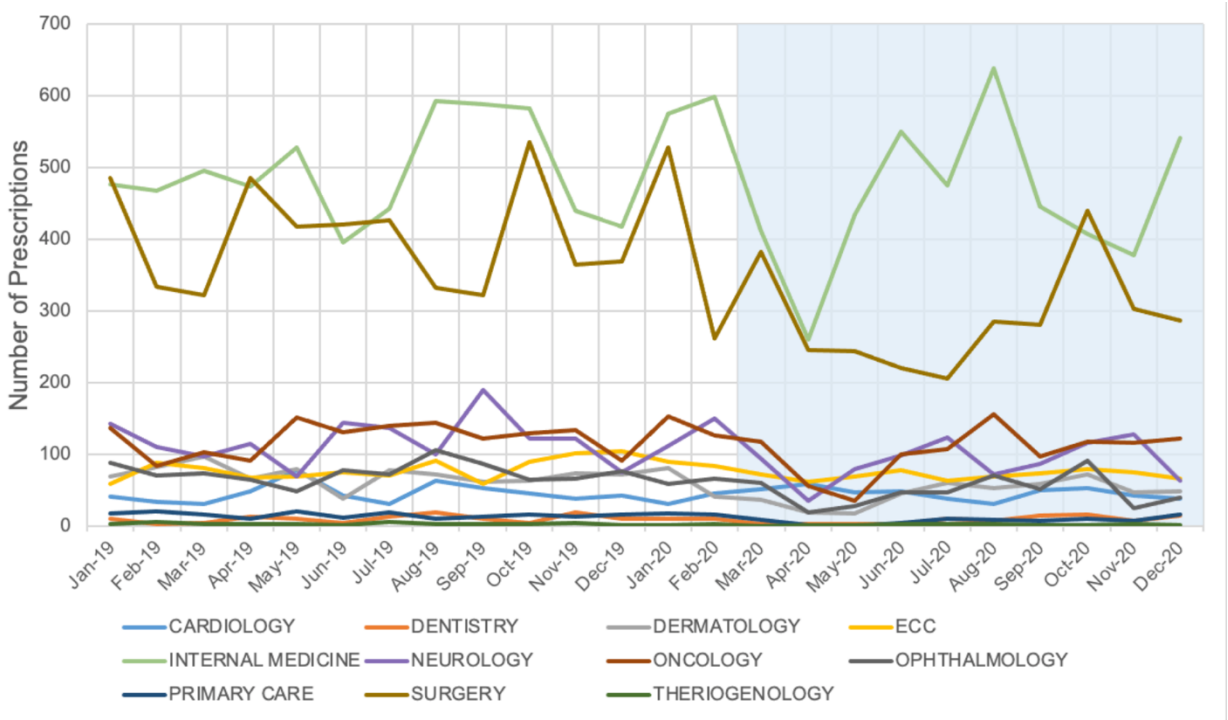

Figure 2.2. Monthly antimicrobial drug prescriptions at NC State Veterinary Hospital, from 01/01/2019-12/31/2020 by service. Blue shaded region indicates the pandemic period (03/16/2020-12/31/2020). ECC (Emergency and Critical Care).

Table 2.3. Clinical service and patient signalment data accompanying antimicrobial prescription records at the NC State Veterinary Hospital (01/01/2019-12/31/2020).

Predictor	**Category**	**Canine**		**Feline**		**Total Patients**	
		n	**Mean**	**n**	**Mean**	**n**	**Mean**
Patient Age *(years)*	--	28449	7.2	3320	8.1	31769	7.3 years
Weight *(pounds)*	–	28449	48.6	3320	10.1	31769	44.6 lbs.
			Proportion		**Proportion**		**Proportion**
Service	Internal Medicine	9829	34.5%	1787	53.8%	11616	36.6%
	Cardiology	1047	3.7%	23	0.7%	1070	3.4%
	Dentistry	167	0.6%	39	1.2%	206	0.6%
	Dermatology	1264	4.4%	155	4.7%	1419	4.5%
	ECC	1513	5.3%	311	9.4%	1824	5.7%

Table 2.3	(Continued)						
	Neurology	2434	8.6%	138	4.2%	2572	8.1%
	Oncology	2589	9.1%	163	4.9%	2752	8.7%
	Ophthalmology	1373	4.8%	114	3.4%	1487	4.7%
	Primary Care	199	0.7%	78	2.3%	277	0.9%
	Surgery	7983	28.1%	512	15.4%	8495	26.7%
	Theriogenology	51	0.2%	0	0.0%	51	0.2%
Patient Sex	Male	14595	51.3%	1858	56.0%	16453	51.8%
	Female	13854	48.7%	1462	44.0%	15316	48.2%
Patient Species	Canine	28449	--	--	--	28449	89.6%
	Feline	--	--	3320	--	3320	10.5%

ECC (Emergency and Critical Care).

3.2 Pandemic Effects On The Proportion Of Antimicrobials Prescribed In Each Medically-Important Category

The proportional odds model found that changes in the importance of antimicrobials used during the pandemic varied by service (Table 2.4); a statistically significant increase in the importance of antimicrobials used was seen in internal medicine, dermatology, and surgery services, with a significant reduction seen in cardiology. Other services did not see a significant change in the distribution of antimicrobial importance during the pandemic. Cats tended to receive more antimicrobials of higher importance (OR = 3.22, 95% CI (2.67, 3.87)), as did older patients (OR = 1.09 per year, 95% CI (1.07, 1.10)). Heavier animals tended to receive fewer antimicrobials of higher importance (OR = 0.96 per 10 lbs. bodyweight, 95% CI (0.94, 0.98)) (Appendix Table A.1). Patient sex did not significantly improve model fit, and was not found to be a confounder on other terms in the model.

Table 2.4. Service-specific rate ratio estimates for the proportional odds model assessing the likelihood of prescribing a higher ranked antimicrobial at the NC State Veterinary Hospital pre-pandemic (01/01/2019-03/15/2020) versus during the pandemic (03/16/2020-12/31/2020).

Service	Rate Ratio (95% CI)	p-value
Internal Medicine	1.20 (1.02, 1.43)	0.03
Cardiology	0.53 (0.29, 0.98)	0.04
Dentistry	1.11 (0.43, 2.84)	0.83
Dermatology	1.57 (1.09, 2.26)	0.01
ECC	0.99 (0.73, 1.34)	0.95
Neurology	0.76 (0.53, 1.10)	0.14
Oncology	0.89 (0.65, 1.21)	0.46
Ophthalmology	0.84 (0.55, 1.30)	0.44
Primary Care	0.48 (0.20, 1.14)	0.10
Surgery	1.82 (1.46, 2.26)	<0.005
Theriogenology	0.77 (0.09, 6.74)	0.81

ECC (Emergency and Critical Care).

3.3 Pandemic Effects On Prescribing Rates

Out of the set of four caseload-normalized negative binomial models for the rate of antimicrobial prescriptions per patient visit, only one found a significant difference during the pandemic (Appendix Table A.2); Highly Important antimicrobials were found to be prescribed at a higher rate per patient during the pandemic period (RR = 1.19, 95% CI (1.02, 1.61)) compared to the pre-pandemic period. The rate of prescriptions per patient was not significantly different between the pre-pandemic and pandemic periods for Important antimicrobials (RR = 1.20, 95% CI (0.89, 1.72)), Critically Important antimicrobials (RR = 1.17, 95% CI (0.95, 1.44)), or all antimicrobials combined (RR = 1.21, 95% CI (0.99, 1.47)).

In the time-normalized negative binomial models for weekly prescribing rates, there were significant interactions between pandemic and either service, species, or both (Appendix Tables A.3 - 6). Rates of prescribing Important antimicrobials per week significantly decreased during the pandemic period in the dermatology and surgical services, and significantly increased in oncology (Table 2.5). Rates of prescribing Critically Important antimicrobials were significantly decreased in dermatology, neurology, oncology, and primary care (Table 2.6). For Highly Important antimicrobials, dogs received significantly fewer prescriptions per week during the pandemic period (RR = 0.70, 95% CI (0.64, 0.77)) but cats did not see a significant change in weekly prescribing rate (RR = 0.88, 95% CI (0.76, 1.02)). For all antimicrobials combined, a significant decrease was found for dogs in all services except internal medicine, cardiology, and dentistry (Table 2.7). For cats, the weekly rate for all antimicrobials was significantly reduced in ophthalmology, primary care, and surgery during the pandemic period.

Table 2.5. Stratum-specific rate ratio estimates for the time-normalized negative binomial model assessing weekly prescriptions of Important antimicrobials at the NC State Veterinary Hospital pre-pandemic (01/01/2019-03/15/2020) and during the pandemic (03/16/2020-12/31/2020).

Service	Rate Ratio (95% CI)	p-value
Internal Medicine	1.02 (0.78, 1.34)	0.88
Cardiology	1.09 (0.84, 1.43)	0.51
Dentistry*	N/A	—
Dermatology	0.33 (0.18, 0.60)	<0.005
ECC	0.71 (0.48, 1.05)	0.09
Neurology	0.78 (0.60, 1.02)	0.06
Oncology	1.57 (1.01, 2.43)	0.04

Table 2.5 (Continued)

Ophthalmology	0.81 (0.60, 1.08)	0.15
Primary Care	0.70 (0.28, 1.77)	0.45
Surgery	0.61 (0.49, 0.76)	<0.005
Theriogenology	0.58 (0.27, 1.25)	0.16

ECC (Emergency and Critical Care).
*Dentistry was omitted from this model because the service had only a single instance of prescribing a Critically Important antimicrobial. Model summaries are provided in the Appendix.

Table 2.6. Stratum-specific rate ratio estimates for the time-normalized negative binomial model assessing weekly prescriptions of Critically Important antimicrobials at the NC State Veterinary Hospital pre-pandemic (01/01/2019-03/15/2020) and during the pandemic (03/16/2020-12/31/2020).

Service	Rate Ratio (95% CI)	p-value
Internal Medicine	1.08 (0.89, 1.31)	0.41
Cardiology	0.82 (0.43, 1.55)	0.54
Dentistry	0.56 (0.24, 1.30)	0.18
Dermatology	0.77 (0.59, 1.00)	0.05
ECC	0.89 (0.68, 1.17)	0.41
Neurology	0.58 (0.43, 0.78)	<0.005
Oncology	0.70 (0.54, 0.89)	<0.005
Ophthalmology	1.04 (0.69, 1.58)	0.83
Primary Care	0.33 (0.17, 0.61)	<0.005
Surgery	0.83 (0.67, 1.04)	0.83
Theriogenology*	N/A	—

ECC (Emergency and Critical Care).
*Theriogenology was omitted from this model because the service had only a single instance of prescribing a Critically Important antimicrobial. Model summaries are provided in the Appendix.

Table 2.7. Stratum-specific rate ratio estimates for the time-normalized negative binomial model assessing weekly prescriptions of all antimicrobials at the NC State Veterinary Hospital pre-pandemic (01/01/2019-03/15/2020) and during the pandemic (03/16/2020-12/31/2020).

Table 2.7 (Continued)

Service	Canine		Feline	
	Rate Ratio (95% CI)	**p-value**	**Rate Ratio (95% CI)**	**p-value**
Internal Medicine	0.85 (0.72, 1.02)	0.08	1.02 (0.85, 1.22)	0.86
Cardiology	1.00 (0.80, 1.26)	0.98	1.19 (0.93, 1.53)	0.16
Dentistry	0.76 (0.54, 1.07)	0.12	0.91 (0.63, 1.30)	0.59
Dermatology	0.71 (0.57, 0.87)	<0.005	0.84 (0.66, 1.06)	0.15
ECC	0.80 (0.65, 0.98)	0.03	0.95 (0.76, 1.18)	0.65
Neurology	0.73 (0.60, 0.89)	<0.005	0.87 (0.70, 1.08)	0.20
Oncology	0.74 (0.61, 0.90)	<0.005	0.88 (0.71, 1.09)	0.24
Ophthalmology	0.65 (0.53, 0.81)	<0.005	0.78 (0.61, 0.99)	0.04
Primary Care	0.40 (0.28, 0.55)	<0.005	0.47 (0.33, 0.67)	<0.005
Surgery	0.66 (0.55, 0.79)	<0.005	0.79 (0.65, 0.95)	0.01
Theriogenology	0.51 (0.26, 0.98)	0.04	0.60 (0.31, 1.19)	0.14

ECC (Emergency and Critical Care).

Discussion

4.1 Changes In AMU Trends During The Pandemic

The COVID-19 pandemic substantially impacted the healthcare sector on a global scale, affecting both human and veterinary medicine [AVMA A (2020), CDC (2022)]. Consequences of the pandemic on healthcare delivery are still being quantified. One area of uncertainty is how the pandemic affected AMU in companion animals, and its potential downstream effects on AMR [CDC (2022), Seneghini (2022)]. At the NCSU-CVM hospital, changes in AMU often varied by service; the internal medicine, dermatology, and surgery services used significantly more antimicrobials of higher importance during the pandemic, and cardiology used significantly

fewer. Our findings indicate that the overall number of prescriptions was reduced, as indicated by the decrease in rates of prescriptions per week for dogs and cats in most services (Table 2.7). Changes in the rate of antimicrobial prescriptions per patient visit depended on the service and antimicrobial category. Specifically, the Highly Important prescriptions per visit showed a significant increase overall during the pandemic period (Appendix Table A.2).

The changes in antimicrobial administration rates in companion animals at the NCSU-CVM during the pandemic appear to be largely similar–albeit for different reasons–to the patterns noted in human medicine (i.e., fewer prescriptions overall, but an increase in prescriptions per patient) [Dieringer (2021), Khan (2021), Winders (2021)]. However, our study stratified the results by service; the decrease in prescriptions per week varied by service and species, and the increase in prescriptions per patient only occurred in the Highly Important category. The cases seen at the NCSU-CVM during the pandemic reflected the shift to emergency/urgent-only services and away from wellness visits and elective procedures starting March 16, 2020. This change in case composition coupled with decreased availability of recheck appointments due to reduced operations could have promoted the use of increasingly important antimicrobials in an attempt to resolve diseases more quickly.

4.2 Factors Influencing Antimicrobial Prescribing

The inclusion of the selected covariates in the various models reflect their importance in antimicrobial prescribing decisions; patient-specific factors such as age, weight, and species can influence the type and dose of antimicrobial prescribed [Redding (2020)]. For example, cats were estimated to be prescribed significantly higher ranked antimicrobials than dogs (Appendix

Table A.1). Previous studies have demonstrated that AMU in cats involves higher ranked antimicrobials than dogs due to a relatively reduced selection of approved drugs [Murphy (2012), Papich (2021)]. Fewer options for feline-approved drugs also support the results of the negative binomial models; where AMU in most services was reduced in dogs, it typically saw no change in cats (Table 2.7).

Most services were estimated to use significantly fewer antimicrobials of higher importance than the referent level, internal medicine. The only services to use significantly more antimicrobials of higher importance than internal medicine before the pandemic were dermatology and oncology (Appendix Table A.1). Dermatology is known to treat a plethora of bacterial skin pathogens (e.g., *Staphylococcus* and *Pseudomonas* spp.) that often require extended treatment with antimicrobials [Goggs (2021), Summers (2012)]. Oncology also commonly utilizes antimicrobials both prophylactically and therapeutically for treatment of radiation side effects (e.g., mucositis/moist desquamation), chemotherapy-induced side effects (e.g., febrile neutropenia), and cancer-related comorbidities [Boudreaux (2014)]. Adding in the pandemic-by-service interactions, surgery became the only service to use significantly more antimicrobials of higher importance than internal medicine during the pandemic (Appendix Table A.1). Surgery was the second most frequent prescriber of antimicrobials throughout the study after internal medicine (Table 2.3).

Our findings agree with previous reports that dogs were more likely to be prescribed an antimicrobial than cats; however, cats were more likely than dogs to receive drugs of higher importance (Appendix Tables A.1 - 2)—specifically third-generation cephalosporins [Buckland (2016), Goggs (2021), Hardefeldt (2018), Hur (2020), Singleton (2017)]. Typically, the most

frequently prescribed antimicrobials are cefpodoxime and amoxicillin/clavulanic acid for dogs, and cefovecin for cats [Bollig (2022), Goggs (2021), Hardefeldt (2018), Hur (2020), Singleton (2017)]. When choosing a cephalosporin or beta-lactam combination agent, the relatively longer duration of action of cefpodoxime (24 hours) and cefovecin (14 days) can make these agents more desirable in terms of client adherence compared to other agents in the same drug classes. Cefpodoxime and cefovecin were two of only three third-generation cephalosporins included in this study, making up less than 3% of the total prescriptions (Table 2.1); this is a notable difference in AMU at the NCSU-CVM compared to what is reported in the literature, especially for cefovecin. Alternatively, amoxicillin/clavulanic acid made up almost 12% of the hospital's prescriptions, supporting its importance as the third most prescribed antimicrobial in this study.

4.3 Limitations

The FDA's GFI #152 Appendix A is not the universally agreed method for classification of antimicrobials, and is one of many such schemes across various agencies and regions. Similarly, this study included prescription data from a single academic veterinary hospital in North Carolina, and may not reflect broader trends in other such hospitals or states. It should also be noted that the majority of canine and feline cases (91.86%) seen at the NCSU-CVM are patients of the specialty services. As the NCSU-CVM is a tertiary referral hospital, the caseload is expected to be more complex or severe than primary care practices; however, the impacts of COVID-19 that this study sought to describe affected all types of veterinary hospitals. Given the ongoing disruptions due to the COVID-19 pandemic, it is possible that the effects of the changes early in the pandemic may not apply to the latter parts of the pandemic in 2021 and beyond. Further, as this study's primary objective was to characterize AMU, it was out of the scope of

this research to speculate how these trends may have impacted AMR in patients or in the ecosystem. Future research on this topic should include similar studies of veterinary primary care prescribing before and during the pandemic to compare trends to what was observed at this academic veterinary hospital.

The AMU data available in this study were limited to drugs administered in the hospital or dispensed from the hospital pharmacy for use at home. Clients may have used external sources to fill prescriptions due to factors such as cost or convenience; however, information about antibiotic prescriptions written by NCSU-CVM clinicians but filled by external pharmacies was not available. These external prescriptions could introduce bias into the estimate, but it is difficult to predict in which direction this may have occurred without such data. At the NCSU-CVM, writing prescriptions to be filled by external pharmacies occurs uncommonly, and hence is not expected to significantly bias the estimated results in the current study.

Approximately 2% of the original records in this study could not be assigned a service and were omitted. This occurred most frequently when there was no assigned service, and the signing clinician could not be reliably assigned to a service (e.g., interns rotating through multiple services). Medication typically will not have an assigned service when the patient is not physically in the hospital; a situation that likely arose more frequently during the pandemic. If these unassignable medications were systematically different than the medications included in these data, the study may have missed trends in AMU during the pandemic. Due to the small proportion of records this affected, it is not expected to substantially impact the study's findings. Additionally, we could not assess whether the patients prescribed antimicrobials in this study had

differing signalments compared to the overall NCSU-CVM's patient population, as our caseload data were limited to service and species information.

Misclassification of service due to assignment by admission may also have taken place, but such data were not available. At the NCSU-CVM, patients may be admitted by one service for evaluation (e.g., ECC) and subsequently prescribed medication by another service on consultation. In these cases, the antimicrobial would be assigned to the original service and not the consulting service that prescribed the medication. Assuming this occurred at random in the data, such non-differential misclassification tends to bias estimated effects towards the null value. This means that the effect of service may have been underestimated in some cases.

Conclusions

The internal medicine, dermatology, and surgery services used significantly more antimicrobials of higher importance during the pandemic, while cardiology used significantly fewer. The rate of antimicrobial prescriptions per patient visit was significantly increased for Highly Important drugs during the pandemic, but not significantly different for any other category of drugs during this time. For antimicrobial prescriptions per week, the rates for Important and Critically Important drugs were significantly decreased in several services over the pandemic period. Rates of Highly Important prescriptions per week were significantly lower in dogs but unchanged in cats. For the rates of all antimicrobials prescribed per week during the pandemic, use in dogs showed significant decreases in multiple services while use in cats remained mostly unchanged. Service and species were important predictors, present in all models in this study. Overall, these

results indicate that the COVID-19 pandemic had a significant effect on several areas of antimicrobial prescribing for companion animals at the NCSU-CVM.

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COI Statement

The authors of this study declare no knowledge of conflicting interests.

Ethics Statement

This material is the authors' own original work, which has not been previously published elsewhere. The paper is not currently being considered for publication elsewhere.

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CHAPTER 3: Effects of regional diversity on antimicrobial prescribing in companion animals in North Carolina from 2019-2020

Abstract

Background

Data on antimicrobial use (AMU) in companion animals is lacking in the United States, along with information regarding drivers of such prescribing.

Objectives

The objectives of this study are to 1) describe spatiotemporal trends in AMU for dogs and cats in North Carolina (NC) from January 1, 2019 – December 31, 2020, and 2) evaluate multiple social, economic, and demographic factors and the COVID-19 pandemic influence on prescribing practices.

Methods

In cooperation with IDEXX Laboratories, Inc. (IDEXX), we collected AMU data from dogs and cats treated at 389 practices during 2019 and 2020. Practices were stratified by geographic region (mountain, piedmont, coastal plain) and urbanization (rural, urban). Variables from the Centers for Disease Control and Prevention's (CDC) Social Vulnerability Index (SVI) were summarized for each of the six areas. Prescriptions were categorized as before (January 1, 2019 – March 14, 2020) or during (March 15, 2021 – December 31, 2021) the COVID-19 pandemic. Poisson family models were used to estimate prescribing rates and rate ratios for prescription predictors

as well as the total number of patients prescribed per the number of patients seen by stratum monthly.

Results

Region and urbanicity only significantly affected prescribing rates for 1st-generation cephalosporins in dogs, and prescribing rates did not significantly change during the COVID-19 pandemic. Patient sex was the most consistently significant independent variable for prescribing rates.

Conclusions

The current study found that prescribing rates of the most common antimicrobials in dogs and cats were fairly uniform across the state, with a few exceptions including patient sex.

Introduction

Antimicrobials have long served as a cornerstone of modern medicine, ranking among the top medical achievements of the 20th century. However, the evolution of resistance to these drugs in microbes has increasingly threatened their therapeutic effectiveness. Due to the limited number of FDA-approved antimicrobial agents for companion animals, human-approved antimicrobial agents are often used extra-label in veterinary patients, increasing the overlap in antimicrobials used in both animals and people [FDA B (2023]. While human antimicrobial use (AMU) data are readily available in the United States (US), information regarding AMU in animals is limited and focused more on food animals. Current practices for veterinary prescribing in companion animals are inferred from methodologically heterogeneous reports that are limited in scope or

restricted to academic settings [Goggs (2021), Baker (2012), Escher (2011), Murphy (2012), Radford (2011)]. Consequently, the existing reports do not provide a comprehensive picture of companion animal AMU in the US.

Drivers of antimicrobial agent prescribing in companion animal practice are also not fully understood. Recent studies have suggested factors such as cost and antimicrobial stewardship knowledge influence cat and dog owners' treatment choices for their animals [Stein (2021), Stein (2022), Frey (2023), Lavigne (2021)]. The client's sex, education, professional background, age and race have been associated with the client's clinical understanding and subsequent decision-making for patient antimicrobial therapy [Frey (2023)]. Socioeconomic and demographic characteristics, like ethnicity, gender, and household size, influence the likelihood of companion animal ownership and thus the potential for veterinary care and AMU prescription [Applebaum (2020), Murray (2010), Martins (2013)].

Similar socioeconomic and demographic factors, including race and ethnicity, sex, age, and socioeconomic factors, have been shown to impact antimicrobial prescribing in human medicine [Kim (2023)]. Since an individual's community can influence these factors, one method to quantify them is through social vulnerability, which is defined by the Centers for Disease Control and Prevention (CDC) as "demographic and socioeconomic factors that contribute to communities being more adversely affected by public health emergencies and other external hazards and stressors that cause disease and injury" [CDC (2024)]. The CDC has classified communities according to their social vulnerability index (SVI), which includes domains of

socioeconomic status, household composition and disability, minority status and language, and housing and transportation [CDC (2024)].

In this study, we aimed to describe spatiotemporal trends in companion animal AMU across North Carolina (NC) from 2019-2020 while investigating the relationships between AMU prescribing and animal- and community-level factors defined by the CDC's SVI, geographic regions, and urbanicity as explanatory variables at the community level. Additionally, since the data coincided with the beginning of the COVID-19 pandemic, we evaluated its effect on companion animal AMU and hypothesized that modified veterinary operations due to the COVID-19 mandates and staffing shortages changed AMU prescription patterns [AVMA (2020), CDC B (2022), Jolley (2023)].

Materials and Methods

Data Collection

Patient data were collected from veterinary practice information management systems (PIMS) records from 389 North Carolina primary, specialty, and emergency veterinary practices accessible via existing data sharing agreements through IDEXX. The accessible PIMS included: Cornerstone, DVMAX, Animana, Neo, Intravet, Intravet SQL, Impromed, Avimark, and ClienTrax. Records from PIMS were de-identified by IDEXX with all practice, client, and patient data removed and aggregated prior to data analysis.

Records of in-hospital AMU and prescriptions between January 1, 2019 and December 31, 2020 were collected from billing and pharmacy records using an analytic pipeline previously

developed and validated by IDEXX and NCSU [Jolley, 2023]. Natural language processing was used to identify billing codes for antimicrobial products containing one or more of the pharmaceuticals identified for the current study (Appendix Tables A.8-9). The pipeline identified product characteristics including active ingredients, formulation, and route of administration. Route of administration was categorized as topical or systemic, with the latter category being further subdivided as oral or injectable. Instances where one drug was administered or prescribed to a single patient multiple times in a single day were collapsed into a single record. Examples of this data modification included prescription of multiple formulations of the same drug (e.g., a dog being prescribed both 250 mg and 500 mg cephalexin capsules to achieve a total dose of 750 mg per dose) or multiple administrations of the same drug in the same day (e.g., multiple injections of ampicillin for an inpatient for antimicrobial coverage).

The county in which each clinic was located was used as a proxy for patient location. Counties in North Carolina were divided based on two criteria—geographic region and urbanicity—resulting in six areas (Figure 3.1, Appendix Table A.7). Three county geographic regions were used: the eastern Coastal Plain, the central Piedmont, and the western Mountains (Figure 3.1). County urbanicity was assigned using the consensus of three sources [NCpedia (2012), USDA (2023), Pitt (n.d.), NC OSBM (2021)]. The Mountain region comprised 23% of NC counties, the Piedmont 36%, and the Coastal Plain 41%. Rural counties represented 68% of all counties.

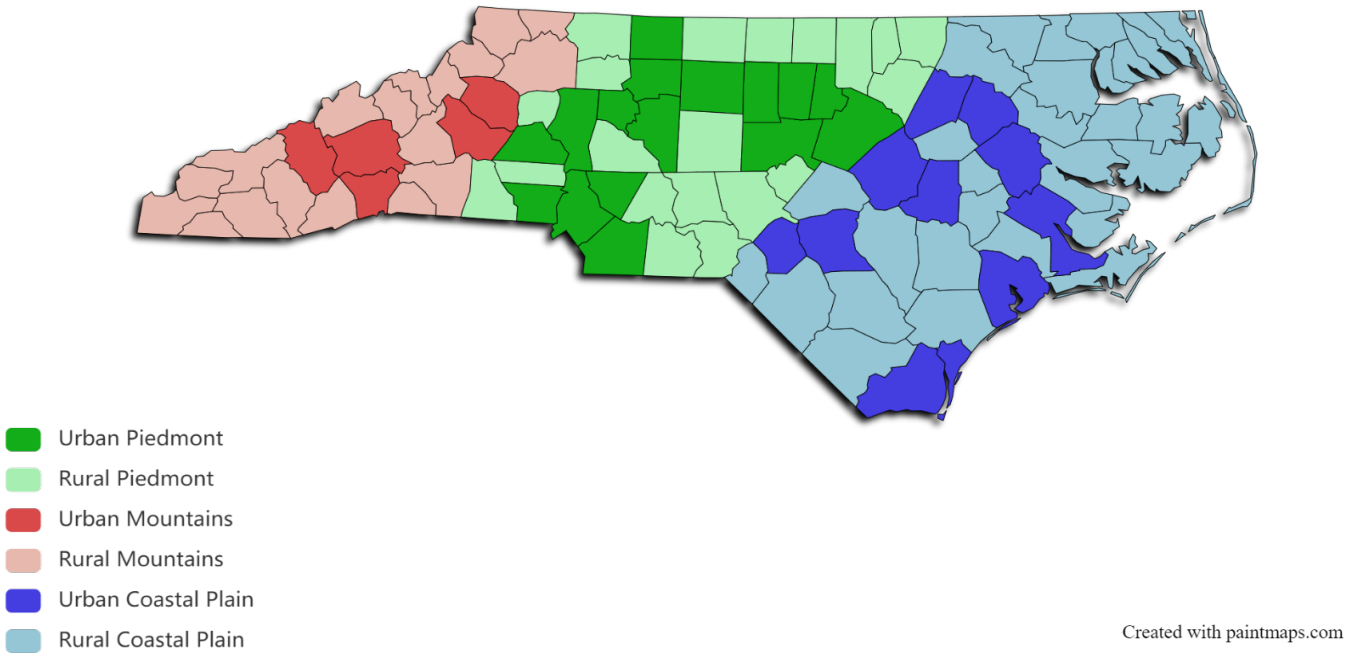

Figure 3.1. Map of region and urbanization areas in North Carolina.

The CDC's SVI was used to assign vulnerability rankings to each NC county based on 4 domains: socioeconomic status, household characteristics, racial & ethnic minority status, and housing type & transportation [CDC (2024)]. Each of these domains are comprised of 1-5 measures describing various aspects of its theme. SVIs were calculated for each area by averaging the SVIs of their respective counties. Antibiotic prescriptions were stratified by species (dogs or cats), and sex was included as an independent variable. For each of the 6 areas, the median SVI of all census tracts in a region were aggregated and assigned to each region. Additionally, median SVI was multiplied by ten to facilitate interpretation; the resultant rate ratio represents a 10% change in the region's median index.

A variable representing the period in which the COVID-19 pandemic was present classified all prescriptions occurring after 03/2020 as "pandemic", to reflect the onset of pandemic-related

mandates in North Carolina [State of North Carolina (2020)]. Data from after 12/31/2020 was not included to align with our previous work, in which factors including staffing after this date had led to volatility in case load [Jolley (2023)]. Prescription counts were normalized across the six areas defined above to account for heterogeneity in pet populations and clinical caseloads. Each clinic in the study, the number of unique dog and cat patients seen each calendar month were collected and then aggregated by area; aggregation was performed prior to delivery of the data to the researchers to maintain clinic anonymity. In total, there were 7,030,527 canine patient-months and 1,623,021 feline patient months during the two years of the study.

Statistical Analyses

Negative binomial regression was used to estimate the prescribing rate and rate ratios for the models' independent variables on systemic (i.e., oral and injectable formulations) antimicrobials. Species-specific differences in AMU were observed in previous research, so separate sets of models were fit for cats and dogs [Jolley (2023)]. Four models were fit for each of the most frequently prescribed antimicrobial classes in dogs: beta-lactam combination agents, fluoroquinolones, 1st-generation cephalosporins, and 3rd-generation cephalosporins. Three models were fit for each of the most frequently prescribed antimicrobial classes in cats: beta-lactam combination agents, fluoroquinolones, and 3rd-generation cephalosporins. These classes accounted for 64% and 78% of prescriptions for dogs and cats respectively.

These negative binomial models fit the total number of each antimicrobial class (y) in each stratum (i), normalized by the respective number of patients seen (n_i) (Eq 1.) [Hilbe (2011), Schober (2021)]. Independent variables (x_i) included geographic region, urbanicity, pandemic

timeframe, and median SVI were included in all models. Patient sex was a potential covariate and evaluated for improvement of fit using AIC. Interactions between all included main effects were evaluated via likelihood ratio testing and included if significant (α = 0.05). Analyses were conducted in R Studio (R v4.2.2) with the *MASS* package (v7.3-58.1).

$$ln(y_i) = \beta_0 + \sum_{p \epsilon P}^{p} X_{ip}\beta_p + ln(n_i) + e_i \qquad \textbf{Eq 1}$$

Results

Descriptive Statistics for All Prescriptions

Prescriptions were categorized as oral (55%), injectable (14%), topical (21%), or antiseptic (4%) formulations, with some unclassified (6%) due to lack of data entry. Aminoglycosides were the most frequently prescribed topical antimicrobial class throughout the study period followed by polypeptides and phenicols in dogs and tetracyclines and polypeptides in cats (Table 3.1). Neomycin sulfate (aminoglycoside) was the leading topical drug prescribed to both species, followed by gentamicin (aminoglycoside) and florfenicol (phenicol) for dogs and tobramycin (aminoglycoside) and oxytetracycline (tetracycline) for cats.

Table 3.1. Topical antimicrobial prescriptions by species and class from 01/01/2019-12/31/2020.

Drug Class	Canine	Feline	Total
Aminoglycoside	201,613	27,270	228,883
Cephalosporin III	5	0	5
Fluoroquinolone	20,689	5,200	25,889
Lincosamide	561	132	693
Macrolide	1,280	3,676	4,956
Penicillin	2	0	2

Table 3.1 (Continued)

Phenicol	51,397	2,994	54,391
Polypeptide	57,644	7,110	64,754
Sulfonamides	7,335	1,425	8,760
Tetracycline	4,669	10,534	15,203
Total	345,195	58,341	**403,536**

Beta-lactam combination agents, 3rd-generation cephalosporins, fluoroquinolones, and nitroimidazoles were among the top five prescribed systemic antimicrobial classes for both dogs and cats (Table 3.2, Appendix Tables A.8-A.9). Nitroimidazoles–composed solely of the drug metronidazole– and amoxicillin/clavulanic acid (a beta-lactam combination agent) were two of the top three drugs prescribed to both species. 3rd-generation cephalosporins were the most prescribed drug class for cats, driven primarily by cefovecin, which accounted for almost half of all systemic feline prescriptions. Cephalexin–a 1st-generation cephalosporin–was also one of the top three drugs prescribed to dogs in this study. The rural Coastal Plains counties typically had the highest number of total antimicrobial prescriptions per month, while the Piedmont Rural had the lowest (Figure 3.2).

Table 3.2. Systemic (oral or injectable) antimicrobial prescriptions by species and class from 01/01/2019-12/31/2020.

Drug Class	Canine	Feline	Total
Aminoglycoside	1,012	276	1,288
Beta-lactam Comb.	158,970	53,298	212,268
Carbapenems	143	10	153
Cephalosporin I	188,871	3,229	192,100
Cephalosporin III	189,363	122,275	311,638
Fluoroquinolone	126,495	31,479	157,974

Table 3.2 (Continued)

Lincosamide	75,765	10,077	85,842
Macrolide	10,454	7,537	17,991
Nitroimidazole	205,867	16,852	222,719
Penicillin	50,136	11,005	61,141
Phenicol	1,402	24	1,426
Sulfonamides	15,081	3,349	18,430
Tetracycline	67,563	4,903	72,466
Total	1,091,122	264,314	**1,355,436**

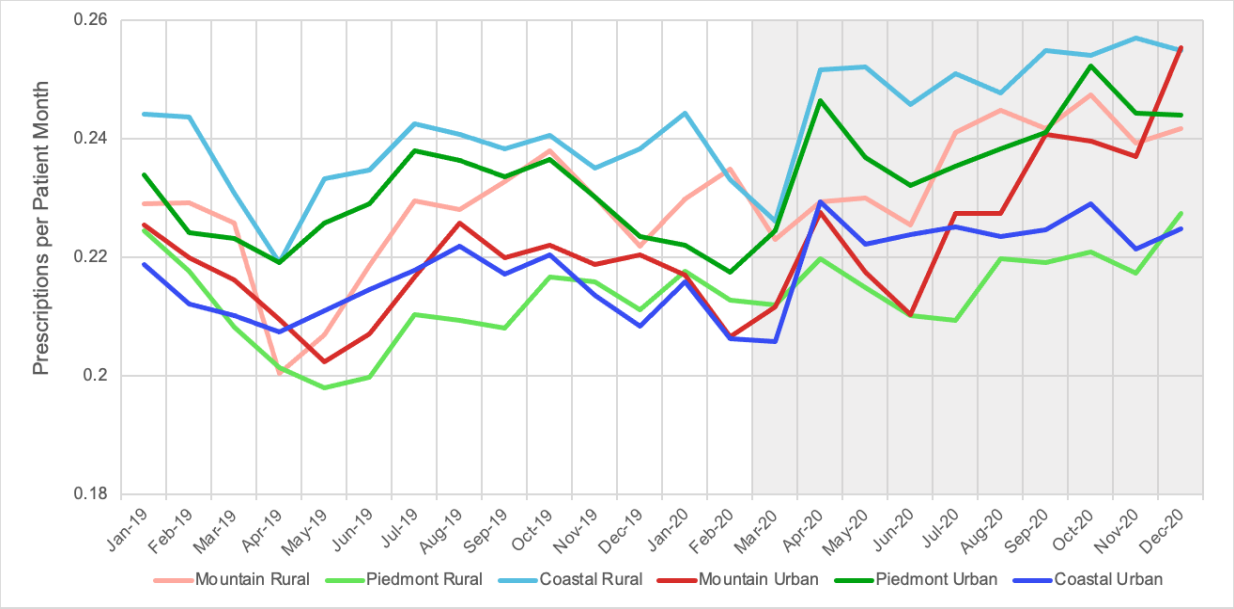

Figure 3.2. Number of antimicrobial prescriptions per patient-month (i.e., prescribing rate) from 01/01/2019-12/31/2020. Gray-shaded area represents the COVID-19 pandemic era (04/01/2020-12/31/2020). Individual patients were able to contribute to multiple months and multiple antimicrobial classes within the same month.

Table 3.3. Number of practices and patient-months in each area from 01/01/2019-12/31/2020.

Count	Mountain Rural	Mountain Urban	Piedmont Rural	Piedmont Urban	Coastal Plain Rural	Coastal Plain Urban	Total
Practices	19	28	41	198	43	60	389
Canine	312,014	526,911	825,438	3,298,096	814,020	1,254,048	7,030,527

Table 3.3 (Continued)

Feline	76,462	135,342	179,668	782,970	173,425	275,154	1,623,021
Total	388,476	662,253	1,005,106	4,081,066	987,445	1,529,202	**8,653,548**

Note: Individual patients were able to contribute to multiple months and multiple antimicrobial classes within the same month.

Negative Binomial Models for Canine Prescriptions

Overdispersion was evident in all four models for canine prescribing rates, with theta values ranging from 0.67 for augmented penicillins to 1.34 for 3rd-generation cephalosporins. Patient sex significantly improved model fit for beta-lactam combination agents, fluoroquinolone, and 3rd-generation cephalosporin models for dogs; therefore, it was also included in the model for 1st-generation cephalosporin prescribing rates for comparability. No significant interactions were found between any of the models' main effects, including patient sex. Patient sex was the only significant covariate in the beta-lactam combination, fluoroquinolone, and 3rd-generation cephalosporin models, with females being prescribed respective antibiotics significantly more frequently in all three cases (penicillin + BLI RR 1.41, $p < 0.005$; fluoroquinolone RR 1.16, $p < 0.005$; 3rd-generation cephalosporins RR 1.11, $p = 0.03$).

The North Carolina county region and urbanization significantly improved the fit for the 1st-generation cephalosporin model; dogs in mountain and urban counties were prescribed 1st-generation cephalosporins at lower rates than elsewhere in the state.

Table 3.4. Estimated rate ratios (RR) for prescribing rate factors in dogs treated at veterinary clinics across North Carolina between 1/1/2019 and 12/31/2020.

Factor	Level	Combination beta-lactam	Fluoroquinolones	Cephalosporins (1st gen)	Cephalosporins (3rd-gen)
Region	Coastal	*Referent*			

Table 3.4	(Continued)				
	Piedmont	0.70 (0.42, 1.18)	0.97 (0.65, 1.43)	0.70 (0.44, 1.11)	0.79 (0.56, 1.12)
	Mountains	0.87 (0.50, 1.52)	0.92 (0.60, 1.42)	0.54 (0.33, 0.90)*	0.86 (0.59, 1.26)
Urbanization	Rural	*Referent*			
	Urban	0.86 (0.54, 1.36)	0.89 (0.63, 1.27)	0.60 (0.39, 0.90)*	0.94 (0.69, 1.28)
Pandemic	Pre-Pandemic	*Referent*			
	Pandemic	1.11 (0.95, 1.29)	1.03 (0.90, 1.14)	1.03 (0.90, 1.18)	1.11 (1.00, 1.23)†
Vulnerability	per unit	0.83 (0.62, 1.11)	1.01 (0.81,1.26)	0.83 (0.64, 1.08)	0.84 (0.69, 1.03)†
Sex	Male	*Referent*			
	Female	1.41(1.22, 1.63)**	1.16 (1.04, 1.30)**	0.98 (0.86, 1.12)	1.11 (1.01, 1.23)*

† $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

Negative Binomial Models for Feline Prescriptions

Overdispersion was evident in all three models for feline prescribing rates, with theta values ranging from 0.46 for 3rd-generation cephalosporins to 0.78 for fluoroquinolones. Patient sex significantly improved model fit for the fluoroquinolone model for cats, and hence was also included in the other models as well for comparability. No significant interactions were found between any of the models' main effects, including patient sex.

None of the independent variables were significant for either the combination beta-lactam agents or the 3rd-generation cephalosporins, though borderline significant effects were noted for cats treated in mountain regions and counties with increased SVI. Female cats were prescribed fluoroquinolones at a significantly lower rate than male cats (RR 0.86, $p = 0.04$). Patient sex did not significantly affect the prescribing rates for combination beta-lactam agents or 3rd-generation cephalosporins.

Table 3.5. Estimated rate ratios (RR) for prescribing rate factors in cats treated at veterinary clinics across North Carolina between 1/1/2019 and 12/31/2020.

Factor	Level	Combination beta-lactam	Fluoroquinolones	Cephalosporins (3rd-gen)
Region	Coastal	*Referent*		
	Piedmont	1.21 (0.67, 2.19)	0.83 (0.51, 1.36)	1.72 (0.86, 3.45)
	Mountains	1.51 (0.81, 2.82)	0.95 (0.55, 1.63)	1.87 (0.87, 4.01)
Urbanization	Rural		*Referent*	
	Urban	0.88 (0.52, 1.50)	0.89 (0.56, 1.39)	1.41 (0.76, 2.63)
Pandemic	Pre-Pandemic	*Referent*		
	Pandemic	1.01 (0.86, 1.19)	0.98 (0.85, 1.14)	1.11 (0.90, 1.36)
Vulnerability	10% Incr. in median index	1.12 (0.80, 1.55)	1.01 , (0.76, 1.33)	1.38 (0.94, 2.04)
Sex	Male	*Referent*		
	Female	1.00 (0.86, 1.17)	0.86 (0.75, 0.99)*	0.90 (0.74, 1.09)

* $p < 0.05$

Discussion

Combination beta-lactam agents (e.g., amoxicillin-clavulanic acid), fluoroquinolones, and cephalosporins were some of the most-prescribed classes in this study and consistent with previous findings; these drugs are frequently cited as top contributors to AMU in cats and dogs [Bollig (2022), Singleton (2017), Hardefeldt (2018), Hur (2020), Goggs (2021), Jolley (2023)]. Amoxicillin-clavulanic acid is also widely prescribed in human out-patient settings, which are a comparable prescribing setting to small animal primary care veterinary practices [CDC C (2022), Durkin (2018)]. Other frequently prescribed antimicrobial drugs in people include cephalexin, ciprofloxacin, amoxicillin, and azithromycin [Durkin (2018), CDC C (2022), Hicks (2015)]. While all of these were also prescribed to cats and dogs in this work, only cephalexin ranked among the top five agents. Top antimicrobial drug classes prescribed to people also overlapped with the most used classes in this study, specifically beta-lactams, including penicillins for cats, and cephalosporins [CDC C (2022), Hicks (2015), King (2020), Suda (2014), Suda (2016)].

Notably, macrolides represent one of the top two classes prescribed in people but made up less than 2% of agents prescribed here [CDC C (2022), Hicks (2015), Durkin (2018), King (2020), Suda (2014), Suda (2016)]. This is likely due to the greater number of indications for macrolides in human respiratory infections (e.g., azithromycin) [Hicks (2015), Durkin (2018), Suda (2014)].

Third-generation cephalosporins–specifically cefovecin–accounted for nearly half of the systemic antimicrobial agents prescribed to cats within this study. This drug is one of the most prescribed antimicrobial agents for cats in veterinary medicine [Bollig (2022), Goggs (2021), Hardefeldt (2018), Hur (2020), Singleton (2017)]. It is often selected due to its long-acting effects, making it a more convenient feline treatment option compared to other antimicrobial agents that need to be administered one or more times per day [Cazer (2023)]. The broad-spectrum of activity from 3rd-generation cephalosporins against both gram-negative and gram-positive bacterial infections make them one of a few agents capable of treating certain complex bacterial infections; this classifies them at the highest level of importance for human medicine according to the FDA [FDA (2023), Arumugham (2023), Klein (1995)]. Although it was hypothesized that the relative scarcity of veterinary appointments during the pandemic might increase the use of the long acting cefovecin, in cats, no significant effect was seen on 3rd-generation cephalosporin prescribing rates during the pandemic (RR 1.11, $p = 0.34$) or median SVI (RR 1.38 for 10% index increase, $p = 0.104$). In contrast, in dogs a nearly significant result consistent with an increased prescription rate of 3rd-generation cephalosporins was seen (RR 1.11, $p = 0.06$). However, 3rd-generation cephalosporins (e.g., cefpodoxime and cefovecin) can be relatively expensive compared to earlier generation cephalosporins (e.g., cephalexin and

cefazolin) which may have a minor limiting impact on the former's accessibility for dogs to more socioeconomically vulnerable owners as shown (RR 0.84 for 10% index increase, p = 0.09).

According to the CDC's SVIs, the Coastal Plain was the most vulnerable region overall. This was led by the Coastal Rural area, which was the most vulnerable of the 6 and had the highest proportion of total antimicrobial agents per animal. Similarly, the Mountain region, which was the least vulnerable, had the lowest proportion of AMU for the top systemic antimicrobial classes. This trend is also observed in human AMU, with overall prescribing typically increased in more vulnerable areas [(Mölter (2018), Devine (2022), Jensen (2016), Covvey (2014), Adekanmbi (2020), Staub (2019)]. However, the opposite trend appeared when the effects of urbanicity were considered; prescribing of beta-lactam combination agents, fluoroquinolones, and 3rd-generation cephalosporins for dogs in this study was higher in urban areas, which had a lower SVI than rural areas in North Carolina. Prescribing of 3rd-generation cephalosporins was also higher for cats in urban areas of lower vulnerability.

While this current study did not interrogate the underlying prescribing indications, we hypothesize female dogs increased susceptibility to bacterial cystitis compared to male dogs [Bryon (2018)] could be one reason for increased relative prescribing rate for beta-lactam combination agents, 3rd-generation cephalosporins, and fluoroquinolones. In contrast, it is unclear why male cats were prescribed fluoroquinolones more frequently than females. On detailed examination of the data, there were more prescriptions in males than females for all five fluoroquinolone drugs noted in cats: ciprofloxacin, enrofloxacin, marbofloxacin, orbifloxacin, and pradofloxacin (data not shown). Male cats are more likely to engage in intra-specific fighting

that commonly leads to abscessed fight wounds, for which antimicrobial therapy would be appropriate; however, fluoroquinolones are not one of the suggested first-choice antibiotics for treating cat fight abscesses. Another possibility is that there were more male cats seen in North Carolina veterinary practices than female cats. The patient-time data used as the offset in the regression analysis was not stratified by patient sex and sex parity was assumed. If this assumption is violated and more male cats were seen, more male cats would be treated. If there were a sex disparity in patients seen unaccounted for in the denominator data, we would expect a similar trend in the prescribing rates for other antimicrobial classes. No trend was noted with beta-lactam combination agents (RR = 1.0, p = 0.99), but a non-significant trend toward males receiving more 3rd-generation cephalosporins was seen (OR = 0.9, p = 0.28). Given the apparent importance of sex in prescribing rates for both cats and dogs, it will be important to stratify the denominator data by sex in future studies.

Strengths And Limitations

The major strength of the current study is the breadth of the passive sampling across the state made possible by the pipeline developed to collect PIMS systems. With the variety of PIMS and the number of clinics included, we expect the current study collected a representative sample of clinics and patients from the state. However, more data about unsampled clinics would be needed to confirm this assertion. The use of transaction and pharmacy records is expected to be a very accurate source of antibiotic use given the importance of accurate monetary and inventory accounting to effectively manage practices. The passive collection method also avoids potential biases due to practitioners' reluctance to participate or omissions due to effort required for a more active sampling method.

Despite the breadth of the sampling in the current study, it is possible that these results are not generalizable to practices outside IDEXX's network or those in other states or regions. For example, in people, antimicrobial agent consumption in the US South region is consistently higher than in other US regions [Hicks (2015), Kim (2023)]. Additionally, as only the most common systemic antimicrobial agents were analyzed in the Poisson models, they do not cover all drugs prescribed in this study and should not be used to describe total use.

Certain patient signalment variables (i.e., patient age and weight) accompanying the prescription records could not be assessed as main effects or confounders in the models due to substantial (>10%) missing data. Likewise, approximately 6% of records (i.e., unclassified agents) did not have a route of administration listed and could not be included in the analysis. However, given the large number of records, the missing records are unlikely to bias the overall findings. Finally, this data incorporated only primary care and emergency outpatient clinics and may not describe use in other settings.

Conclusions

This is the first project to take a comprehensive look at companion animal AMU in North Carolina. In dogs, females were prescribed beta-lactam combination, fluoroquinolone, and 3rd-generation cephalosporins more often than males. 1st-generation cephalosporins were also prescribed less frequently to dogs in the mountain region compared to the coast, and in urban areas compared to rural. In cats, fluoroquinolones were prescribed at a lower rate to females than

to males. These results suggest that factors such as species, region, urbanicity, and patient sex may impact AMU for cats and dogs in NC.

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Transparency Declaration

The authors do not declare any competing interests regarding this study.

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CHAPTER 4: Conclusions

The rapidly evolving threat of AMR threatens the therapeutic effectiveness of antimicrobial drugs in all species [CDC (2019), Murray (2022), WHO (2021), AVMA (2020)]. A primary method for preventing the advancement of AMR is the creation of effective intervention strategies that consider all contributing species. While numerous data exist describing human and food animal AMU, data on companion animal use in the U.S. is scarce. New techniques for extraction and collection of AMU data in dogs and cats is essential to filling this gap.

This dissertation aimed to address this issue by creating a novel approach to acquiring and analyzing companion animal use data. We first described in Chapter 1 barriers to this initiative as summarized by our own experience and that of other researchers. Here we determined that NLP tools could provide a promising solution to AMU data acquisition in companion animals, and results from such studies could be transformable into useful metrics for comparing prescribing across species. We followed this with the foundation of such techniques at our own tertiary referral hospital in Chapter 2, and described how prescribing was affected in response to the COVID-19 pandemic. These results suggested that the pandemic did have significant effects at the level of our study, and should be considered in future analyses of use. Finally, we applied the methods established to the state level for Chapter 3, and incorporated prescription records for over 8 million dogs and cats across NC. This chapter not only demonstrated the feasibility of applying such a framework to large data, but also uncovered trends in prescribing across diverse locations.

In summary, we have described challenges to companion animal AMU data collection, piloted potential solutions in the form of NLP to extract and analyze prescriptions with regard to the COVID-19 pandemic, and further applied these optimized methods to the entire state of NC to identify potential relationships between prescribing, region, urbanization, and social vulnerability. In future work, we hope to expand this framework to the national level by applying the data science techniques established here. Such a system would help to fill the critical gap of information surrounding companion animal use in the U.S. while allowing for One-Health based comparisons of use across species and subsequent development of holistic intervention strategies against AMR.

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APPENDIX

Table A.1. Cumulative link mixed model summary for distribution of proportions: important (I), highly important (H), and critically important (C) antimicrobials.

Variable	Level	Beta	S.E.	P
Intercepts	I|H	-2.41	0.10	<0.005
	H|C	2.07	0.10	<0.005
Date	Pre-pandemic		Referent	
	Pandemic	0.19	0.09	0.03
Species	Canine		Referent	
	Feline	1.17	0.09	<0.005
Age	(per year)	0.08	0.01	<0.005
Weight	(per lbs.)	-0.005	0.00	<0.005
Service	Internal Medicine		Referent	
	Cardiology	-3.88	0.21	<0.005
	Dentistry	-0.60	0.29	0.04
	Dermatology	0.46	0.13	<0.005
	Neurology	-2.27	0.13	<0.005
	Oncology	0.33	0.11	<0.005
	Ophthalmology	-2.14	0.14	<0.005
	ECC	-0.25	0.11	0.02
	Primary Care	0.29	0.23	0.21
	Theriogenology	-3.66	0.52	<0.005
	Surgery	-3.06	0.09	<0.005
Pandemic x Service Interactions	Pandemic x Cardiology	-0.82	0.32	0.01
	Pandemic x Dentistry	-0.08	0.49	0.86
	Pandemic x Dermatology	0.27	0.20	0.19
	Pandemic x Neurology	-0.46	0.21	0.03

Pandemic x Oncology	-0.30	0.18	0.09
Pandemic x Ophthalmology	-0.36	0.24	0.13
Pandemic x ECC	-0.20	0.18	0.27
Pandemic x Primary Care	-0.92	0.45	0.04
Pandemic x Theriogenology	-0.45	1.11	0.68
Pandemic x Surgery	0.41	0.14	<0.005

ECC (Emergency and Critical Care).

Table A.2. Summary of negative binomial models for antimicrobial prescription rates per patient visit in dogs and cats from 2019 and 2020.

		Model							
		I†		**H†**		**C†**		**All**	
Predictor	**Level**	β	SE	β	SE	β	SE	β	SE
Intercept	N/A	-2.43	0.24	-0.07	0.12	-0.94	0.16	0.38	0.17
Pandemic	Pre-pandemic				Referent				
	Pandemic	0.18	0.15	0.16*	0.08	0.16	0.11	0.40	0.17
Service	Internal Medicine				Referent				
	Cardiology	0.64*	0.31	-2.96*	0.18	-3.68	0.16	-1.98*	0.22
	Dentistry	-1.66*	0.48	-1.12*	0.18	-2.24*	0.11	-1.40*	0.23
	Dermatology	-1.72*	0.36	-1.83*	0.17	-1.23*	0.26	-1.51*	0.22
	Neurology	1.25*	0.31	-0.52*	0.17	-1.17	0.28	-0.46*	0.22
	Oncology	-1.83*	0.34	-1.53*	0.16	-1.71*	0.21	-1.66*	0.22
	Ophthalmology	0.91*	0.31	-1.65*	0.17	-2.42*	0.22	-1.38*	0.22
	ECC	-1.50*	0.32	-1.83*	0.16	-2.24	0.21	-1.92*	0.22
	Primary Care	-2.77*	0.40	-3.15*	0.18	-3.01	0.23	-3.05*	0.23
	Theriogenology	-1.54*	0.40	-4.83*	0.33	-6.56	1.03	-4.03*	0.31
	Surgery	2.47*	0.30	-0.02	0.16	-0.47	0.21	0.22	0.22
Species	Dog				Referent				
	Cat	-1.24*	0.17	-0.55*	0.08	0.35	0.11	-0.39*	0.10

ECC (Emergency and Critical Care).
* $p < 0.05$.
†GFI 152 Appendix A Rank: I=Important, H=Highly Important, and C=Critically Important.

Table A.3. Negative binomial model summary of weekly prescription rates for important antimicrobials in dogs and cats from 2019 and 2020.

Variable	Level	Beta	S.E.	P
Intercept	N/A	1.78	0.09	<0.005
Date	Pre-pandemic		Referent	
	Pandemic	0.02	0.14	0.88
Species	Canine		Referent	
	Feline	-3.13	0.08	<0.005
Service	Internal Medicine		Referent	
	Cardiology	0.12	0.12	0.33
	Dentistry*		Not Fit	
	Dermatology	-1.74	0.17	<0.005
	Neurology	0.35	0.12	<0.005
	Oncology	-1.98	0.18	<0.005
	Ophthalmology	-0.18	0.13	0.16
	ECC	-1.20	0.15	<0.005
	Primary Care	-3.26	0.28	<0.005
	Theriogenology	-2.72	0.23	<0.005
	Surgery	1.88	0.11	<0.005
Pandemic x Service Interactions	Pandemic x Cardiology	0.07	0.19	0.73
	Pandemic x Dentistry		Not Fit	
	Pandemic x Dermatology	-1.14	0.34	<0.005
	Pandemic x Neurology	-0.27	0.19	0.16
	Pandemic x Oncology	0.43	0.26	0.10
	Pandemic x Ophthalmology	-0.24	0.20	0.25
	Pandemic x ECC	-0.36	0.24	0.14

Pandemic x Primary Care	-0.38	0.49	0.45
Pandemic x Theriogenology	-0.57	0.42	0.17
Pandemic x Surgery	-0.51	0.18	<0.005

ECC (Emergency and Critical Care).

Table A.4. Negative binomial model summary of weekly prescription rates for highly important antimicrobials in dogs and cats from 2019 and 2020.

Variable	Level	Beta	S.E.	P
Intercept	N/A	4.45	0.05	<0.005
Date	Pre-pandemic		Referent	
	Pandemic	-0.35	0.05	<0.005
Species	Canine		Referent	
	Feline	-2.45	0.06	<0.005
Service	Internal Medicine		Referent	
	Cardiology	-3.78	0.10	<0.005
	Dentistry*	-3.91	0.10	<0.005
	Dermatology	-2.45	0.08	<0.005
	Neurology	-1.94	0.07	<0.005
	Oncology	-1.64	0.07	<0.005
	Ophthalmology	-2.38	0.08	<0.005
	ECC	-1.81	0.07	<0.005
	Primary Care	-3.96	0.11	<0.005
	Theriogenology	-6.43	0.38	<0.005
	Surgery	-0.96	0.07	<0.005
Pandemic x Species Interaction	Pandemic x Feline	0.22	0.09	0.01

ECC (Emergency and Critical Care).

Table A.5. Negative binomial model summary of weekly prescription rates for critically important antimicrobials in dogs and cats from 2019 and 2020.

Variable	Level	Beta	S.E.	P
Intercept	N/A	3.41	0.07	<0.005
Date	Pre-pandemic		Referent	
	Pandemic	0.08	0.10	0.41
Species	Canine		Referent	
	Feline	-1.60	0.05	<0.005
Service	Internal Medicine		Referent	
	Cardiology	-4.35	0.21	<0.005
	Dentistry	-4.66	0.23	<0.005
	Dermatology	-1.83	0.10	<0.005
	Neurology	-2.17	0.11	<0.005
	Oncology	-1.52	0.10	<0.005
	Ophthalmology	-3.44	0.15	<0.005
	ECC	-2.11	0.11	<0.005
	Primary Care	-3.27	0.14	<0.005
	Theriogenology*		Not Fit	
	Surgery	-1.08	0.09	<0.005
Pandemic x Service Interactions	Pandemic x Cardiology	-0.28	0.34	0.41
	Pandemic x Dentistry	-0.66	0.44	0.13
	Pandemic x Dermatology	-0.34	0.17	0.04
	Pandemic x Neurology	-0.63	0.18	<0.005
	Pandemic x Oncology	-0.44	0.16	0.01
	Pandemic x Ophthalmology	-0.04	0.23	0.88
	Pandemic x ECC	-0.20	0.17	0.25

Pandemic x Primary Care	-1.17	0.29	<0.005
Pandemic x Theriogenology*		Not Fit	
Pandemic x Surgery	-0.26	0.15	0.08

ECC (Emergency and Critical Care).

Table A.6. Negative binomial model summary of weekly prescription rates for all antimicrobials in dogs and cats from 2019 and 2020.

Variable	Level	Beta	S.E.	P
Intercept	N/A	4.87	0.06	<0.005
Date	Pre-pandemic		Referent	
	Pandemic	-0.16	0.09	0.08
Species	Canine		Referent	
	Feline	-2.34	0.05	<0.005
Service	Internal Medicine		Referent	
	Cardiology	-2.77	0.09	<0.005
	Dentistry	-4.14	0.12	<0.005
	Dermatology	-2.21	0.08	<0.005
	Neurology	-1.76	0.08	<0.005
	Oncology	-1.69	0.08	<0.005
	Ophthalmology	-2.22	0.08	<0.005
	ECC	-1.85	0.08	<0.005
	Primary Care	-3.58	0.10	<0.005
	Theriogenology	-5.48	0.18	<0.005
	Surgery	-0.57	0.08	<0.005
Pandemic x Species Interactions	Pandemic x Feline	0.17	0.07	0.02
Pandemic x Service Interactions	Pandemic x Cardiology	0.16	0.14	0.26
	Pandemic x Dentistry	-0.12	0.19	0.55
	Pandemic x Dermatology	-0.19	0.14	0.16
	Pandemic x Neurology	-0.16	0.13	0.22
	Pandemic x Oncology	-0.15	0.13	0.26

	Pandemic x Ophthalmology	-0.27	0.14	0.05
	Pandemic x ECC	-0.07	0.13	0.60
	Pandemic x Primary Care	-0.77	0.19	<0.005
	Pandemic x Theriogenology	-0.52	0.35	0.14
	Pandemic x Surgery	-0.25	0.12	0.03

ECC (Emergency and Critical Care).

Table A.7. NC Counties are categorized into 6 areas by urbanization and geographic region.

Region	Urbanicity	Counties	# Counties	# Clinics	Med. Dogs/ Month	Med. Cats/ Month	Med. Census Tract SVI
Coastal Plains	Urban	Brunswick, Craven, Cumberland, Edgecombe, Hoke, Johnston, Nash, New Hanover, Onslow, Pitt, Wayne	11	60	53,196	11,279	0.576
Coastal Plains	Rural	Beaufort, Bertie, Bladen, Camden, Carteret, Chowan, Columbus, Currituck, Dare, Duplin, Gates, Greene, Halifax, Harnett, Hertford, Hyde, Jones, Lenoir, Martin, Northampton, Pamlico, Pasquotank, Pender, Perquimans, Robeson, Sampson, Scotland, Tyrrell, Washington, Wilson	30	43	34,274	7,080	0.721
Piedmont	Urban	Alamance, Cabarrus, Catawba, Chatham, Davidson, Davie, Durham, Forsyth, Gaston, Guilford, Iredell, Mecklenburg, Orange, Stokes, Union, Wake	16	198	137,576	32,318	0.378

Piedmont	Rural	Alexander, Anson, Caswell, Cleveland, Franklin, Granville, Lee, Lincoln, Montgomery, Moore, Person, Randolph, Richmond, Rockingham, Rowan, Stanly, Surry, Vance, Warren, Yadkin	20	41	34,421	7,419	0.591
Mountains	Urban	Buncombe, Burke, Caldwell, Haywood, Henderson	5	28	22,365	5,535	0.421
Mountains	Rural	Alleghany, Ashe, Avery, Cherokee, Clay, Graham, Jackson, McDowell, Macon, Madison, Mitchell, Polk, Rutherford, Swain, Transylvania, Watauga, Wilkes, Yancey	18	19	13,030	3,110	0.510

Table A.8. Summary of included antimicrobial agents in dogs.

Class	Name	Oral	Injectable	Topical
Penicillin	Amoxicillin	28,022	4	2
Penicillin	Ampicillin Sodium		16,148	
Penicillin	Oxacillin		45	
Penicillin	Penicillin G		5,909	
Penicillin	Ticarcillin		7	
Beta-lactam combination agent	Amoxicillin/ Clavulanic Acid	147,111		
Beta-lactam combination agent	Ampicillin/ Sulbactam		11,844	
Beta-lactam combination agent	Piperacillin/ Tazobactam		2	
Cephalosporin I	Cefadroxil	20		
Cephalosporin I	Cefazolin		22,115	
Cephalosporin I	Cephalexin	166,731		
Cephalosporin III	Cefovecin		44,842	
Cephalosporin III	Cefpodoxime	139,846		
Cephalosporin III	Ceftazidime		177	2
Cephalosporin III	Ceftiofur		4,369	
Cephalosporin III	Ceftriaxone		127	
Carbapenems	Imipenem		45	
Carbapenems	Meropenem		98	
Aminoglycoside	Amikacin		146	16
Aminoglycoside	Gentamicin	73	792	78,865
Aminoglycoside	Neomycin sulfate			100,766
Aminoglycoside	Tobramycin			21,519
Macrolide	Azithromycin	2,558	13	
Macrolide	Clarithromycin	4		
Macrolide	Erythromycin	13		1,280
Macrolide	Tulathromycin		7	
Macrolide	Tylosin	7,434	425	
Lincosamide	Clindamycin	70,159	4,276	670
Lincosamide	Lincomycin		3	
Fluoroquinolone	Ciprofloxacin	23,557		
Fluoroquinolone	Enrofloxacin	40,883	17,129	7,362
Fluoroquinolone	Levofloxacin	48		
Fluoroquinolone	Marbofloxacin	8,765		
Fluoroquinolone	Moxifloxacin			81
Fluoroquinolone	Ofloxacin	14	2	13,196
Fluoroquinolone	Orbifloxacin	35,937		
Fluoroquinolone	Pradofloxacin	80		

Nitroimidazole	Metronidazole	197,431	7,436	
Tetracycline	Doxycycline	66,316	109	4
Tetracycline	Minocycline	999		
Tetracycline	Oxytetracycline			4,665
Tetracycline	Tetracycline	40		
Sulfonamides (FPI)	Silver Sulfadiazine			7,334
Sulfonamides (FPI)	Sulfadimethoxine	7,657		
Sulfonamides (FPI)	Sulfamethoxine/ Ormetoprim	1,349		
Sulfonamides (FPI)	Sulfasalazine	792		
Sulfonamides (FPI)	Trimethoprim/ Sulfamethoxazole	5,283		
Phenicol	Chloramphenicol	1,338		
Phenicol	Florfenicol		64	51,384
Polypeptide	Bacitracin			27,473
Polypeptide	Polymyxin B			30,171
Other	Fosfomycin	1		
Other	Linezolid	2		
Other	Mupirocin			5,822
Other	Nitrofurantoin	117		
Other	Rifampin		11	
Other	Tigecycline		1	

Table A.9. Summary of included antimicrobial agents in cats.

Class	Name	Oral	Injectable	Topical
Penicillin	Amoxicillin	4,344	2	
Penicillin	Ampicillin Sodium		4,471	
Penicillin	Oxacillin		7	
Penicillin	Penicillin G		2,180	
Beta-lactam combination agent	Amoxicillin/ Clavulanic Acid	50,617		
Beta-lactam combination agent	Ampicillin/ Sulbactam		2,681	
Cephalosporin I	Cefadroxil	17		
Cephalosporin I	Cefazolin		2,662	
Cephalosporin I	Cephalexin	549		
Cephalosporin III	Cefovecin		120,873	
Cephalosporin III	Cefpodoxime	1,070		
Cephalosporin III	Ceftazidime		38	
Cephalosporin III	Ceftiofur		274	
Cephalosporin III	Ceftriaxone		20	
Carbapenems	Imipenem		2	
Carbapenems	Meropenem		8	
Aminoglycoside	Amikacin		13	
Aminoglycoside	Gentamicin	3	260	2,428
Aminoglycoside	Neomycin sulfate			14,217
Aminoglycoside	Tobramycin			10,574
Macrolide	Azithromycin	6,726	33	
Macrolide	Clarithromycin	4		
Macrolide	Erythromycin	12		3,676
Macrolide	Tulathromycin		19	
Macrolide	Tylosin	726	16	
Lincosamide	Clindamycin	8,214	1,081	150
Fluoroquinolone	Ciprofloxacin	343		
Fluoroquinolone	Enrofloxacin	4,118	3,821	653
Fluoroquinolone	Marbofloxacin	6,653		
Fluoroquinolone	Moxifloxacin			14
Fluoroquinolone	Ofloxacin	1		4,532
Fluoroquinolone	Orbifloxacin	10,811		
Fluoroquinolone	Pradofloxacin	5,723		
Nitroimidazole	Metronidazole	15,976	602	
Tetracycline	Doxycycline	4,369	43	
Tetracycline	Minocycline	271		
Tetracycline	Oxytetracycline			10,533
Tetracycline	Tetracycline	1		

Sulfonamides (FPI)	Silver Sulfadiazine			1,425
Sulfonamides (FPI)	Sulfadimethoxine	3,214		
Sulfonamides (FPI)	Sulfamethoxine/ Ormetoprim	4		
Sulfonamides (FPI)	Sulfasalazine	38		
Sulfonamides (FPI)	Trimethoprim/ Sulfamethoxazole	93		
Phenicol	Chloramphenicol	23		
Phenicol	Florfenicol		1	2,994
Polypeptide	Bacitracin			3,997
Polypeptide	Polymyxin B			3,113
Other	Mupirocin			765
Other	Nitrofurantoin	19		
Other	Rifampin		2	