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Effects of regional diversity on antimicrobial prescribing in dogs and cats in North Carolina from 2019 to 2020

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

Objectives: To describe trends in AMU for dogs and cats in North Carolina (NC) over geography, urbanicity, time, and patient sex from 1 January 2019 to 31 December 2020 and evaluate the influence of summarized measures of social vulnerability and the COVID-19 pandemic on prescribing practices.

Methods: In cooperation with IDEXX Laboratories, Inc. (IDEXX), we collected prescribing 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). Social vulnerability was measured using the CDC published Social Vulnerability Index (SVI) data and was summarized for each of the six areas. Poisson family models were used to estimate prescribing rates and rate ratios for independent variables, normalized by the total number of monthly patients.

Results: Combination beta-lactam agents, fluoroquinolones, nitroimidazole, and cephalosporins were the most prescribed drug classes. Region and urbanicity only significantly affected prescribing rate for first-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 with some increased prescribing in rural and vulnerable areas of the state.

Introduction

Antimicrobials are a cornerstone of modern medicine and rank among the top medical achievements of the 20th century. However, pathogens' evolution of resistance to these drugs has increasingly threatened their therapeutic effectiveness. To implement effective stewardship practices to mitigate antimicrobial resistance, it is crucial to characterize current AMU and its drivers. While human antimicrobial use (AMU) data are readily available in the United States (US), data regarding AMU in companion animals is more limited.[1] For companion animals, veterinarians can use both animal-approved antimicrobial classes and extra-label human-approved antimicrobial agents.[2,3] Thus, there could be high heterogeneity in companion animal prescribing practices. Current practices for veterinary prescribing in companion animals are inferred from methodologically heterogeneous reports that are limited in scope or restricted to academic settings.[4–6] Consequently, the existing reports do not provide a comprehensive picture of companion animal AMU in USA.

Drivers of antimicrobial prescribing in companion animal practice are not fully understood. Recent studies have suggested that factors such as cost and antimicrobial stewardship knowledge influence cat and dog owners' treatment choices for their animals.[7–12] The client's sex, education, professional background, and age have been associated with their clinical understanding and subsequent decision-making for patient antimicrobial therapy.[9] Socioeconomic and demographic characteristics influence the likelihood of companion animal ownership and thus the potential for veterinary care and AMU prescription.[13–15] Based on recent survey data, there is evidence that pressure from owners may influence the prescribing frequency of one of the third-generation cephalosporins in cats in USA.[16]

Similar socioeconomic and demographic factors have been shown to impact antimicrobial prescribing in human medicine.[17] 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'.[18] Determinants of the social vulnerability index (SVI) include economic well-being, household composition and family details, community characteristics, and housing and transportation.[18]

In this study, we aimed to describe heterogeneity in prescribing practices in companion animal AMU throughout North Carolina (NC) across geographic regions and county urbanicity from 2019 to 2020 and investigate the relationships between AMU prescribing and animal- and community-level factors utilizing the CDC's SVI. Additionally, since the data coincided with the beginning of the COVID-19 pandemic, we evaluated its effect on companion animal AMU. Based on our prior work, we hypothesized that modified veterinary operations due to the COVID-19 mandates and staffing shortages changed AMU prescription patterns.[19–21]

Materials and methods

Data collection

In collaboration with IDEXX Laboratories, Inc., patient data were collected from electronic medical records within veterinary practice information management systems (PIMS) records from 389 primary, specialty, and emergency veterinary practices in North Carolina. Prior to analysis, all data were de-identified and aggregated to remove identifiable information related to the practice, pet owner, and pet before sharing.

Records of inpatient AMU and prescriptions between 1 January 2019 and 31 December 2020 were collected from invoice and prescription records using an analytic pipeline previously developed and validated by IDEXX and NCSU. An IDEXX proprietary natural language processing algorithm was used to characterize and extract antimicrobial products containing one or more of the pharmaceuticals identified for the current study (Tables S1 and S2, available as Supplementary data at *JAC-AMR* Online). 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 further subdivided as oral or injectable. Antibiotics were classified using definitions published by the Clinical and Laboratory Standards Institute (CLSI).[22] To ensure that the pipeline was extracting data appropriately, we developed a data dictionary listing the generic and proprietary names associated with different antimicrobial drugs and established rules to assign routes of administration. The complete data extraction pipeline was evaluated in a group of sentinel clinics for which NCSU had access to raw and aggregated data.

The study outcome was the rate of prescriptions per patient-month. The count of prescriptions for each drug was based on whether unique patients were administered or prescribed a product containing the drug during a calendar month. Therefore, instances where one drug was administered or prescribed to a single patient multiple times in 1 month were collapsed into a single record. For example, a patient receiving injectable ampicillin every 8 hours for 3 days would be counted as a single prescription of injectable penicillin.

The rate denominator was determined by the number of unique patients seen at the included clinics, aggregated by area and calendar month; each patient seen each month contributed one patient-month of study time. In total, there were 7 030 527 canine patient-months and 1 623 021 feline patient-months during the 2 years of the study. Calendar month was chosen as a time unit to aggregate the data because it was the smallest interval that preserved the data-sharing

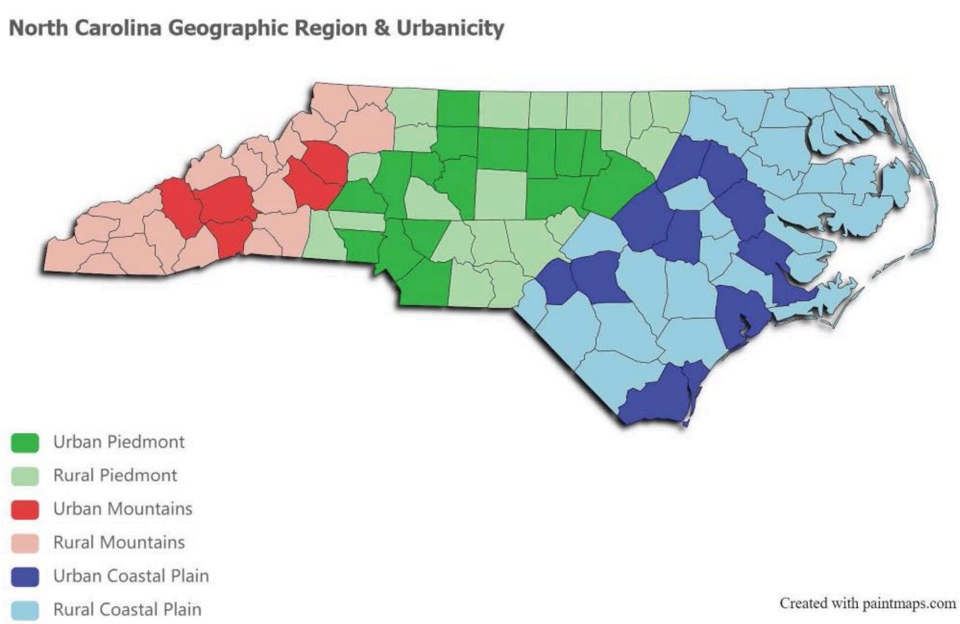

Figure 1. Map of geographic and urbanicity areas in North Carolina.

agreements protecting the identity of clinics and owners, while trends over time, such as seasonality, could still be explored.

The county in which each clinic was located was used as a proxy for patient location. There are 100 counties in North Carolina, which were divided into six areas based on two criteria—geographic region and urbanicity—resulting in six areas (Figure 1, Table S3). Three geographic regions were defined: the eastern Coastal Plain (41 counties), the central Piedmont (36 counties), and the western Mountains (23 counties).[23] County urbanicity was assigned using the consensus of several sources (see Table S3 for counties' classification). Rural counties represented 68% of all counties.

The CDC's SVI was used to assign vulnerability rankings to each NC county.[18] Antibiotic prescriptions were stratified by species (dogs or cats), and sex was included as an independent variable. The median SVI across all census tracts in an area was respectively assigned to each of the six areas. Census tracts are small, relatively permanent geographic entities that are as homogenous as possible with respect to population characteristics and contain between 2500 and 8000 residents.[24] North Carolina counties contain between 1 census tract (Tyrell County) and 305 census tracts (Mecklenburg County). The SVI scores were indexed so the county with the lowest SVI was assigned the value zero and the highest assigned 1. These indices were multiplied by 10 to extend the variable range to 0 to 10, hence a one unit change on the expanded SVI scale represented a 10% change in a region's median SVI and the corresponding rate ratio described the estimated change in prescribing rate associated with a 10% change in median SVI.

Prescriptions were stratified by species (dogs or cats), and sex was included as an independent variable. Records for prescriptions after April 1, 2020 were considered to be prescribed during the COVID-19 pandemic to reflect the onset of pandemic-related mandates in North Carolina. Prescription counts were normalized across the six areas defined above to account for heterogeneity in pet populations and clinical caseloads.

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.[21] Four models were fit for each of the most frequently prescribed antimicrobial classes in dogs: beta-lactam combination agents, fluoroquinolones, first-generation cephalosporins, and third-generation cephalosporins. While nitroimidazoles were one of the most common antimicrobial classes prescribed to dogs, we did not fit a model for this class because metronidazole—the only drug in the class—is often used to treat conditions other than bacterial infections. Three models were fit for each of the most frequently prescribed antimicrobial classes in cats: beta-lactam combination agents, fluoroquinolones, and third-generation cephalosporins. The drugs prescribed from these classes combined accounted for 64% and 78% of prescriptions for dogs and cats, respectively.

These negative binomial models fit the total number of prescribing episodes for each antimicrobial class (y) in each stratum (i), normalized by the respective number of patients seen (n_i) (Eq. 1).[25,26] The independent variables (x_i) geographic region, urbanicity, pandemic timeframe, and median SVI were included in all models. As a potential covariate, patient sex was evaluated for improvement of fit using AIC.[27] Interactions between all included main effects were evaluated via likelihood ratio testing and included if significant ($\alpha = 0.05$). Analyses were conducted in R Studio (R v4.2.2) with the *MASS* package (v7.3-58.1).

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

Table 1. Topical antimicrobial prescriptions by species and class from 1 January 2019 to 31 December 2020

Drug Class	Canine	Feline	Total
Aminoglycoside	201 613	27 270	228 883
Cephalosporin III	5	0	5
Fluoroquinolone	20 689	5200	25 889
Lincosamide	561	132	693
Macrolide	1280	3676	4956
Penicillin	2	0	2
Phenicol	51 397	2994	54 391
Polypeptide	57 644	7110	64 754
Sulfonamides	7335	1425	8760
Tetracycline	4669	10 534	15 203
Total	345 195	58 341	**403 536**

Table 2. Systemic (oral or injectable) antimicrobial prescriptions by species and class from 1 January 2019 to 31 December 2020

Drug class	Canine	Feline	Total
Aminoglycoside	1012	276	1288
Beta-lactam Comb.	158 970	53 298	212 268
Carbapenems	143	10	153
Cephalosporin I	188 871	3229	192 100
Cephalosporin III	189 363	122 275	311 638
Fluoroquinolone	126 495	31 479	157 974
Lincosamide	75 765	10 077	85 842
Macrolide	10 454	7537	17 991
Nitroimidazole	205 867	16 852	222 719
Penicillin	50 136	11 005	61 141
Phenicol	1402	24	1426
Sulfonamides	15 081	3349	18 430
Tetracycline	67 563	4903	72 466
Total	1 091 122	264 314	**1 355 436**

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 1). Topical formulations included ophthalmic and otic products. Neomycin sulphate (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.

Beta-lactam combination agents, third-generation cephalosporins, fluoroquinolones, and nitroimidazoles were among the most prescribed systemic antimicrobial classes for both dogs and cats (Table 2). Tables S1 and S2 provide the number of prescriptions by drug. In terms of drugs, metronidazole and

Table 3. Number of practices and total patient-months in each area from 1 January 2019 to 31 December 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
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.

amoxicillin/clavulanic acid (a beta-lactam combination agent) were commonly prescribed in both species (Tables S1 and S2). Additionally, cefovecin (a third-generation cephalosporin) was the most prescribed systemic drug for cats, which accounted for almost half of all systemic feline prescriptions (Table S2). Cephalexin—a first-generation cephalosporin—was also a commonly prescribed oral drug to dogs in this study (Table S1). Table 3 provides the breakdown of clinics and patient-months by region and urbanicity. Although the Piedmont Urban area has the largest number of practices and patient-months, the rural Coastal Plains counties typically had the highest number of total antimicrobial prescriptions per patient-month, followed by the Piedmont Urban (Figure 2). Piedmont Rural had the lowest number of antimicrobial prescriptions per patient-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 combination beta-lactams to 1.34 for third-generation cephalosporins. Patient sex significantly improved model fit for beta-lactam combination agents, fluoroquinolones, and third-generation cephalosporin models for dogs, and hence was included in the model for first-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 combination beta-lactam, fluoroquinolone, and third-generation cephalosporin models, with females being prescribed respective antibiotics significantly more frequently in all three cases (Table 4). The North Carolina county region and urbanization significantly improved the fit for first-generation cephalosporin model; dogs in coastal counties and rural counties were prescribed first-generation cephalosporin at higher rates than elsewhere in the state.

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 third-generation cephalosporins to 0.78 for fluoroquinolones. Patient sex significantly improved model fit for the fluoroquinolone model for cats, and hence was included in the other models for comparability. No significant interactions were found between any of the models' main effects, including patient sex (Table 5).

None of the independent variables were significant for either the combination beta-lactam agents or the third-generation cephalosporins (Table 5). 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.

Discussion

Combination beta-lactam agents (e.g. amoxicillin-clavulanic acid), fluoroquinolones, nitroimidazoles, and cephalosporins were some of the most prescribed drug classes in this study, consistent with previous recent findings in the USA[4,21,28] and other countries, including UK and Australia.[11,29] These drug classes are frequently cited as top contributors to veterinary AMU in cats and dogs, including amoxicillin/clavulanic acid as one of the leading antimicrobial agents.[4,28–31] Likewise, amoxicillin-clavulanic acid is also widely prescribed to human outpatients, a setting comparable to primary care veterinary practices.[1,32] Other antimicrobials drugs frequently prescribed to people include cephalexin, ciprofloxacin, amoxicillin, and azithromycin.[1,32,33] While these antibiotics appeared in prescription data for cats and dogs in the current study, only cephalexin ranked among the top five agents (Table S1). Notably, macrolides represent one of the top two classes prescribed in people but made up <2% of systemic agents prescribed here.[1,32,33] This is likely due to the greater number of indications for macrolides in humans, which are predominantly used to treat respiratory infections in people (e.g. azithromycin) coupled with the lack of FDA-approved macrolide products for systemic use in veterinary patients.[32,33]

Third-generation cephalosporins—specifically cefovecin—accounted for nearly half of the systemic antimicrobial agents (46%) prescribed to cats within this study. Cefovecin is one of the most prescribed antimicrobial agents for cats in veterinary medicine.[4,28] 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.[16] Although we hypothesized that the relative scarcity of veterinary service availability during the pandemic might have increased the use of the long acting cefovecin in cats, no significant effect was seen on third-generation cephalosporin prescribing rates for cats during the pandemic (RR 1.11, $P = 0.34$). Changes in prescription rate of third-generation cephalosporins in dogs during the pandemic were not significant (RR 1.11, $P = 0.06$). Later-generation cephalosporins can be relatively expensive compared to earlier-generation cephalosporins such as cephalexin and cefazolin. However, for dogs and cats, the median SVI had no effect (RR 0.84 for 10% index increase, $P = 0.09$ for dogs, and RR 1.38 for 10% index increase, $P = 0.104$ for cats). The

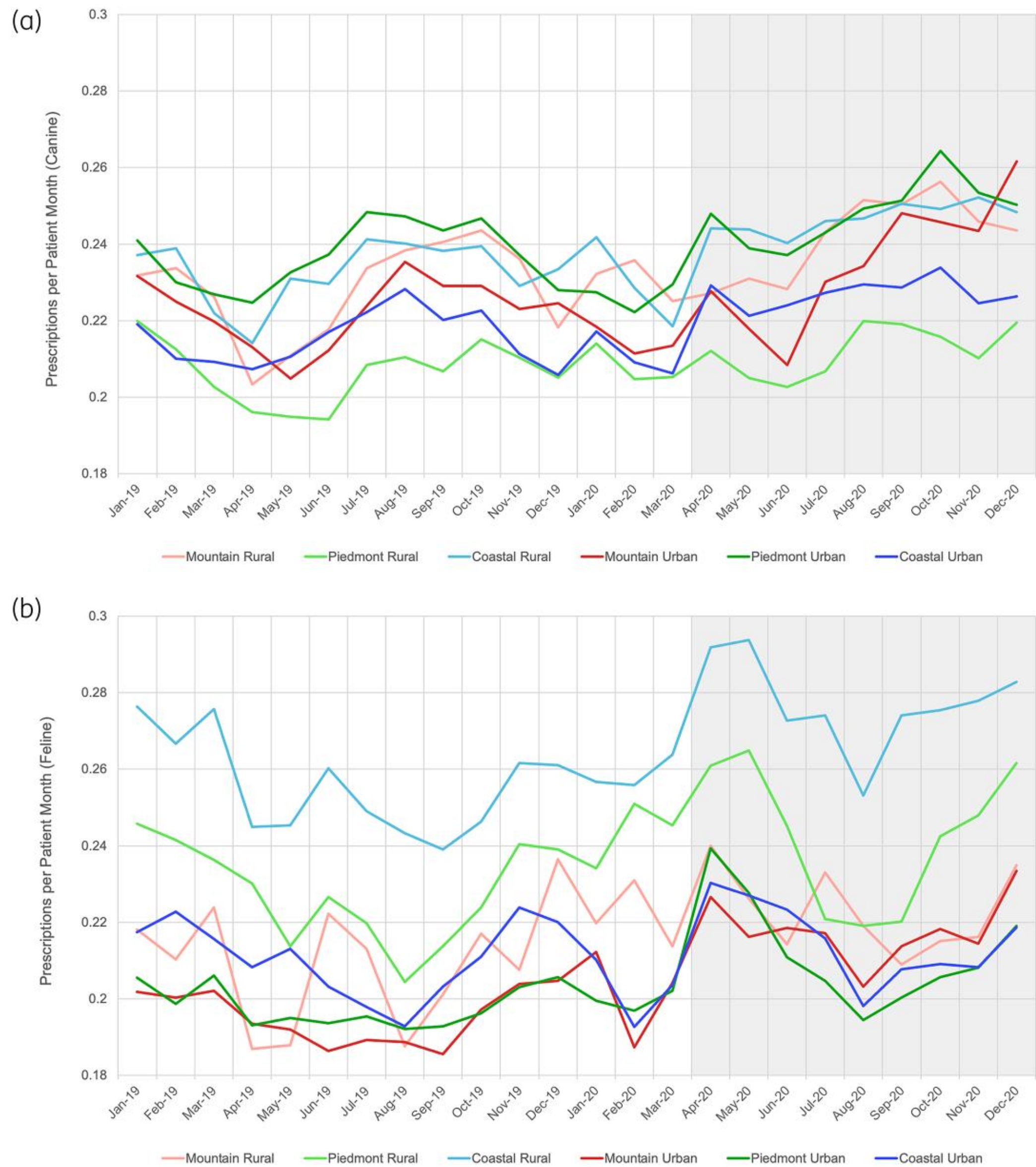

Figure 2. Number of antimicrobial prescriptions per patient-month (i.e. prescribing rate) from 1 January 2019 to 31 December 2020 for dogs (a) and cats (b). Gray-shaded area represents the COVID-19 pandemic era (1 April 2020 to 31 December 2020). Individual patients were able to contribute to multiple months and multiple antimicrobial classes within the same month.

convenience of dosing may influence these prescribing practices. Cefovecin can be administered once every 14 days in dogs and cats. Cephalexin is a twice-daily oral antimicrobial in dogs, but cefpodoxime can be administered once-daily.[34]

When considering antimicrobial use by geographic region, urbanicity, and vulnerability, some trends in relative use did arise. The Rural Coastal Plains area was the most vulnerable of the six defined areas (Table S3) and had the highest antimicrobial prescribing rate (Figure 2). Similarly, the Mountain region, which was the least vulnerable, had the lowest prescribing rate for the top systemic antimicrobial classes. This trend is also observed in human AMU, with overall prescribing typically increased in more vulnerable areas.[35,36]

Similarly, patient sex was found to affect some prescribing rates. Although this study did not interrogate the underlying prescribing indications, we hypothesize female dogs' increased susceptibility to bacterial cystitis compared to male dogs could be one reason for the increased relative prescribing rate for beta-lactam combination agents, third-generation cephalosporins, and fluoroquinolones.[37] 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 (Table S4). This was unexpected because ciprofloxacin is not adequately absorbed in cats,[38] and

Table 4. Estimated rate ratios (95% CIs) for prescriptions per patient-month in dogs treated at veterinary clinics across North Carolina between 1 January 2019 and 31 December 2020

Factor	Level	Combination beta-lactam	Fluoroquinolones	Cephalosporins (first gen)	Cephalosporins (third gen)
Region	Coastal			*Referent*	
	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)[a]	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)[a]	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)[b]
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)[b]
Sex	Male			*Referent*	
	Female	1.41 (1.22, 1.63)[c]	1.16 (1.04, 1.30)[c]	0.98 (0.86, 1.12)	1.11 (1.01, 1.23)[a]

[a]$P < 0.05$.
[b]$P < 0.10$.
[c]$P < 0.01$

Table 5. Estimated rate ratios (RR) for prescriptions per patient-month in cats treated at veterinary clinics across North Carolina between 1 January 2019 and 31 December 2020

Factor	Level	Combination beta-lactam	Fluoroquinolones	Cephalosporins (third-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)[a]	0.90 (0.74, 1.09)

[a]$p < 0.05$.

enrofloxacin carries a risk of retinal toxicity in cats.[39] Male cats are more likely to engage in intra-specific fighting that commonly leads to abscessed fight wounds, for which antimicrobial therapy may be appropriate; however, fluoroquinolones are not indicated as first-choice antibiotics for treating cat fight abscesses, though they may be used by some clinicians due to their 24-hour dosing interval. Another possibility is that more male cats were 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 third-generation cephalosporins was seen ($RR = 0.9$, $P = 0.28$). 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.

The major strength of the current study is the breadth of the passive sampling across the state, made possible by a pipeline developed to collect data from diverse PIMS systems. Given the variety of PIMS and the large number of clinics included, we expect our sample to likely be representative of the state population of clinics and patients. Nonetheless, unsampled clinics may be different from those sampled. For example, clinics that do not use PIMS may differ in other ways from those that use PIMS. The use of invoice and prescription 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 the 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 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.[17] A limitation of our data extraction approach is that includes the use of a proprietary natural language processing algorithm and thus it is not open access.

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, these data incorporated only primary care and emergency outpatient clinics and may not describe use in other settings such as academic tertiary hospitals.

This is the first study to comprehensively examine companion animal AMU in North Carolina. In dogs, females were more often prescribed beta-lactam combination, fluoroquinolone, and third-generation cephalosporins than males. First-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 males. These results suggest that species, region, urbanicity, and patient sex may impact AMU for cats and dogs in NC.

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Transparency declarations

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

Supplementary data

Tables S1 to S4 is available as Supplementary data at *JAC-AMR* Online.

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