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Automated Disease Classification of Veterinary Clinical Narratives for Antimicrobial Stewardship Guideline Monitoring

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Automated Disease Classification of Veterinary Clinical Narratives for Antimicrobial Stewardship Guideline Monitoring

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ABSTRACT

Antimicrobial resistance (AMR) is a global challenge for public health with increasing impacts for animal welfare. Companion animals are increasingly being recognised as critical agents in the proliferation and transmission of AMR bacteria. Existing approaches to monitoring antimicrobial utilisation, such as annual aggregate sales data, provide very limited insights into the specific disease contexts and prescribing practices driving antimicrobial use. In this study, we employ a hierarchical large language model to analyse 195,012 highest priority critically important antimicrobials (HPCIA) prescriptions in companion animals and over 1.2 million antimicrobial non-HPCIA prescriptions, revealing the nuances of disease patterns and prescribing motivations that have previously remained obscure. Our model achieves an accuracy exceeding 88% in identifying 39 distinct diseases associated with antimicrobial prescriptions. We demonstrate that the tool provides a robust foundation for assessing the influence of antimicrobial stewardship guidelines (ASGs) on prescribing practices. Our novel methodology advances our understanding of AMR dynamics within veterinary care by bridging the gap between what is actual practiced and guideline-aligned prescribing. We outline an actionable path towards preserving the efficacy of essential antimicrobial agents, safeguarding the health of future generations of humans and animals.

1 Introduction

There is an escalating recognition of companion animals as significant players in the proliferation and transmission of antimicrobial-resistant (AMR) bacteria[1–3]. AMR has emerged as a global public health concern, posing significant challenges to the efficacious treatment of infectious diseases. The overuse of antimicrobials in human and animal healthcare has contributed to the emergence of resistant strains[1,4,5]. Numerous studies have documented the presence of AMR bacteria in companion animals such as fluoroquinolone-resistant *Escherichia coli*[4,6], Methicillin-resistant *Staphylococci aureus* (MRSA)[7,8], methicillin-resistant *Staphylococcus pseudintermedius* (MRSP)[8,9], and ampicillin-resistant *Enterococcus faecium*[10]. The proximity in which companion animals live with humans considerably increases the transmission risk due to the heightened opportunities for direct contact within communal environments, facilitating the exchange of bacteria[5]. Likewise, companion animals can sustain infections within a household; for example, the persistence of MRSA bacteria in a domestic setting may arise from companion animals acting as reservoirs[11,12]. Recognising the interconnectedness between humans, companion animals, and the environment, as advocated by the World Health Organisation (WHO) One Health approach, is crucial in addressing antimicrobial resistance (AMR)[13]. This approach underscores the necessity of collaborative, interdisciplinary efforts to comprehensively address all antimicrobial use within a unified system, thereby mitigating resistance effectively[14,15].

Antimicrobials remain amongst the most commonly prescribed pharmaceutical agents in companion animals, with the extensive utilisation of broad-spectrum antimicrobial agents having been documented in small animal veterinary practice in Europe[16–18]. High Priority - Critically Important Antimicrobials (HPCIAs) represent a category of antimicrobial drugs designated by the WHO as of paramount significance in human medicine[19]. In companion animal medicine, the most commonly prescribed HPCIAs for dogs are fluoroquinolones including but not limited to enrofloxacin, ciprofloxacin, marbofloxacin, and

pradofloxacin[20]. In contrast, for cats, extended-spectrum cephalosporins, such as cefovecin and, in some regions, cefpodoxime, are predominant[20]. Additionally, first-generation cephalosporins are commonly prescribed, particularly in dogs[21–23]. The underlying rationale specific to antimicrobial prescribing patterns remains inadequately understood. National-level reports, though they provide basic sales data for antimicrobial agents in the United Kingdom (UK), do not significantly illustrate the precise clinical indications that drive individual prescribing decisions by clinicians.

Frameworks such as the Small Animal Veterinary Surveillance Network (SAVSNET) and VetCompass have played a crucial role in collecting electronic health records (EHRs) from first-opinion veterinary practices from across the UK[24,25]. These datasets offer an extensive array of information concerning the health and medical background of companion animals, affording researchers an unprecedented view of why companion animals attend veterinary practice and how they are treated at national scales. Previous studies conducted by SAVSNET and VetCompass have primarily focused on utilising product dispensary information and gathering tabular features as components of their research[22,26–29]. While both frameworks capture free-text narratives detailing clinical events, such as the presenting symptoms and diagnoses, these narratives have often been underutilised due to the considerable challenge in automating large-scale extraction of relevant information. These barriers include the substantial time and labour required, the risk of human errors, the subjective nature of text interpretation, and the complexities of managing large datasets, all of which contribute to the significant challenges around extracting relevant information at scale[30,31]. As a result, manually annotated data frequently suffers from issues with uniformity and scalability, making the comprehensive identification and analysis of diseases impractical.

The recent innovations in Natural Language Processing (NLP), particularly in the transformer architecture found in such models as BERT[32], LaMDA[33], GPT-3[34], and Gemini[35] demonstrate exceptional performance across diverse set of NLP benchmarks[36–38]. Optimising transformer performance for domain-specific language tasks through fine-tuning pre-trained models on in-domain data, as evidenced by BioBERT and BioClinicalBERT, showcasing marked improvements across various biomedical tasks compared to the original BERT model[39–44]. These innovations in transformer-based models open new avenues to leverage the wealth of free-text narratives in veterinary EHR datasets, enhancing precision and scalability in disease classification and analysis within companion animal medicine. In a prior investigation, we trained PetBERT, a Large Language Model (LLM) trained on over 500 million tokens from 5.1 million UK EHRs, which we showed to outperform clinician-assigned point-of-care labels in a disease outbreak case study[45,46].

This study aims to bridge the gap in understanding antimicrobial prescribing practices. We will explore a free text EHR dataset derived from HPCIA prescriptions to extract disease and syndromic diagnoses for training disease classifiers. We will expand PetBERT's capabilities from our previous works to not only annotate diseases at a syndromic level but also adopt the hierarchical disease-level classification adopting the International Classification of Disease 11 (ICD-11) framework[46]. Our primary objective is to reveal common antimicrobial prescriptions, both non-HPCIA and HPCIA, for diseases. We will verify these prescriptions against antimicrobial stewardship guidelines (ASGs) in a case study and observe prescribing compliance.

2 Results

A snapshot of the SAVSNET dataset, collected over more than nine years from March 2014 to September 2023, incorporates 8,822,743 first-opinion veterinary consultations from across the UK. Of these consultations, 2,458,440 involved cats, while 6,332,504 pertained to dogs. We analysed a dataset of 53,582 prescriptions for HPCIA in dogs and 141,430 in cats. These data form part of the broader context of antimicrobial prescriptions, totalling 1,239,534 prescriptions for dogs and 309,321 for cats. Our findings suggest that approximately two out of every ten dog consultations (19.6%) result in an antimicrobial prescription. The ratio in cats was slightly lower, with just over one out of every ten consultations (12.6%) ending with an antimicrobial prescription. However, when considering HPCIA prescribing, there appeared to be distinctions between the two species. HPCIA prescriptions accounted for 4.1% of all antimicrobial prescriptions in the canine population, while in felines, they constituted a substantial 31.4%. For the canine population, the fluoroquinolone class of antimicrobials emerged as the dominant category of HPCIA prescriptions, accounting for 60.2% of all HPCIAs prescribed. Notably, enrofloxacin was the most frequently prescribed individual HPCIA, making up 20.1% of the total HPCIA prescriptions, with marbofloxacin following closely at 17.9%. In contrast, feline HPCIA prescribing saw Cefovecin, belonging to the cephalosporin class of antimicrobials, overwhelmingly predominant, representing 94.3% of all such cat prescriptions.

2.1 Model Performance

In evaluating the performance of the disease classifier, the initial criteria for disease selection focused on their prevalence within the HPCIA dataset. The inclusion criteria were disease occurrences exceeding 100 instances within the HPCIA training set, species independent, based on the preliminary regular expression of narratives for keywords describing the disease, their

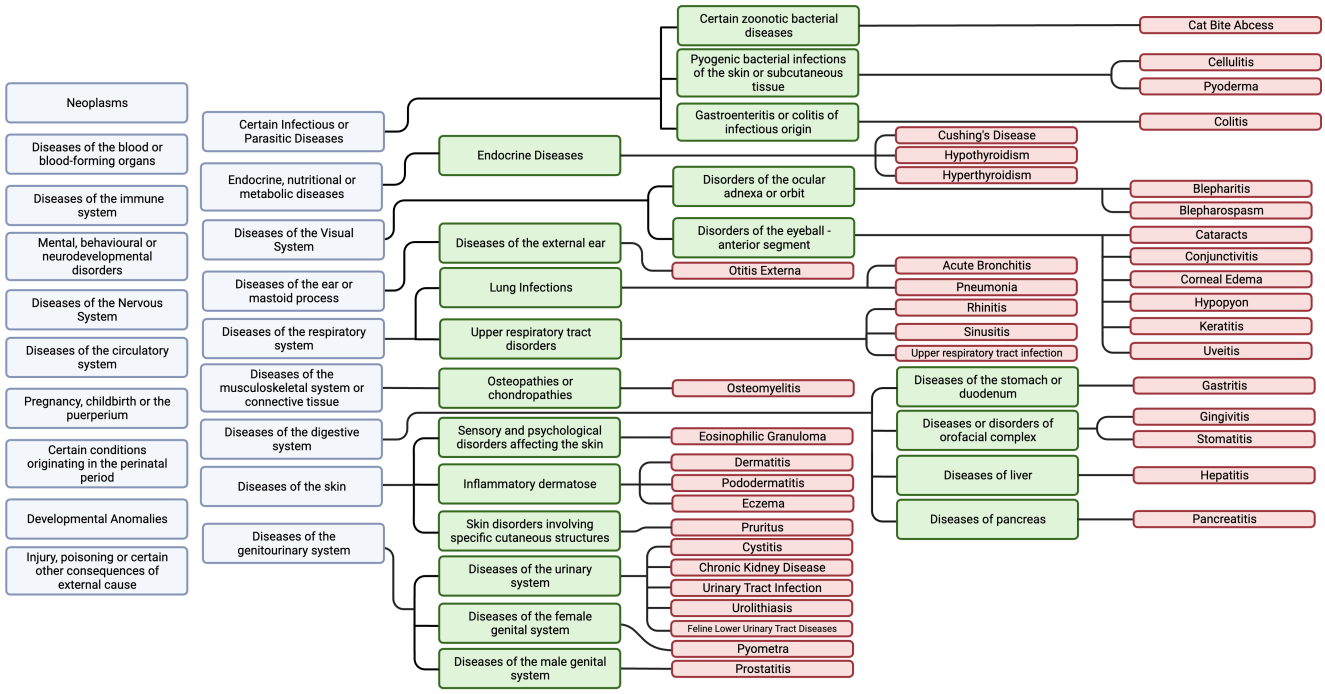


Figure 1. Outline of the full hierarchical model architecture following the ICD-11 framework, with the 19 syndromic labels (blue, left), 20 grouping labels (green, central), and 39 disease labels (red, right)

common abbreviations and basic negations. The performance metrics of precision, recall, and F1-score for each respective classifier are presented in Table 3. These metrics are derived from a test set of 17,000 narratives annotated with supervision by a practising clinician for syndrome or presumed diagnosis. The table also provides the entire dataset's total count of disease instances. Additionally, Figure 1 presents an overall representation of the entire hierarchical structure with the ICD-11 'chapters', 'groupings', and finally, single 'diseases'.

2.2 Antimicrobial Prescriptions in Disease

Table 1 showcases the most frequently prescribed types of HPCIA for the diseases studied in cats and dogs. The table is divided into several columns, where the first column lists the diseases under study. The subsequent columns detail the name of the most commonly prescribed HPCIA, the frequency of these prescriptions for each disease, and the relative percentage these prescriptions represent out of the total HPCIA usage for the respective animal. Additionally, Table 2 provides insights into the predominant non-HPCIA antimicrobial types prescribed in a similar context. We show that certain diseases, such as sinusitis, eczema, and rhinitis in cats, as well as stomatitis in dogs, stand out as examples where HPCIA prescribing is more dominant than non-HPCIA prescribing. Figure 2 visually highlights treatment choices, revealing considerable dependence on HPCIA treatments for specific conditions, complemented by numerical breakdowns in supplementary tables 1 and 2 for dogs and cats, respectively.

For dogs, of the 39 diseases studied, specific patterns were evident surrounding the prevalence of certain antimicrobial prescriptions. Marbofloxacin was prominent, appearing across twelve conditions and representing the most widely prescribed HPCIA. Similarly, enrofloxacin was the primary HPCIA for ten studied conditions, while ofloxacin was the most frequently prescribed HPCIA for eight conditions. For non-HPCIA prescriptions, amoxicillin-clavulanate emerged as the most frequently prescribed antimicrobial, accounting for 38.0% of all prescriptions. It was the preferred choice in 23 out of the 39 studied diseases. Fusidic acid and cefalexin were less frequent yet significant, each emerging as the principal non-HPCIA prescriptions for four conditions within the study scope. Relative to all prescriptions, fusidic acid and cefalexin constituted 8.7% and 8.5%, respectively. Cefovecin was the most frequently prescribed HPCIA for cats for 36 of these conditions and accounted for nearly a third of all antimicrobial prescriptions in felines, with 29.6% in total. Remarkably, Cefovecin was the most preferred antimicrobial overall for a subset of 17 conditions, including pruritus, pyoderma, rhinitis, and sinusitis. For non-HPCIA prescriptions, Amoxicillin clavulanate was the most commonly prescribed, with 53.5% total prescriptions, and was the most popular antimicrobial in 12 of the 39 study conditions, such as hepatitis, bronchitis, and cellulitis. This was followed by fusidic

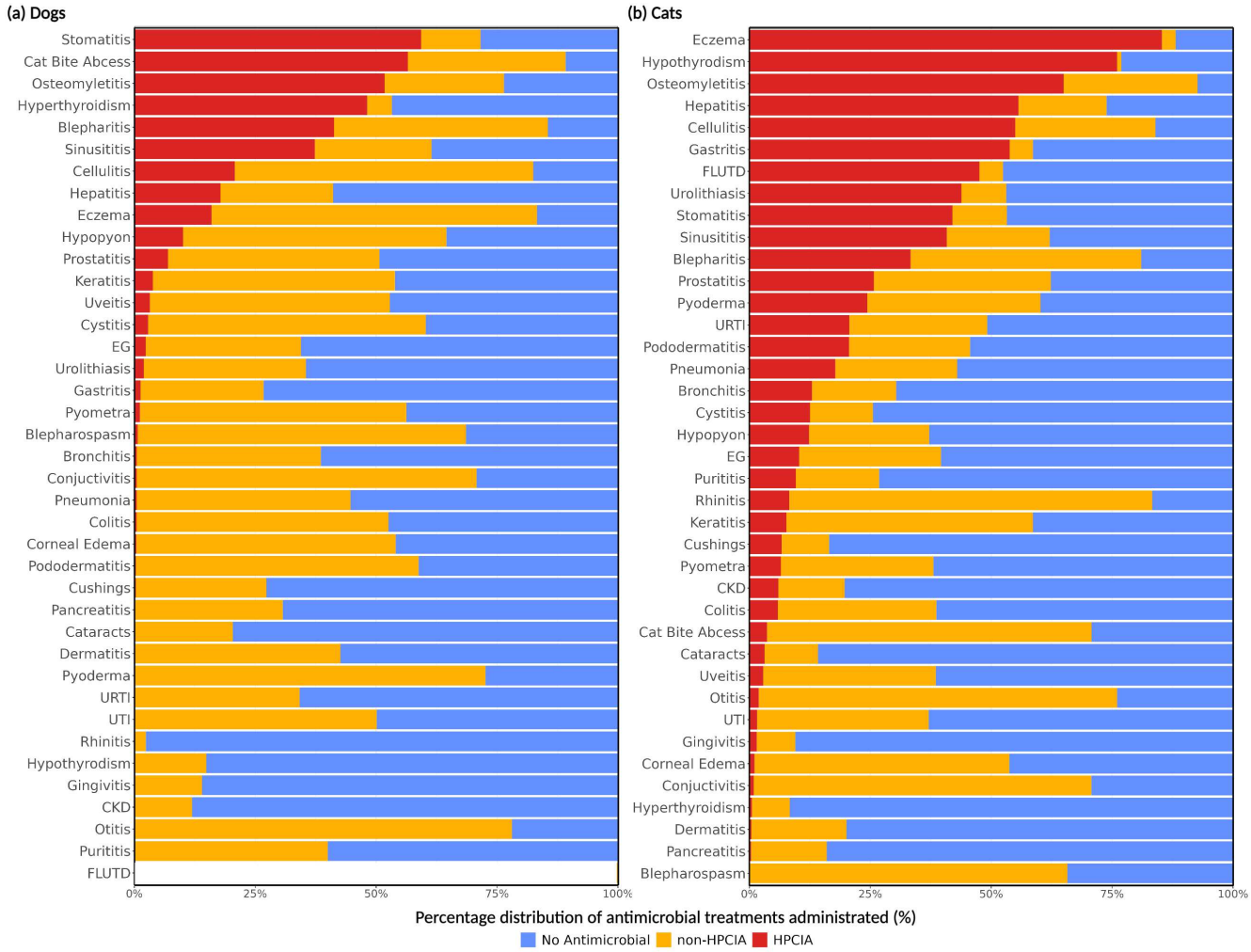


Figure 2. Proportion of treatments for each of disease with no antimicrobial (blue), non-HPCIA antimicrobial (yellow) and HPCIA antimicrobial (red). FLUTD = Feline Lower Urinary Tract Disease, URTI = Upper Respiratory Tract infection, EG = Eosinophilic Granuloma, CKD = Chronic Kidney Disease, UTI = Urinary Tract Disease

acid at 11.4%, which was most popular in five conditions such as blepharitis, blepharospasm, and conjunctivitis.

2.3 Case Study: Antimicrobial Stewardship Guidelines

The escalating concern over AMR impact has led national bodies, government institutions, and special interest groups to produce antimicrobial stewardship guidelines (ASGs), aimed at encouraging more judicious use of antimicrobials among veterinarians treating companion animals[47–49]. Guidelines are an integral part of an enablement strategy of stewardship[50]. Conversely, a restrictive stewardship strategy, which involves impeding the use of certain antimicrobials in animals owing to their critical role in managing severe, life-threatening infections in humans, like the Veterinary Medicinal Products Regulation (Regulation (EU) 2019/6), places a formulary restriction on veterinarians[51]. Despite the continuous roll out of ASGs with an increasing emphasis on minimising prescribing, there is no system to verify adherence to these guidelines. In the UK context, government-collated annual reports primarily focus on overall antimicrobial sales data without an in-depth analysis of the reasoning behind a clinician's prescription choice. This oversight underscores a significant gap in understanding and monitoring antimicrobial prescribing practices. Here, we examined ASG's role in shaping prescribing patterns among companion animal veterinarians. We identified from a preceding survey study that, among a wide array of existing ASGs, the PROTECT ME guideline emerged as the most widely adopted within the UK veterinary system[52]. Over 71.0% of responding active companion animal clinicians affirming they employed the PROTECT ME framework in their practice[53]. Additionally, the 'Guidance for the Rational use of Antimicrobials' (GRAM) and the 'Recommendations for Appropriate Antimicrobial Therapy' by FECAVA were employed by 22.0% and 12.5% of respondents, respectively[54,55]. Analysis using FECAVA and GRAM can be found in

our supplementary materials table 3.

We first identified specific conditions within our disease classifier that were concurrently mentioned within the PROTECT ME framework. In cases where an antimicrobial was prescribed, we assessed the alignment between the prescribed treatment and the recommendations by the ASG. We considered recorded compliance with the guideline relative to their first introduction for PROTECT ME in November 2018. These results are in table 4. There is an observed broad range of agreements with the guidelines. For example, certain conditions, such as pyometra, recommended amoxicillin-clavulanate, which saw adherence greater than 80% in cats and dogs. Other examples saw higher compliance in one species compared to the other; for instance, in the case of cystitis, 85% of prescriptions in dogs complied with the recommendation of amoxicillin-clavulanate, whereas in cats, this dropped to 28%. There is advocacy for prioritising a primary prescription before a secondary, often HPCIA class, antimicrobial in certain conditions. For the following example, we analysed the previous consultations to see if they occurred within three months, leading to the clinician's diagnosis and subsequent prescription, to verify whether this ordering was compliant. For example, in cat bite abscesses, PROTECT ME advises that initial antimicrobials be 'amoxicillin-clavulanate' or 'cefalexin', preceding the consideration of fluoroquinolones. Fluoroquinolones were prescribed in cats on 387 occasions, of which 240 instances (62.0%) designated it as the first prescribed choice.

As of March 2024, the PROTECT ME framework has issued updated ASGs[56]. We offer preliminary insight into veterinary practices' adoption patterns for these new guidelines. Due to the release's restricted time scope, our analysis retrospectively examines compliance with these guidelines to records occurring after November 2018. A critical update discourages using antimicrobials for cat bite abscesses – a significant deviation from the former recommendations for amoxicillin-clavulanate or cefalexin, with fluoroquinolones as a secondary option. Historical data suggests that an antimicrobial was prescribed in 60.9% of feline cases, of which 89.0% followed the previous guidelines. Consequently, the revised, non-use recommendations would have reduced adherence to below 40.0%. The earlier guidelines favouring amoxicillin-clavulanate, clindamycin, or metronidazole to manage gingivitis demonstrated an adherence rate exceeding 44.0% for feline cases and 53.0% for canine cases. Intriguingly, the adherence rate to the updated guidelines, which advocate forgoing antimicrobials, has increased to 89.0%, thus mirroring pre-existing treatment patterns. For other conditions, such as conjunctivitis, treatment options for veterinarians have expanded. The initial suggestion of fusidic acid or chlortetracycline was compliant for 42.0% of feline and 39.0% of canine prescriptions. Including chloramphenicol as a treatment option has modestly improved treatment guideline compliance, lifting adherence rates to 49.0% for dogs and 46.0% for cats, thus indicating a moderate adherence to of the revised guidelines.

3 Discussion

The judicious prescribing of antimicrobials is a pivotal public health challenge, as inappropriate use significantly contributes to the escalating emergence of AMR bacteria. However, current approaches to monitoring antimicrobial utilisation, such as relying on annual aggregate sales data, provide limited insights into the specific disease contexts and prescribing practices driving antimicrobial use. This is particularly problematic in the companion animal sector, where comprehensive diagnostic data can be challenging to obtain from clinicians. To address these limitations, this study introduces a novel hierarchical disease modelling framework leveraging LLMs specifically designed to extract fine-grained, contextually relevant meanings embedded within the free text of clinical EHRs. This framework facilitates the systematic monitoring and tracking of the prevalence levels of 39 unique diseases/syndromes. Consequently, a broader understanding of antimicrobial prescribing trends and their associated disease contexts can be achieved across the UK companion animal population.

The authorisation of third-generation cephalosporins in Europe in 2006 has led to a significant increase in the usage of the HPCIA cefovecin, particularly among cats in the UK[21,57]. Cefovecin emerged as the predominant HPCIA prescribed in cats, encompassing 36 out of 39 diseases within this study, such as cellulitis, eczema, sinusitis, and rhinitis. Several interconnected factors likely influence the preference for using cefovecin, namely, its primary formulation as a long-acting preparation with broad-spectrum efficacy, and owner reluctance to administer daily oral tablets to their pets, especially cats, preferring the simplicity of a single, veterinarian-administered injection every two weeks[57,58]. This multifaceted rationale behind the preference for cefovecin underscores the complex interplay of clinical, practical, and owner-related considerations in clinical decision-making. However, despite these conveniences, clinicians need to consider the broader implications of relying predominantly on cefovecin, including the risk of promoting AMR and the necessity for a balanced approach towards antimicrobial stewardship within veterinary medicine.

Our case study offers insights into the deviations and compliance with ASGs among UK veterinarians, unveiling significant differences in adherence when treating diverse disease conditions. Most clinicians within the UK claim to use an ASG actively

to some extent. The PROTECT ME framework is widely adopted and utilised by a majority percentage (71.0%) of active companion animal clinicians in the UK, as indicated by a prior study[52,53]. However, it may not always be apparent why a veterinarian diverges from an ASG within their clinical notes or which guidelines they follow in their practice, if any. Minor deviations from prescribed guidelines might indicate an overall adherence. However, it is challenging to determine whether these minor deviations can be attributed to biological factors such as disease severity, lab reports indicating lower antimicrobial sensitivity, or specific circumstances rendering the recommended drugs unsuitable—such as allergies. Prior research has examined the influence of non-clinical prescription reasons, such as owner pressure, differing antimicrobial costs, or additional laboratory diagnostic testing expenses, as well as the availability of the antimicrobial[52,59,60]. Such factors are often beyond the control of clinicians and have significant implications on prescribing behaviours.

There were occasions where practitioners appeared to deviate substantially from ASG recommendations. For example, in cases of keratitis, the guideline recommendation for PROTECT ME of gentamicin, ciprofloxacin, and ofloxacin was prescribed only in 4.0% of dog cases and 6.0% in cats. The preference for cefovecin in feline treatments resulted in comparatively lower adherence to ASGs in cats than in dogs. For instance, amoxicillin-clavulanate, the recommended treatment for cystitis in cats and dogs, had a high compliance rate in dog consultations (over 85.0%), whereas its prescription in cats was 28.0%. In our findings, certain instances emerged where the high use of specific antimicrobials in practice contradicted the guidelines' explicit non-use recommendations, typically due to known inefficacies. For example, in the case of prostatitis, amoxicillin/clavulanate is expressly discouraged due to its inability to cross the blood-prostate barrier. Nevertheless, it was the most commonly employed antimicrobial, accounting for 32.0% of prescriptions, thus revealing an intriguing discrepancy between actual prescribed practice and the recommendation of guidelines. Inversely, veterinarians may deviate from antimicrobial guidelines due to observed discrepancies between real-world clinical efficacy and current literature. Investigating these differences could reveal insights that inform updates to ASGs, aligning recommendations with actual treatment outcomes in practice.

Creating disease classifiers in this study can only be as powerful as the information clinicians enter into the SAVSNET dataset. In the first-opinion veterinary practice, clinicians often need more specialised expertise and advanced diagnostic facilities to diagnose many conditions definitively. Pet owners may decline or cannot afford the costs of such additions to attain a confirmed diagnosis. Therefore, the model will not correctly differentiate between accurate diagnoses and misdiagnoses/provisional diagnosis, nor will it be able to capture unconsidered diseases; it will only annotate diseases described by clinicians. Additionally, quantifying antimicrobial prescriptions relies on practitioners charging for antimicrobial agents through their practice management software. Therefore, any antimicrobial not charged for will not be considered. We also highlight that when an antimicrobial is prescribed for a patient with comorbidities (e.g. gingivitis and pneumonia), we are unable to attribute the prescribed medication to one specific disease definitively. Finally, the SAVSNET population of practices is recruited based on convenience and so cannot necessarily be considered representative of the wider UK population[61].

In summary, here we apply a hierarchical LLM to reveal where antimicrobial prescriptions are being used and offer a novel approach to assess the influence of ASGs. Through our analysis of 195,012 HPCIA prescriptions and over 1.2 million antimicrobial prescriptions, we have illustrated the nuances of disease patterns and prescribing motivations, which have, until now, remained obscured by the limitations of existing reporting mechanisms. The accuracy of our model in identifying 39 distinct diseases associated with antimicrobial prescriptions exceeds 88%, providing a robust foundation for analysing antimicrobial use and its alignment with ASGs. Our findings, particularly the prevalent use of Cefovecin in feline treatments, highlight the urgent need for enhanced stewardship practices to reduce the threat of AMR to animal welfare and public health. Therefore, this study advances our understanding of AMR dynamics within veterinary care and outlines an actionable path towards enhanced ASG monitoring. By bridging the gap between actual practice and guideline-aligned prescribing, we can preserve the efficacy of essential antimicrobial agents, safeguarding public health and ensuring the welfare of future generations of both humans and animals.

4 Methods

4.1 Dataset

Data for this study was obtained from SAVSNET, which has collected EHRs from participating veterinary practices across the United Kingdom since March 2014. The network consists of 253 veterinary practices. A comprehensive description of SAVSNET's data collection methodology has been previously published[24]. In brief, veterinary practices with compatible practice management software to securely exchange data with SAVSNET are recruited on a convenience basis. EHRs are collected from each participating practice during booked consultations, which include appointments with veterinary practitioners or nurses. Owners can opt out of data collection during the consultation. The collected EHRs include information on species, breed, sex, neuter status, age, owner's postcode, insurance and microchipping status, products sold or prescribed, and a free-text

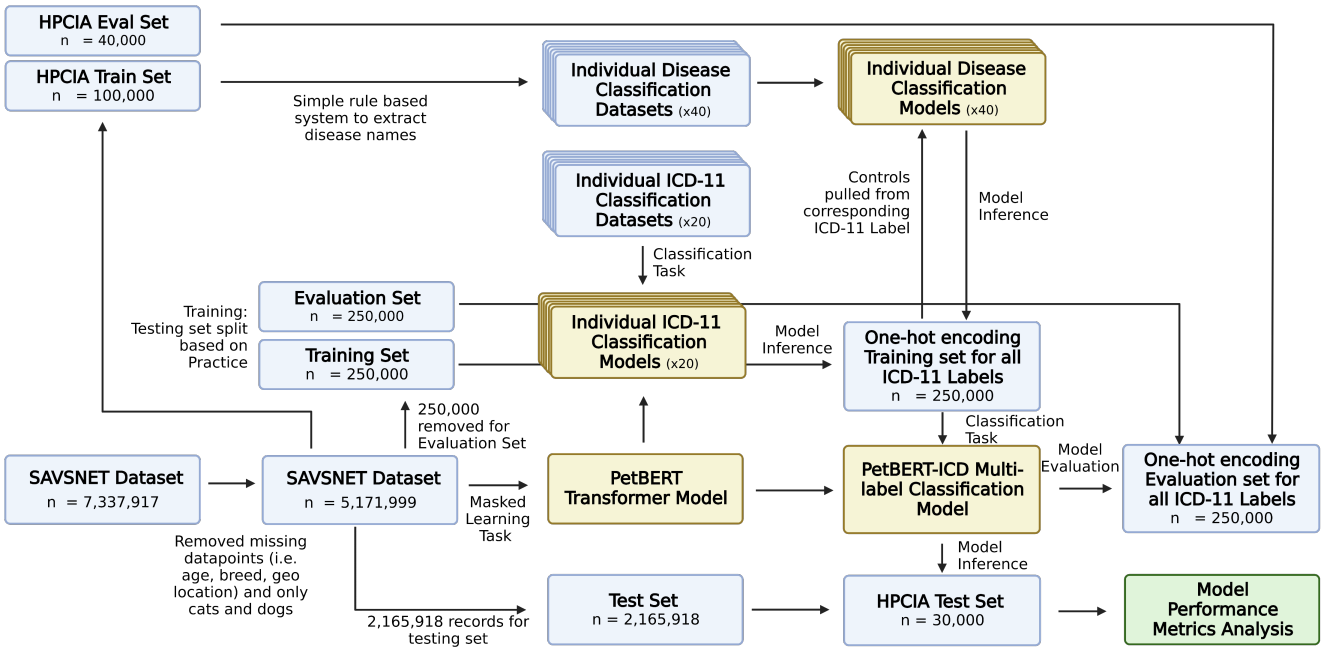


Figure 3. Schematic representation of the complete model development process: practice-level split of datasets for training and testing, additional pretraining of PetBERT on the first opinion veterinary clinical text corpus, individual binary classification models training using the HPCIA dataset, application of the individual models to a 250k combined dataset, and establishment of the hierarchical disease classification model.

clinical narrative recorded by the attending practitioner. This narrative provides insights into the events and observations during the consultation. Prior to analysis, sensitive information, including personal identifiers, are removed from the text data. SAVSNET has obtained ethical approval for its data collection and research activities from the University of Liverpool Research Ethics Committee (RETH001081). The free-text product dispensed description field was utilised to identify instances of antimicrobial prescribing. The mapping of products in these free texts to established lists of drug names and their active compound was accomplished through a semi-automated reviewing process instigated with keywords based on drug names, drug concentrations and active substances as described in the Veterinary Medicine Directorate's Product Information Database for veterinary-authorised pharmaceutical agents[62] and subsequently iteratively updated based on identified unmapped products such as those not licensed for animal use. Antimicrobials listed as HPCIA by the WHO were identified and additionally classified[19].

4.2 Data Extraction

Over nine and a half years, from March 2014 to September 2023, the SAVSNET dataset gathered 8,822,743 veterinary first-opinion consultations from across the UK. These were divided into 2,458,440 consultations with cats and 6,332,504 with dogs. In order to maintain the integrity of the data, incomplete records were eliminated from the dataset, including 22,230 lacking animal age, 67,595 missing postcodes, 3,109 missing pet sex and 405,811 omitting breed details. Reflecting the methodology from previous research, only records from 177 of the collective 253 veterinary practices were included in the training set, reinforcing the validity and wider generalisability of the resulting models. The remaining 76 practices formed the test set, from which 17,000 random records were selected for manual review and annotation under supervsion of a parctising clinician. This subset was used to gauge and verify the model's final performance metrics. No additional preprocessing were applied to the text. The free-text product dispensed description field was utilised to identify instances of antimicrobial prescribing. The mapping of products in these free texts to established lists of drug names and their active compound was accomplished through a semi-automated reviewing process instigated with keywords based on drug names, drug concentrations and active substances as described in the Veterinary Medicine Directorate's Product Information Database for veterinary-authorised pharmaceutical agents[62] and subsequently iteratively updated based on identified unmapped products such as those not licensed for animal use. Antimicrobials listed as HPCIA by the WHO were identified and additionally classified[19].

4.3 Model Training

The complete training process for the PetBERT transformer model and PetBERT-ICD syndromic disease multi-label classifier has been previously described elsewhere[45]. Briefly, the ULMFiT framework was adapted to develop 'PetBERT' with minor alterations to the BERT architecture[32,39]. The pre-trained BERT-base model was further fine-tuned on approximately 500 million tokens from clinical narratives from the SAVSNET dataset through Masked Language Modeling (MLM) and Next Sentence Prediction (NSP) tasks, mimicking the pretraining steps in the initial training of BERT. Using the chapters of the ICD-11 framework, a training set was constructed utilising 20 binary sequence classification models with the aid of a semi-supervised Teacher-Student model approach, inspired by Yalniz et al. (2019)[63]. This approach used a small number of manually annotated records containing the target class and equal proportions of controls. After iterative testing, the developed binary classification models were applied to the "training set" and "test set". These dataset splits were maintained from the original publication and were selected based on a practice-level split, providing additional confidence in the generalisability of the model and avoiding data contamination issues[45]. The resulting multi-label classification model was then trained using the annotations from the binary classification models. Lastly, the trained PetBERT-ICD categorical classifier was applied to a 2.1 million record testing set to evaluate its performance and generalisability.

ICD-11 chapters used previously are high-level and lack information on specific diseases or clinical signs. We expand the previous capabilities of PetBERT-ICD to develop hierarchical LLMs to classify clinical narratives with a probable disease classification and thus provide a possible explanation for an antimicrobial prescription. The dataset for our study was derived from the SAVSNET database, mainly focusing on instances where an HPCIA was dispensed. These instances were consolidated with training and testing records while upholding the practice-level splits established in prior research. To help reveal the disease causality within the HPCIA datasets, we crafted simple regular expressions that included major disease names, abbreviations, and common misspellings as well whilst excluding common negations (i.e. 'no evidence of', 'no signs of', 'no', 'not showing symptoms of'); where a given disease regular expression identified over 100 cases among dogs and cats, the consultations were set aside for manual review by a domain expert to identify true cases; those sustaining more than 100 instances after this review remained within the study's scope. A random sample of cases was collated and balanced with an equivalent number of control records from the same HPCIA datasets and syndromic ICD-11 chapters, which underwent additional review to ensure the absence of the target disease. The combined dataset was used to train individual binary disease classification models based on the PetBERT architecture. We adopted an initial learning rate of 2e-5 and a mini-batch size of 16, with early stopping criteria to ascertain the optimal epoch number, averaging around six. The relatively small size of these models facilitated training on a single Nvidia A6000 GPU in under 20 minutes.

To produce the final hierarchical PetBERT model, second-order ICD-11 "groupings" were formed derived from the original ICD framework[46]. Diseases within the same grouping were organised together (e.g. under *'Disease of the Respiratory System'* has the grouping *e.g. 'Lung Infection'*, which has the studied diseases (e.g. *'Bronchitis'* and *'Pneumonia'*). Therefore, individual multi-label classifiers for each grouping were trained via the individual binary disease classifiers being applied to a single 250k consultation training and evaluation sets previously used within the initial PetBERT-ICD training. These records were indexed according to their groupings and labelled as a one-hot encoding vector. The final model was trained on the 19 syndromic models assigned by the initial PetBERT-ICD model, followed by the 20 grouping labels, and finally, the 39 studied disease labels. The entire hierarchy, which can be viewed in Figure 1, was applied against the 2.1 million testing set. The model would only annotate individual single diseases (e.g. the *'pneumonia'*) if the 'groupings' layer (e.g. the *'Lung Infection'*) in the hierarchy was annotated, and if the top level 'chapters' (e.g. the *'Diseases of the Respiratory system'*) were annotated. The model was trained as a multi-label classifier, and thus, each record can be annotated with multiple classifications.

4.4 Evaluation

The model was evaluated using a 17,000 record dataset of manually annotated under supervision of a practising clinician for each of the diseases trained within the classifiers. Precision, recall, and F1-score metrics were computed for each disease within the hierarchical model approach. Subsequently, the trained hierarchical model was applied to the entire dataset with antimicrobial prescription data relative to each reported disease affiliated with each consultation. An analysis of the treatment outcomes for the diseases studied here was explored.

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6 Data availability

The datasets analysed during the current study are not publicly available due to issues surrounding owner confidentiality. Reasonable requests can be made to the SAVSNET Data Access and Publication Panel (savsnet@liverpool.ac.uk) for researchers who meet the criteria for access to confidential data.

7 Competing interests

All authors declare no financial or non-financial competing interests.

8 Contributions

SF conceived the study with PJ-N and NA, performed the annotations with PJ-N, wrote the code, conducted the analysis, and wrote the manuscript. GP, AR, and PJ-N set up the SAVSNET dataset, and AR established the pipeline to map free text sales items to mapped products. DS provided guidance on the case study and offered specific recommendations for antimicrobial stewardship guidelines. All authors reviewed and approved the final manuscript.

Table 1. Most common HPCIA antmicrobial prescription for each disease with counts and relative percentage to the total HPCIA prescriptions (FLUTD - Feline Lower Urinary Tract Disease, URTI = Upper Respiratory Tract Infection)

		Dogs		Cats	
Grouping	**Disease name**	**Most Common HPCIA**	**Count (%)**	**Most Common HPCIA**	**Count (%)**
Certain Zoonotic Bacterial Diseases	**Cat Bite Abcess**	Cefovecin	33 (49.3%)	Cefovecin	10628 (99.5%)
Diseases Of External Ear	**Otitis**	Marbofloxacin	4220 (85.5%)	Cefovecin	764 (83.8%)
Diseases Of Liver	**Hepatitis**	Marbofloxacin	4 (57.1%)	Cefovecin	12 (80.0%)
Diseases Of Pancreas	**Pancreatitis**	Cefovecin	59 (44.4%)	Cefovecin	327 (95.9%)
Diseases Of The Female Genital System	**Pyometra**	Marbofloxacin	34 (45.9%)	Cefovecin	26 (92.9%)
Diseases Of The Male Genital System	**Prostatitis**	Enrofloxacin	89 (60.5%)	None	None
Diseases Of The Stomach Or The Duodenum	**Gastritis**	Enrofloxacin	37 (45.7%)	Cefovecin	124 (98.4%)
Diseases Of The Urinary System	**Cystitis**	Enrofloxacin	84 (36.2%)	Cefovecin	4849 (97.7%)
	Urinary Tract Infection	Enrofloxacin	150 (33.2%)	Cefovecin	3403 (98%)
	Urolithiasis	Enrofloxacin	18 (50%)	Cefovecin	204 (96.7%)
	Chronic Kidney Disease	Cefovecin	27 (52.9%)	Cefovecin	1077 (98.7%)
	FLUTD	-	- (-.-%)	Cefovecin	1341 (99.2%)
Diseases Or Disorders Of Orofacial Complex	**Gingivitis**	Cefovecin	65 (41.7%)	Cefovecin	6610 (98.6%)
	Stomatitis	Enrofloxacin	5 (31.3%)	Cefovecin	1835 (98.2%)
Disorders Of The Eyeball - Anterior Segment	**Conjunctivitis**	Ofloxacin	1667 (76.1%)	Cefovecin	4272 (80.2%)
	Corneal Edema	Ofloxacin	753 (89.2%)	Ofloxacin	657 (80.2%)
	Hypopyon	Ofloxacin	57 (62.0%)	Cefovecin	26 (50.0%)
	Keratitis	Ofloxacin	115 (72.3%)	Cefovecin	52 (59.1%)
	Uveitis	Ofloxacin	200 (80.0%)	Cefovecin	98 (51.3%)
	Cataracts	Ofloxacin	116 (46.6%)	Cefovecin	67 (90.5%)
Disorders Of The Ocular Adnexa Or Orbit	**Blepharitis**	Ofloxacin	34 (49.3%)	Cefovecin	78 (86.7%)
	Blepharospasm	Ofloxacin	980 (68.1%)	Cefovecin	987 (80.0%)
Endocrine Diseases	**Cushings**	Marbofloxacin	37 (31.9%)	None	None
	Hypothyrodism	Marbofloxacin	22 (50.0%)	None	None
	Hyperthyroidism	Cefovecin	2 (40.0%)	Cefovecin	2264 (98.6%)
Gastroenteritis Or Colitis Of Infectious Origin	**Colitis**	Tylosin	131 (44.4%)	Cefovecin	136 (90.7%)
Inflammatory Dermatose	**Pododermatitis**	Marbofloxacin	73 (47.7%)	Cefovecin	160 (97.6%)
	Eczema	Marbofloxacin	21 (47.7%)	Cefovecin	213 (99.5%)
	Dermatitis	Marbofloxacin	442 (47.1%)	Cefovecin	8397 (99.1%)
Lung Infections	**Bronchitis**	Enrofloxacin	77 (38.9%)	Cefovecin	118 (90.8%)
	Pneumonia	Enrofloxacin	88 (48.9%)	Cefovecin	124 (81.6%)
Osteopathies Or Chondropathies	**Osteomyletitis**	Marbofloxacin	7 (36.8%)	Cefovecin	178 (94.7%)
Pyogenic Bacterial Infections Of The Skin Or Subcutaneous Tissues	**Pyoderma**	Pradofloxacin	671 (46.4%)	Cefovecin	2976 (99.3%)
	Cellulitis	Enrofloxacin	34 (33.7%)	Cefovecin	1256 (98.2%)
Sensory And Psychological Disorders Affecting The Skin	**Pruritus**	Marbofloxacin	1094 (68.3%)	Cefovecin	3549 (98.6%)
Skin Disorders Involving Specific Cutaneous Structures	**Eosinophilic Granuloma**	Marbofloxacin	3 (75.0%)	Cefovecin	1932 (99.7%)
Upper Respiratory Tract Disorders	**Sinusitis**	Marbofloxacin	5 (33.3%)	Cefovecin	895 (97.1%)
	URTI	Enrofloxacin	179 (37.2%)	Cefovecin	6850 (96.2%)
	Rhinitis	Cefovecin	34 (45.3%)	Cefovecin	1038 (92.3%)

Table 2. Most common non-HPCIA antmicrobial prescription for each disease with counts and relative percentage to the total non-HPCIA prescriptions (FLUTD - Feline Lower Urinary Tract Disease, URTI = Upper Respiratory Tract Infection

		Dogs		Cats	
Grouping	**Disease name**	**Most common non-HPCIA**	**Count (%)**	**Most common non-HPCIA**	**Count (%)**
Certain Zoonotic Bacterial Diseases	**Cat Bite Abcess**	Amoxicillin Clavulanate	1697 (58.5%)	Amoxicillin Clavulanate	10560 (71.6%)
Diseases Of External Ear	**Otitis**	Polymyxin B Sulphate	28044 (37.8%)	Polymyxin B Sulphate	1326 (31.8%)
Diseases Of Liver	**Hepatitis**	Amoxicillin Clavulanate	105 (67.3%)	Amoxicillin Clavulanate	87 (92.6%)
Diseases Of Pancreas	**Pancreatitis**	Metronidazole	3827 (47.8%)	Amoxicillin Clavulanate	517 (61.3%)
Diseases Of The Female Genital System	**Pyometra**	Amoxicillin Clavulanate	6098 (91.6%)	Amoxicillin Clavulanate	77 (46.4%)
Diseases Of The Male Genital System	**Prostatitis**	Amoxicillin Clavulanate	319 (65.2%)	None	None
Diseases Of The Stomach Or The Duodenum	**Gastritis**	Amoxicillin Clavulanate	2238 (52.9%)	Amoxicillin Clavulanate	212 (47.9%)
Diseases Of The Urinary System	**Cystitis**	Amoxicillin Clavulanate	7633 (85.5%)	Amoxicillin Clavulanate	2621 (25.7%)
	Urinary Tract Infection	Amoxicillin Clavulanate	13375 (79.2%)	Amoxicillin Clavulanate	2946 (68.2%)
	Urolithiasis	Amoxicillin Clavulanate	773 (55.9%)	Amoxicillin Clavulanate	185 (32.8%)
	Chronic Kidney Disease	Amoxicillin Clavulanate	397 (58.3%)	Amoxicillin Clavulanate	1378 (61.5%)
	FLUTD	-	- (-.-%)	Amoxicillin Clavulanate	409 (74.4%)
Diseases Or Disorders Of Orofacial Complex	**Gingivitis**	Amoxicillin Clavulanate	2941 (38.0%)	Amoxicillin Clavulanate	3403 (35.6%)
	Stomatitis	Amoxicillin Clavulanate	210 (41.2%)	Clindamycin	938 (56.5%)
Disorders Of The Eyeball - Anterior Segment	**Conjunctivitis**	Fusidic Acid	60052 (49.6%)	Fusidic Acid	23266 (50.1%)
	Corneal Edema	Chloramphenicol	3987 (35.1%)	Fusidic Acid	1260 (44.5%)
	Hypopyon	Amoxicillin Clavulanate	726 (74.8%)	Amoxicillin Clavulanate	43 (28.3%)
	Keratitis	Polymyxin B Sulphate	995 (30.1%)	Polymyxin B Sulphate	705 (40.1%)
	Uveitis	Polymyxin B Sulphate	1130 (24.4%)	Fusidic Acid	216 (24%)
	Cataracts	Polymyxin B Sulphate	1971 (25.5%)	Fusidic Acid	74 (27.8%)
Disorders Of The Ocular Adnexa Or Orbit	**Blepharitis**	Fusidic Acid	1044 (44.9%)	Chloramphenicol	505 (51.9%)
	Blepharospasm	Fusidic Acid	9445 (37.6%)	Fusidic Acid	4346 (38%)
Endocrine Diseases	**Cushings**	Amoxicillin Clavulanate	2720 (61.1%)	Amoxicillin Clavulanate	8 (36.4%)
	Hypothyrodism	Amoxicillin Clavulanate	229 (22.4%)	Amoxicillin Clavulanate	7 (24.1%)
	Hyperthyroidism	Amoxicillin Clavulanate	12 (34.3%)	Amoxicillin Clavulanate	1283 (55.8%)
Gastroenteritis Or Colitis Of Infectious Origin	**Colitis**	Metronidazole	10198 (61.4%)	Metronidazole	783 (65.1%)
Inflammatory Dermatose	**Pododermatitis**	Cefalexin	3586 (40.0%)	Amoxicillin Clavulanate	103 (41.4%)
	Eczema	Fusidic Acid	1932 (32.7%)	Fusidic Acid	111 (44.0%)
	Dermatitis	Cefalexin	14157 (25.9%)	Amoxicillin Clavulanate	2455 (35.5%)
Lung Infections	**Bronchitis**	Amoxicillin Clavulanate	9512 (70.6%)	Amoxicillin Clavulanate	107 (58.8%)
	Pneumonia	Amoxicillin Clavulanate	1416 (79.2%)	Amoxicillin Clavulanate	202 (71.1%)
Osteopathies Or Chondropathies	**Osteomyletitis**	Clindamycin	370 (50.9%)	Clindamycin	679 (57.2%)
Pyogenic Bacterial Infections Of The Skin Or Subcutaneous Tissues	**Pyoderma**	Cefalexin	19658 (41.9%)	Amoxicillin Clavulanate	827 (44.2%)
	Cellulitis	Amoxicillin Clavulanate	3203 (65.6%)	Amoxicillin Clavulanate	1473 (81.0%)
Sensory And Psychological Disorders Affecting The Skin	**Pruritus**	Cefalexin	12793 (24.7%)	Fusidic Acid	1157 (32.4%)
Skin Disorders Involving Specific Cutaneous Structures	**Eosinophilic Granuloma**	Amoxicillin Clavulanate	57 (31.5%)	Amoxicillin Clavulanate	837 (54.7%)
Upper Respiratory Tract Disorders	**Sinusitis**	Amoxicillin Clavulanate	206 (62.2%)	Amoxicillin Clavulanate	148 (54.2%)
	URTI	Amoxicillin Clavulanate	10684 (59.9%)	Amoxicillin Clavulanate	4758 (48.5%)
	Rhinitis	Amoxicillin Clavulanate	1021 (67.0%)	Amoxicillin Clavulanate	435 (50.8%)

Table 3. Performance metrics for the hierarchical disease classifier model with precision, recall and f1 score with full dog and cat dataset counts for each disease

Grouping	Disease Name	Precision	Recall	F1	Dog (n)	Cat (n)
Certain Zoonotic Bacterial Diseases	Cat Bite Abscess	0.84	0.71	0.77	2767	24154
Diseases Of External Ear	Otitis	0.83	0.85	0.84	74856	4770
Diseases Of Liver	Hepatitis	1.00	0.20	0.33	428	294
Diseases Of Pancreas	Pancreatitis	0.78	0.68	0.72	19810	4363
Diseases Of The Female Genital System	Pyometra	0.68	0.92	0.78	9560	187
Diseases Of The Male Genital System	Prostatitis	0.92	0.36	0.52	913	292
Diseases Of The Stomach Or The Duodenum	Gastritis	0.95	1.00	0.97	13134	3378
Diseases Of The Urinary System	Cystitis	0.93	0.94	0.93	11733	21915
	UTI	0.94	0.95	0.95	25926	12173
	Urolithiasis	0.82	0.98	0.89	1963	1241
	CKD	0.76	0.96	0.84	4354	12650
	FLUTD	0.87	0.96	0.91	-	5362
Diseases Or Disorders Of Orofacial Complex	Gingivitis	0.88	0.96	0.92	35704	74390
	Stomatitis	0.94	0.89	0.91	1223	5921
Disorders Of The Eyeball - Anterior Segment	Conjuctivitis	0.83	0.96	0.90	130978	52670
	Corneal Edema	0.90	0.78	0.84	17007	4381
	Hypopyon	0.67	1.00	0.80	1136	490
	Keratitis	0.77	0.89	0.83	4990	1813
	Uveitis	0.94	0.80	0.86	5975	1982
	Cataracts	0.91	1.00	0.95	30002	1829
Disorders Of The Ocular Adnexa Or Orbit	Blepharitis	0.94	0.80	0.86	1093	2418
	Blepharospasm	0.91	0.90	0.90	12466	30057
Endocrine Diseases	Cushings	0.82	1.00	0.90	12267	193
	Hypothyrodism	0.71	0.75	0.56	5447	602
	Hyperthyroidism	0.86	0.76	0.81	264	24181
Gastroenteritis or Colitis of Infectious Origin	Gastroenteritis	0.95	1.00	0.87	25160	2262
Inflammatory Dermatose	Pododermatitis	0.82	1.00	0.90	11730	746
	Eczema	1.00	1.00	1.00	5389	1134
	Dermatitis	0.73	0.93	0.82	84602	30283
Lung Infections	Bronchitis	0.75	0.89	0.81	27220	802
	Pneumonia	0.85	0.93	0.89	3199	770
Osteopathies Or Chondropathies	Osteomyletitis	1.00	0.88	0.94	1065	1331
Pyogenic Bacterial Infections Of The Skin Or Subcutaneous Tissues	Pyoderma	0.92	0.99	0.95	50193	5197
	Cellulitis	0.98	0.97	0.98	5145	3150
Sensory And Psychological Disorders Affecting The Skin	Pruritus	0.73	0.96	0.69	99825	16688
Skin Disorders Involving Specific Cutaneous Structures	Eosinophilic Granuloma	0.93	0.92	0.93	376	5128
Upper Respiratory Tract Disorders	Sinusitis	0.61	0.81	0.70	642	1021
	URTI	0.92	0.89	0.92	39274	26663
	Rhinitis	0.95	0.93	0.94	3359	3306

Table 4. Antimicrobial Recommendations with total count of prescriptions that adhere to the antimicrobial stewardship guidelines with a a relative percentage of agreement with guidelines over all antimicrobials prescribed a given condition. *AC = Amoxicillin Clavulanate, FA = Fusidic acid, FQ = Fluroquinlones, TMPS = Trimethoprim/Sulphonamide, †= topical, 1. = Primary recommendation, 2. = secondary recommendation*

Disease	Guidance	Cats (%)	Dogs (%)
Cat Bite Abscess	1. AC, Cefalexin 2. FQ	14496 (89%)	1789 (61%)
Conjunctivitis	Chlortetracycline FA, Gentamicin	15365 (42%)	36215 (39%)
Corneal Edema	CH	613 (20%)	2789 (24%)
Cystitis	AC	5052 (28%)	10069 (85%)
Gingivitis	AC, Clindamycin Metronidazole	32845 (44%)	39592 (53%)
Hepatitis	Ampicillin AC, Cefalexin Metronizole	122 (58%)	243 (56%)
Keratitis	Gentamicin† Ciprofloxacin† Ofloxacin†	78 (4%)	331 (6%)
Osteomyelitis	AC, Ceflaexin	259 (32%)	601 (45%)
Otitis externa	FA, Framycetin Gentamicin Marbofloxcin Polymyxin B Orbifloxacin	2808 (55%)	46146 (78%)

Disease	Guidance	Cats (%)	Dogs (%)
Pancreatitis	Not advised	3454 (84%)	13699 (69%)
Pneumonia	Dogs: AC, FQ Doxycycline Metronidzole Cats: AC, Doxycycline	458 (69%)	3191 (96%)
Prostatitis	FQ, TMPS	-	290 (28%)
Pyoderma	Chlorhexidine	0 (0%)	2 (1%)
Pytometra	AC		
Rhinitis	AC	954 (30%)	1174 (59%)
Stomatitis	Metronidazole	4238 (42%)	2934 (60%)
Urolithiasis	AC	346 (32%)	1395 (70%)
UTI	AC, TMPS	4477 (47%)	18637 (71%)

Supplementary Files

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- FARRELLASGHPCIASUPP.pdf