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Antimicrobial prescription in canine and feline gastrointestinal clinical presentations: a mixed-methods approach using Electronic Health Records

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By

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Acknowledgments

To embark in a research project is a journey that above all help us to feel what resilience is about, daily. On a personal level, it is not an easy choice to make to leave our country, family and lifelong friendships away to embrace a new country, a new experience, a new setting. However, experiencing life outside of our comfort zone, both professionally and personally, allow us to experience growth in a different way. If I have reached the milestone of this thesis submission, I owe a huge thank you to everyone that has been crossing my path and has been supporting the achievement of my goals. This thesis is dedicated to each one of them.

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Abstract

Antimicrobial prescription in canine and feline gastrointestinal clinical cases: a mixed-methods approach using Electronic Health Records

Ivo S. Fins

Canine and feline gastrointestinal (GI) presentations are one of the most common clinical presentations for which antimicrobials are systemically prescribed. The use of such products may hasten antimicrobial resistance (AMR), which is a major worldwide health concern. Thus, currently we face the need to preserve antimicrobial efficacy, which requires identification of opportunities to safely reduce antimicrobial prescriptions. Although practice-level prescription guidance is widely available, a greater understanding of antimicrobial prescription at a population level is needed for the veterinary profession, especially for antimicrobials considered Highest Priority Critically Important Antimicrobials (HPCIA). To address this, we used a mixed-methods approach, harnessing veterinary health informatics data, in order to focus on two main objectives:

(i) Characterising canine and feline GI clinical presentations and reappraising the use of antimicrobials: using data from the Small Animal Veterinary Surveillance Network (SAVSNET), we collated 23,337 electronic health records (EHRs) from canine and feline GI consultations, from 225 volunteer veterinary practices between April 2014 and September 2018 in the UK. Most of the canine and feline GI presentations were reported as mild, with non-haemorrhagic diarrhoea and vomiting being the most frequent clinical signs. Systemic antimicrobial prescription occurred in 28.6% of canine GI consultations and 22.4% of GI feline presentations, with HPCIA prescription occurring more frequently in feline consultations. Bacteriological and/or parasitological diagnostic tests were uncommonly used. Results of multivariable modelling showed the presence of non- haemorrhagic diarrhoea (canine GI presentations OR 2.11, 95% CI 1.91-2.33, $p<0.001$; feline GI presentations OR 1.77, 95% CI 1.48-2.11, $p<0.001$) and haemorrhagic diarrhoea (canine GI presentations OR 4.22, 95% CI 3.80-4.68, $p<0.001$; feline GI presentations OR 3.05, 95% CI 2.44-3.82, $p<0.001$) were significantly associated with systemic antimicrobial prescription when compared with the absence of diarrhoea. In addition, moderate/severe GI presentations were also associated with significantly increased odds of receiving a systemic antimicrobial (canine GI presentations OR 1.85, 95% CI 1.65-2.07, $p<0.001$; feline GI presentations OR 2.03, 95% CI 1.68-2.46, $p<0.001$). Older dogs were more likely to receive an antimicrobial prescription.

(ii) Exploring justification and reasoning around antimicrobial use, particularly associated with HPCIA prescription: in a subset of the data, we used a complementary qualitative approach to identify the extent of discussion recorded in EHRs around reasoning for antimicrobial prescription (n=200 EHRs), and to further identify drivers, reasoning and attitudes within the clinical narrative of canine and feline GI consultations around HPCIA prescription (n=516 EHRs). Thematic analysis of clinical narrative content allowed the identification of nine recorded extrinsic factors underpinning reasoning for HPCIA prescription, related with perceived compliance; owner's behaviour; perceived risk of infection; clinical signs; recent clinical history; perceived (positive) previous response to antimicrobial therapy; geriatric patients and euthanasia; concomitant conditions; and diagnostic testing. Moreover, the perceived veterinarian-client relationship and a behavioural trend led by the veterinary professional in trialling antimicrobial therapy indirectly shaped the decision-making process around HPCIA prescription in GI cases.

By taking a complementary mixed-methods approach to EHRs, these studies have identified novel and valuable insights into antimicrobial choices made by veterinary professionals in GI presentations. The results of this work can help inform targeted interventions aimed at helping to preserve the most critical antimicrobials, contributing towards effective antimicrobial stewardship. Intensifying interdisciplinary efforts is crucial to ensure clinical compliance with currently published prescription guidance.

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Abbreviations used

AAGS Antimicrobial-associated Gastrointestinal Signs

ACTH adrenocorticotropic hormone

ACVIM American College of Veterinary Internal Medicine

AHDS Acute Haemorrhagic Diarrhoea Syndrome

AIC Akaike Information Criterion

AIEC adherent-invasive *E. coli*

AMR antimicrobial resistance

AMU antimicrobial use

APHA Animal and Plant Health Agency

ARD Antibiotic-responsive diarrhoea

AST Antimicrobial Susceptibility Testing

BIC Bayesian Information Criterion

BVA British Veterinary Association

CBC complete blood count

CDI *Clostridium difficile* infection

CLOs *Campylobacter*-like organisms

CPE *Clostridium perfringens* enterotoxin

CTA cytotoxicity assay

ECEIM European College of Equine Internal Medicine

EHRs Electronic Health Records

EIEC enteroinvasive *E. coli*

ELISA enzyme-linked immunosorbent assay

EMA European Medicines Agency

EPEC enteropathogenic *E. coli*

ESBL extended-spectrum β-lactamases

ETEC enterotoxigenic *E. coli*

FECAVA Federation of Companion Animal Veterinary Associations

FeLV feline leukaemia virus

FISH fluorescence *in situ* hybridization

FIV feline immunodeficiency virus

GC granulomatous colitis

GDV gastric dilatation and volvus

GI gastrointestinal

HPCIA Highest Priority Critically Important Antimicrobials

IBD inflammatory bowel disease

ID identification number

ISCAID International Society for Companion Animal Infectious Diseases

LRT likelihood ratio tests

MDR multidrug resistance

MIC minimum inhibition concentration

MODS multiple organ dysfunction syndrome

MPC main presenting complaint

NTEC necrotoxigenic *E. coli*

OM outer membrane

OR odds ratio

PAS periodic acid-Schiff

PBPs penicillin binding proteins

PCR polymerase chain reaction

PCV packed cell volume

SAVSNET Small Animal Veterinary Surveillance Network

SE standard error

SIBO Small Intestine Bacterial Overgrowth

SIRS systemic inflammatory response syndrome

TLI trypsin-like immunoreactivity

TLI trypsin-like immunoreactivity

TP total protein.

TS total solids

UK United Kingdom

VARS Veterinary Antibiotic Resistance and Sales Surveillance

VIF Variance Inflation Factor

VMD Veterinary Medicines Directorate

VRE vancomycin-resistant enterococci

WHO CIA World Health Organisation List of Critically Important Antimicrobials for Human Medicine

WHO World Health Organisation

95% CI 95 per cent confidence interval

Chapter One:

Introduction and literature review

1.1. Introduction

Antimicrobial resistance (AMR) is a multifactorial and complex global health problem involving different bacterial species, resistance mechanisms, and reservoirs. Bacterial selection pressure associated with antimicrobial use is one of the most important factors responsible for increased AMR.[1,2] Evidence of resistance development in response to antimicrobial therapy, and transmission of bacterial resistance between humans and companion animals make evident the need of an interdisciplinary approach to preserve antimicrobial efficacy, which involves identification of opportunities to safely reduce antimicrobial prescriptions.[3–7]

Antimicrobial agents are frequently prescribed in companion animals, and recent work using electronic health records (EHRs) has shown gastrointestinal (GI) clinical presentations are one of the most common clinical presentations for which they are systemically prescribed.[3,8,9] Indeed, it has been reported that systemic antimicrobials are prescribed in approximately 38% of dogs and 30% of cats presenting with GI clinical signs.[3] Specific practice level guidance, aiming to promote responsible antimicrobial prescription has been available to veterinary professionals.[10] However, there is a need to understand how these policies are being reflected in practice (chapter 2), and what key factors may influence antimicrobial prescription in GI clinical presentations (chapter 3).

When confronted with an animal showing GI clinical signs a practitioner must make their therapeutic decisions taking into account a wide range of factors including the generic principles of GI clinical presentations and the variety of treatments used in companion animals; the potential and sometimes conflicting role of enteropathogens, and the mechanisms of antimicrobial action and classification under the AMR framework. These headings will form the subject of this introduction. Finally, as new data sets are becoming available to shed new light on the use of antimicrobials in practice, this introduction will also move forward with a brief summary of current surveillance approaches to investigating antimicrobial prescription in the companion animal context, particularly using the Small Animal Veterinary Surveillance Network (SAVSNET) data, concluding with a summary of qualitative methods used to better understand veterinary antimicrobial prescribing behaviour. Together, this will provide the necessary introduction to the key research of this thesis namely, to use EHRs to quantitatively describe antimicrobial use in canine and feline GI presentations, and clinical narratives to qualitatively describe motivations for the use of critical antimicrobials in these cases.

1.2. Approach to the investigation of GI clinical cases and common presenting complaints in small animals

Disorders of the GI tract are one of the most common reasons for seeking veterinary assistance in small animal practice.[11,12] The majority of alimentary disorders in dogs are generally considered to be self-limiting and are most commonly associated with dietary indiscretion.[12] However, diagnosis of GI disease can be challenging as many of the clinical signs are (1) non-specific or vague and may not point directly to an alimentary tract problem, and (2) can be seen with more systemic disease[12,13] and with disorders that can be fatal if left untreated.[14] These factors create a diagnostic challenge for the practitioner faced with a new case of vomiting or diarrhoea. Therefore, it is very important when investigating a patient with suspected GI disease to start with the collection of a thorough history and then carry out a full physical examination. In this way, systemic diseases will not be missed, and vague or misleading presentations of digestive tract disease will not be misinterpreted.[12]

The majority of dogs and cats presented with GI signs will be diagnosed and treated by recognition of a set of clinical signs previously observed by the clinician in similar cases.[12] Patients can respond to a treatment implemented and make full recovery in the absence of any specific diagnostic testing. Good examples of this may be patients with parvovirus infection or GI parasitism. Nonetheless, a systematic logical approach based on identifying all the patient's problems, starting with a detailed exploration of the patient's history and a thorough clinical examination, allowing the establishment of a problem list from which the clinician can determine whether the patient's condition is life-threatening and in need of immediate therapy prior to further investigation. A solving-problem approach and establishing a problem list can help to to establish a diagnostic plan, and eventually to reach a diagnosis, particularly in cases where the patient fails to make a satisfactory recovery or presents a set of clinical signs which do not fit with a recognised pattern.[12,13]

The GI tract has a relatively limited capacity to respond to insults either through the induction of vomiting or as diarrhoea. Both can be acute or chronic in nature and range from mild to severe. Here we will review each in turn focusing on the mechanisms of disease, diagnostic options and common patterns of treatment and management.

1.2.1. Acute and chronic vomiting

1.2.1.1. Definition and pathophysiology

Vomiting or emesis is defined as a complex reflex act initiated by stimulation of the vomiting centre in the medulla.[13,15] Historically, the mechanisms of vomiting were first investigated in the 1950 by Borison and Wang, which hypothesised a two-component model of vomiting. This model involved the activation of a humoral or neural pathway.[16,17] Despite contemporary re-examination, these two general patterns of vomiting are still used nowadays.[18]

The evolution of vomiting probably began as a protective means for removing toxic or noxious ingested substances from the GI tract. This process has evolved further so that when many toxic substances are absorbed into the blood stream, they also induce vomiting.[13]

The vomiting centre may be directly stimulated or indirectly stimulated via the chemoreceptor trigger zone (CRTZ), which is located in the dorsal surface of the medulla oblongata, on the floor the brain's fourth ventricle.[19] Disease or irritation of the GI tract, abdominal organs or peritoneum can directly stimulate the vomiting centre, as can conditions involving the central nervous system (CNS).[15] Moreover, blood-borne substances, such as toxins or drugs, and neurological input from the vestibular nucleus, induce dopamine release in the CRTZ and indirect stimulation of the vomiting centre. After the vomiting centre is stimulated, a set of reflex actions are coordinated to cause an active expulsion of gastric contents from the mouth. The emesis reflex is structured into three components: nausea, retching, and expulsion of gastric contents.[15]

1.2.1.2. Clinical features

Vomiting is a common clinical sign in dogs and cats and holds great significance due to the wide range of medical conditions that may cause or be linked with it.[18,20] These possible causes for vomiting may make recognising the aetiology more challenging, therefore resulting in the need for an extensive diagnostic workup in some dogs and cats.[13]

A thorough signalment and history should be taken. Young unvaccinated dogs and cats are more susceptible to infectious disease, such as parvovirus.[21] Vaccination status, travel history, previous diagnosed medical conditions, medication history, and environment details should be determined.[13] During examination, the veterinary practitioner should differentiate the owner's report of emesis from gagging, coughing, dysphagia, or regurgitation.[13] A comprehensive physical examination helps to further localise the cause of vomiting and to ascertain whether the patient is systemically well or not.[15] The presence of pyrexia may suggest an inflammatory pathogenesis for the vomiting disorder.[13,18] Bradycardia or cardiac arrythmias in a vomiting animal may be a sign of a metabolic disturbance such as hypoadrenocorticism.[13] Respiratory rate and character, mucous membrane colour, capillary refill time and hydration should be evaluated to determine the nature of systemic findings, and the extent of any cardiovascular compromise.[15,18]

1.2.1.3. Diagnosis

Based on the history and physical examination, the dog or cat should be classified as systemically well or unwell, and the vomiting as acute or chronic.[13,15] Causes of acute and chronic vomiting include factors associated directly or indirectly with the GI tract, such as diet, emetogenic substances (acute vomiting), gastrointestinal tract obstruction (acute or chronic vomiting), pancreatitis, and gastrointestinal/abdominal inflammation (acute or chronic vomiting). In addition, non-GI tract causes or diseases causing acute or chronic vomiting

include adrenal insufficiency, hypercalcaemia uraemia, hepatic insufficiency, pyometra, endotoxemia/septicaemia, cholecystitis, and diabetic ketoacidosis.[8]

If vomiting is acute and recent, and the animal is systemically well then the vomiting episodes may be self-limiting.[15] Very often such cases are related to dietary indiscretions, and signs resolve quickly. Such conditions can initially be treated symptomatically with minimal diagnostic investigation. A routine faecal examination may be performed to eliminate the possibility of parasitism. Investigation for environmental intoxicants is also imperative.[13] If the animal is systemically unwell, or has haematemesis, haemorrhagic diarrhoea or localising signs, such as abdominal pain or jaundice, a more comprehensive investigation is necessary to define the nature of the problem.[15,18] The clinical combination of non-productive emesis and abdominal distention may suggest gastric dilation either alone or with volvulus (GDV) which are emergency situations requiring rapid diagnosis and surgical intervention.[15] The diagnostic approach to detect the causes of vomiting is represented in Figure 1.

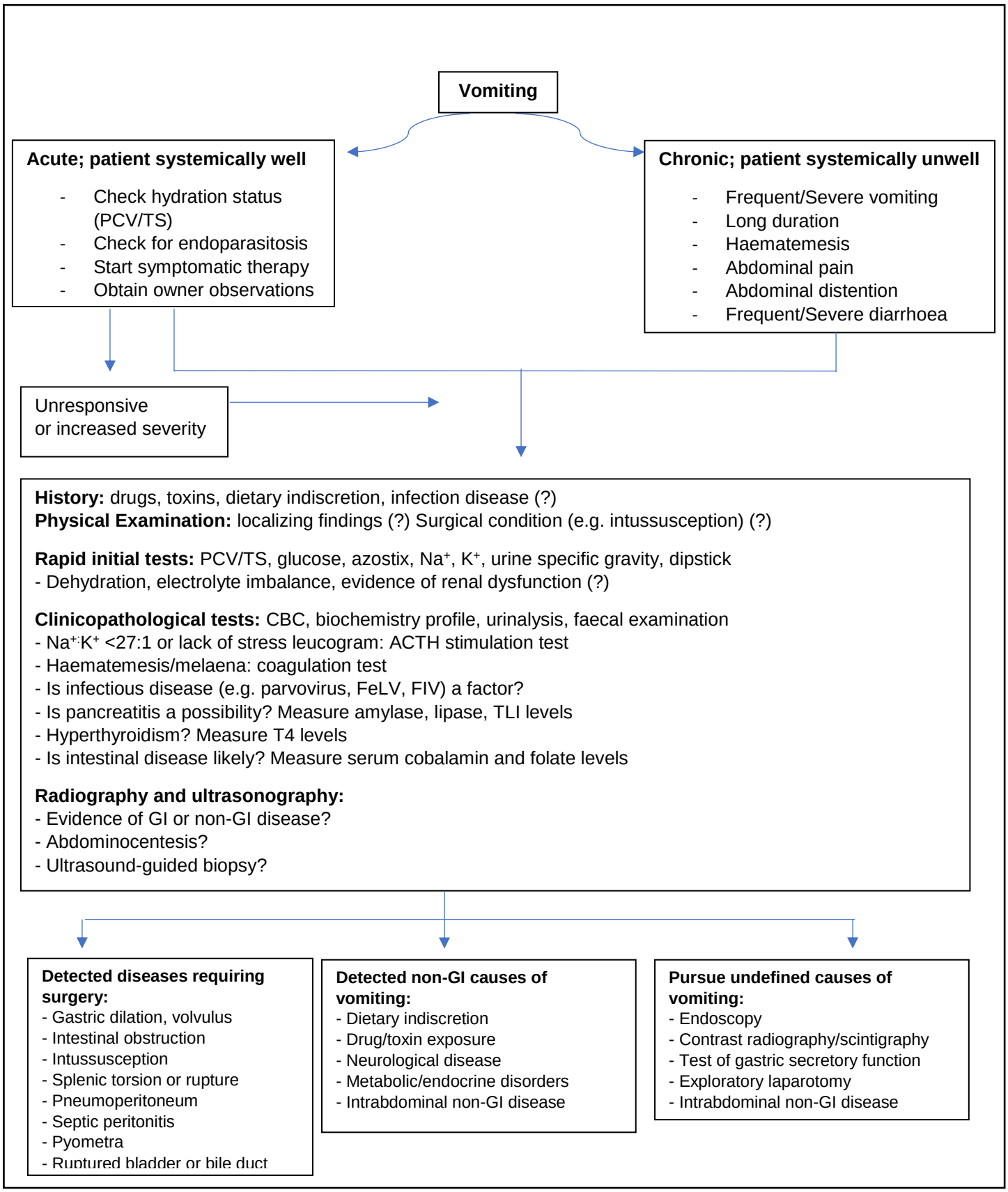

Figure 1. Diagnostic approach to vomiting. (Adapted from Hall E. et al. *BSAVA Manual of Feline and Canine Gastroenterology*. 2005[4])
Legend: ACTH = adrenocorticotropic hormone; CBC = complete blood count; FeLV = feline leukaemia virus; FIV = feline immunodeficiency virus; GDV = gastric dilatation and volvus; GI = gastrointestinal; PCV = packed cell volume; TLI = trypsin-like immunoreactivity; TS = total solids.

1.2.1.4. General treatment and management

A wide range of conditions can be associated with vomiting. Depending on the underlying cause, some clinical presentations are self-limiting not requiring much intervention, while others would need extensive and appropriate support, therapy and rehabilitation. It is important to attempt to identify and eliminate inciting agents. Objectives of the therapeutic support are to sustain blood and plasma volume; to restore blood pressure; to correct acid–base, electrolyte, and fluid deficits; and treat possible complications.[18]

Usually, fasting is indicated for short periods of time, to reduce both severity and frequency of the central emetic response.[18] Generally, where vomiting is acute, it is recommended that oral intake should be discontinued for at least 24 hours. Reintroduction of solid food should be slow for a period of over a week (*'little and often'*), and a bland diet, non-spicy and fat-restricted, is recommended. This can be homemade (e.g. boiled chicken and rice, given 1:3 ratio) or a commercial option, which are generally fat-restricted and rice-based. Gradual reintroduction of the regular diet of the patient should take place after the transition period of one week and once clinical signs have resolved.[15,20] Importantly, fasting in cats should be reserved for severe vomiting cases and risk of aspiration pneumonia, considering that felines are obligate carnivores and can therefore develop mobilisation and hepatic lipidosis in short periods of fasting.[18] In chronic vomiting cases, to facilitate nutrition in anorectic animals, oesophagostomy, gastrostomy, and rarely enterostomy tubes might be used.[13,18]

In respect to fluid therapy, oral fluids can be useful when given in small amounts and frequently, gradually increasing the volume of the fluid as emetic episodes become less frequent. In addition, isotonic balanced electrolyte solution given subcutaneously can be sufficient to correct mild fluid deficits of less than five percent; however in moderate/severe dehydration, intravenous fluid therapy is recommended.[15] In severe vomiting presentations, there is usually the need to correct fluid, electrolyte, and acid–base disturbances, therefore the objectives of the fluid therapy in such cases are to restore volume and composition of body fluids to normal.[15,18]

Antiemetic therapy should be framed based on the most probable underlying pathogenesis, *i.e.* neural or humoral pathway. The NK_1 neurokinin antagonists, such as maropitant (licensed for dogs and cats[22]), α_2 adrenergic antagonists, such as prochlorperazine (currently not licenced for veterinary use[22]), 5-HT_3 serotonergic antagonists, such as ondansetron (currently not licensed for veterinary use[22]), and D_2 dopaminergic antagonists, such as metoclopramide (licensed for dogs and cats[22]) are described to be effective choices as antiemetic agents in small animals, although D_2 dopaminergic antagonists are described to be less efficacious in the cat.[18]

Sucralfate (currently not licensed for veterinary use[22]) can be used in acute vomiting (or diarrhoea) to coat the GI mucosa and to bind bacteria and their toxins. Acid-reducing drugs, such as H2 receptor antagonists, can be useful in animals with signs of gastric

erosion/ulceration (*i.e.* melaena and haematemesis).[15] Additionally, prokinetic agents can be useful in animals that have not responded to dietary and antiemetic therapy. Simultaneous therapy with the use of both a prokinetic and antiemetic can be useful in refractory vomiting patients. Indicated prokinetic agents (5-HT_4 serotonergic agonists) are cisapride, tegaserod, and mosapride (currently not licensed for veterinary use[22]).[18]

Erythromycin (licensed for veterinary use in chickens[22]), a macrolide antimicrobial that is recommended to be reserved for human use by World Health Organisation (WHO)[23], has been described in animals with delayed gastric emptying as it presents prokinetic activity at low doses. However, erythromycin can also cause vomiting because of its prokinetic effects.[20] In addition, antimicrobial use is generally unwarranted in vomiting patients. Moreover, AMR against macrolides and lincosamides has been reported among enterococci isolated from rectal swabs of cats and dogs, suggesting that intestinal microbiota enterococci can be a reservoir of resistance genes for pathogens of public health importance.[24]

1.2.2. Acute and chronic diarrhoea

1.2.2.1. Definition and Pathophysiology

Diarrhoea is defined as augmented faecal fluidity, generally accompanied by more volume and frequency of defecation.[25,26] Diarrhoea can be categorised according to different features, such as its duration (*i.e.* acute versus chronic), pathophysiologic mechanism and origin.[27] Generally, acute presentations of diarrhoea are considered as those of less than 14 days duration; chronic diarrhoeic presentations are those lasting for more than 14 days.

The most common presentation in small animals is acute self-limiting diarrhoea, which frequently does not require extensive diagnostic testing or therapy.[25] Conversely, in chronic diarrhoeic presentations, pets usually have an insufficient clinical response to empirical/support therapies, therefore needing a thorough diagnostic approach and an effective and tailored therapeutic approach. [27]

Secondary clinical signs to diarrhoea, which is the primordial sign of intestinal malfunction, include abdominal distention, abdominal pain, borborygmus, dehydration, halitosis, melena, haematochezia, polydipsia, tenesmus, vomiting, and weight loss.[27] Appetite may vary between polyphagia to anorexia, and sometimes is described to be associated with disease progression, such as in cases of inflammatory bowel disease, intestinal lymphangiectasia, and lymphoma. Other clinical signs such as vomiting can also be present, and nutrient malabsorption is frequently associated with weight loss.[27,28]

The four major pathophysiologic mechanisms that can result in diarrhoea are osmosis, hypersecretion, increased mucosal permeability, and abnormal intestinal motility. In most diarrhoeal diseases of dogs and cats, multiple mechanisms can contribute to diarrhoea.[25] Osmotic diarrhoea is caused by abnormal large quantities of poorly absorbable osmotically active solutes in the intestinal lumen. It is often associated with malabsorptive disorders, such as in cases of exocrine pancreatic insufficiency. Consequent nutrient retention may lead to

changes in intestinal microflora and fermentation of carbohydrate.[27] Other causes of osmotic diarrhoea include sudden dietary modification. [25] Hypersecretion results from an excessive stimulation of crypt enterocytes, which surpass the intestinal absorptive capability. Frequent causes for hypersecretion involve infectious causes, such as salmonellosis.[25] When increased mucosal permeability occurs, fluids, electrolytes, proteins, and red blood cells are lost into the intestinal lumen. Examples of causes of increased mucosal permeability include inflammatory bowel disease (IBD) and neoplastic disorders.[27] Abnormal motility is often a secondary problem in disorders that cause diarrhoea. Decreased segmental contractions result in transport of ingesta at a rate too rapid for efficient digestion and absorption. Additionally, metabolic products produced during bacterial overgrowth can also cause abnormal motility. Abnormal motility occurs in cases with inflammatory diseases, feline hyperthyroidism and following abdominal surgery.[25,28]

1.2.2.2. Clinical features

The animal's clinical details and history, including predisposing factors such as parasitism, infectious agents and drugs, assume particular importance when attempting to reach a diagnosis.[29] Signalment data and knowledge of breed predispositions for GI disease is relevant to establish a list of differential diagnoses.[27,28] Indeed, a surveillance study of diarrhoea in small animal practices has reported that adult dogs had a higher proportional morbidity of diarrhoea than adult cats.[11] However, in both dogs and cats, the proportional morbidity of diarrhoea was significantly higher in animals less than one year of age.[11] The history may detect dietary indiscretion, which can encompass a sudden diet change, ingestion of a low-quality diet, table scraps and treats, or free-roaming behaviour with the potential for waste consumption.[25] The risk factors associated with diarrhoea presentations in canine patients, previously explored by a case control study, include being part of a multi-dog household, receiving a home-prepared or raw meat-based diet, having had a stay at a boarding kennel, shelter or veterinary practice, and having had a recent change in diet.[30]

Acute diarrhoea often originates from small intestinal disease or from mixed small and large bowel disease. On occasion, signs of large bowel disease only can be present. Abdominal palpation may detect gas and/or fluid distended bowel segments and abdominal pain (bowel inflammation, ischaemia). In some cases, a dilated loop of bowel or an abdominal mass may be detected, suggesting the possibility of a foreign body or intussusception.[25,28]

Digital palpation of the rectum is useful for the detection of rectal masses, retroperitoneal obstruction, and the collection of faecal samples for bacterial culture, microscopic examination, ELISAs and/or PCRs for parasites and protozoans screening.[28] Assessing for the presence of dehydration is vital, with clinical signs including dry mucous membranes, diminished skin turgor, prolonged capillary refill time, enophthalmos and cold extremities. Other clinical signs may be related to a systemic cause of diarrhoea and include pyrexia, icterus, ascites, lymphadenopathy, oliguria/anuria, hepatomegaly, ocular and nasal discharge, and coughing, such as in cases of canine distemper.[27,28]

Diarrhoea can also be classified according to the most likely primary anatomical origin as "small bowel" or "large bowel". However, this approach can have some limitations, considering that several diarrhoea presentations with primary manifestations of one specific anatomical compartment can have diffuse GI involvement, and therefore mixed clinical signs.[27]

1.2.2.3. Diagnosis

In order to evaluate animals suffering from acute diarrhoea, the imperative initial step is that of classifying them as either having a self-limiting or potentially life-threatening problem. Such a distinction is essential in guiding the levels of diagnostic testing and therapy required, and should be based upon a thorough history and a careful physical examination.[25] Animals should be considered to have a potentially life-threatening problem if some of the following are present: frequent vomiting; abdominal pain; depression; moderate to severe dehydration; melaena or haematochezia; palpable abdominal mass or dilated loop of bowel; or signs of systemic diseases.[25] The diagnostic approach to acute diarrhoea is summarised in Figure 2.

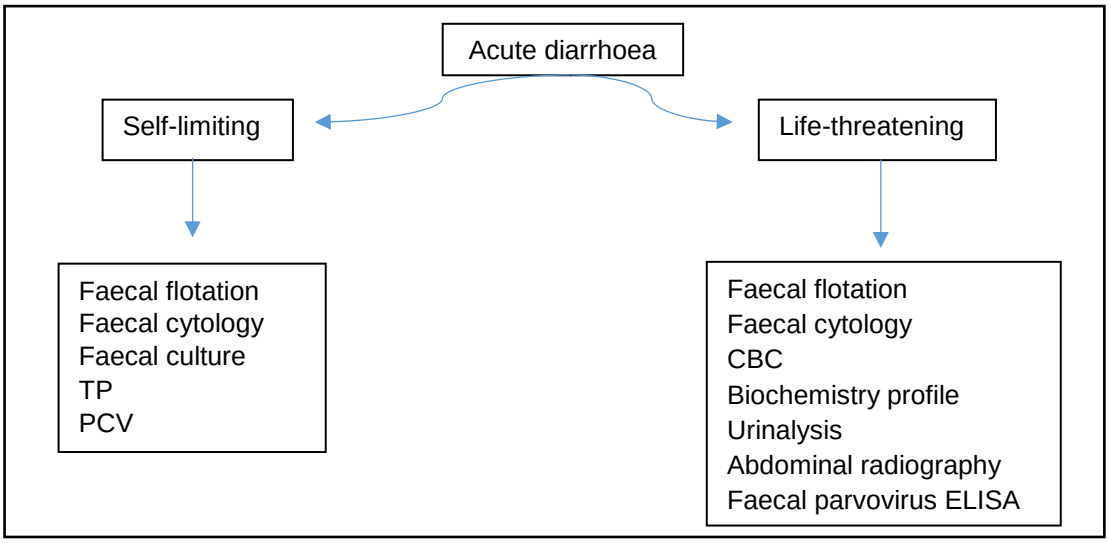

Figure 2. Diagnostic approach to acute diarrhoea. (Leib MS. Acute diarrhoea. Adapted from: Hall EJ, Simpson JW, Williams DA, eds. *BSAVA Manual of Canine and Feline Gastroenterology*. 2nd ed. 2005.[9])

Legend: CBC = complete blood count; ELISA = enzyme-linked immunosorbent assay; PCV = packed cell volume; TP = total protein.

Strategies with which to determine the underlying cause of chronic diarrhoea begin with a clinical examination and with baseline laboratory tests, which should be conducted in order to determine whether primary GI or metabolic/systemic disorders are causing the diarrhoea. Baseline laboratory tests frequently include a complete blood count (CBC), the biochemistry profile, urinalysis, and faecal examinations for parasites and infectious agents.[27,28] Moreover, measurements of serum cobalamin (Vitamin B_{12}) and folate (Vitamin B_9, folate) can help localise the GI tract compartment affected, and cobalamin can be supplemented if required. Low serum cobalamin concentration often indicates severe and established GI disease

involving the distal small intestine. Low serum concentration of cobalamin can also indicate exocrine pancreatic insufficiency in small animals. Whereas cobalamin can be considered as a marker for distal small intestinal disease, folate is a marker of proximal intestinal disease.[31] Further diagnostic tests include diagnostic imaging, specialised GI function tests, e.g. a species-specific assay of trypsin-like immunoreactivity (TLI) destined for the assessment of exocrine pancreatic function, and/or an endoscopic examination with mucosal biopsy.[28]

Differential diagnoses include dietary causes (e.g., sudden dietary change); inflammatory causes such as IBD; infectious causes (parasitic, bacterial, viral, fungal, or rickettsial); extra-GI tract and/or endocrinal causes such as pancreatitis, exocrine pancreatic insufficiency, liver and kidney disease, hypoadrenocorticism, hyperthyroidism; neoplastic causes; and drug- and toxin- related causes, such as the use of antimicrobials *per se*.[27] Indeed, it has been shown that antimicrobial use modifies the faecal microbiome and metabolome, eventually leading to dysbiosis, such that antimicrobial-associated gastrointestinal signs (AAGS) are frequent when clindamycin is used in cats.[32] In dogs, clavulanic potentiated amoxicillin, enrofloxacin, and metronidazole use was also associated with AAGS.[33]

1.2.2.4. General treatment and management principles of acute and chronic diarrhoea

Frequently, symptomatic, empirical therapy for dogs and cats with acute, self-limiting diarrhoea is used, as the causes of many of these diarrheal disorders are often undetermined.[27] The primary objectives of symptomatic therapy are the restoration and maintenance of fluid and electrolyte balance, and dietary modification. Broad-spectrum anti-helminthic drugs may be used.[25] Intravenous fluid therapy may be required in cases of acute diarrhoea associated with severe dehydration. Increasing evidence has highlighted the benefits of early enteral nutritional support in promoting intestinal integrity and weight gain and improving patient outcomes.[27,34]

Dietary options comprising a moderately fat-restricted, highly digestible, low-residue intestinal formula, or an elimination diet comprising a novel, select protein source are typically used for animals suffering from acute diarrhoea.[27] Fat delays gastric emptying and fat-restricted diets seem to be beneficial in different GI diseases. The assimilation of dietary fat has a fairly complex mechanism, bacterial populations in the intestinal microbiome can hydroxylate malabsorbed fatty acids, whereby stimulating colonic water secretion and exacerbating fluid loss and therefore exacerbating diarrhoea.[35] Moreover, fat malassimilation can be associated with the malabsorption of bile acids, resulting in the deconjugation of unabsorbed bile acids and in increased mucosal permeability and secretion, which can also contribute to maintenance of diarrhoea.[27,36]

According to the recently updated *'PROTECT ME'* guidelines, cats and dogs presenting with acute GI signs, including dogs with haemorrhagic diarrhoea that are systemically well, do not require antimicrobial therapy.[10] Bacterial translocation in veterinary patients has been

recognised, however the exact mechanisms associated with systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), and therefore in critical illness, need to be further investigated.[37] It is accepted that in parvoviral infections, the extensive enteritis, which damages the intestinal tract and it is secondary to the viral infection, increases the risk of bacterial translocation and consequent coliform septicaemia, which could lead to the development of a systemic inflammatory response that can progress to septic shock and, ultimately, death.[38] Therefore, antimicrobial therapy is relevant and warranted, in order to prevent progression of parvovirus enteritis to septic shock.

However, in canine acute haemorrhagic diarrhoea, recent studies have shown no difference in the incidence of bacterial translocation, and no improvement in disease severity indices, laboratory parameters, length of hospitalisation, or mortality rates, between patients receiving amoxicillin-clavulanic acid versus placebo.[37] Antimicrobial administration has also been shown to induce translocation from native commensal bacteria and promote an inflammatory response.[37,39] Furthermore, a randomised controlled trial strongly suggested that metronidazole is not essential in the treatment of severe cases of haemorrhagic diarrhoea in dogs, [40] thereby questioning the need for antimicrobial therapy in such cases. In addition, as mentioned before, antimicrobial use can also cause dysbiosis, potentially leading to AAGS. Indeed, a significant alteration of the commensal flora was demonstrated in a study of healthy cats administered oral metronidazole, with reductions in duodenal anaerobic and aerobic bacterial counts, as well as the emergence of *Corynebacterium* and *Streptococcus* species, highlighting the impact that orally administered antimicrobials may have upon normal protective intestinal flora and upon bacterial selective pressure, potentially contributing to antimicrobial resistance.[41]

Gastrointestinal nutraceuticals, which are defined as products not listed as either authorised veterinary or human medicinal products, comprising a range of probiotics, such as kaolin formulations, have been considered a growing therapeutic choice whose purpose is to assist the resolution of diarrhoea.[42] Besides immunomodulatory effects, probiotics in humans are believed to have a protective effect upon the normal microflora of the gut by means of their antimicrobial activities directed towards intestinal pathogens.[27,43]

Although further evidence is needed for the use of probiotics in promoting the health of the GI tract, disease prevention and/or symbiotic effects in healthy small animals, it has been highlighted that probiotics are likely to have benefits in cases of parvoviral infection and acute haemorrhagic diarrhoea syndrome (AHDS).[44] Moreover, a recent longitudinal study in dogs indicated that a combination of dietary modification and gastroenteric nutraceuticals without the prescription of pharmaceutical agents, e.g. antimicrobials and anti-inflammatories, could aid the resolution of diarrhoeic clinical signs.[42]

In a recent randomised, placebo-controlled, double-blinded clinical trial evaluating the efficacy of a probiotic in dogs presenting with acute and uncomplicated diarrhoea, it was found that probiotic was significantly associated with a faster rate of diarrhoea resolution, when compared

to the placebo group.[45] Similarly, in a recent prospective, placebo-controlled, blinded study aiming to evaluate the effectiveness of probiotics in AHDS presentations associated with *Clostridium perfringens*, the probiotic treatment used was linked to a significantly faster clinical recovery, and faster normalisation of the intestinal microbiome.[46] However, a recent systematic review has shown the current evidence available demonstrates a limited clinical benefit associated with the prevention or treatment of acute GI presentations. It has additionally highlighted that in chronic enteropathies, dietary modification assumes an essential role, whilst probiotics are still not considered a significant aid in the therapeutic management of these cases.[47] Further larger, multicentre studies have been advised in companion animals so as to better understand the complex interaction between probiotics and their host environment, their mechanism of action, and which variations to the intestinal microbiome are necessary in order to accomplish the clinical remission of both chronic and acute GI presentations.[47,48]

The underlying diagnosis is vital to establish dietary management in cases of chronic diarrhoea.[27] In IBD, elimination and hydrolysed protein diets are usually beneficial in both cats and dogs. Elimination diets contain single, novel protein sources, while hypoallergenic diets include hydrolysed protein sources that have been enzymatically broken down into polypeptides.[27] Though less palatable and usually more expensive, hydrolysed diets can also be a dietary option, especially when the patient suffers from severe IBD, or has a complex history of allergy to multiple allergens and are not hypersensitive to their individual components.[49,50]

Recently updated guidelines regarding antimicrobial use in small animals advocate that diet manipulation (hydrolysed or novel protein source diets) can alleviate signs in 60–80% of food-responsive patients with chronic enteropathy.[10] As further expanded in the next section, antibiotic-responsive diarrhoea has been recognised as a syndrome in young large-breed dogs, especially in German Shepherds, having a diagnosis of exclusion, which may warrant empirical antimicrobial therapy.[51] An antimicrobial therapeutic trial might also be considered in other breeds with chronic enteropathy, though some veterinary clinicians now advocate prior trial treatment with immunosuppressants, thus avoiding empirical antimicrobial use.[10]

Small animals suffering from severe IBD and exocrine pancreatic insufficiency present subnormal serum cobalamin concentrations. Cyanocobalamin can be supplemented orally or subcutaneously.[52] Cyanocobalamin concentrations should be rechecked every 6–8 weeks, especially in feline patients, considering the shorter half-life of the vitamin in cats.[27] Adjuvant immunotherapy combined with dietary management will often benefit the majority of cats and dogs suffering from moderate to severe IBD (canine IBD disease activity index >6–8). The therapy for IBD must be tailored to the response of each individual.[27] In addition, corticosteroids are still considered the keystone of therapeutics for IBD, in spite of the lack of published controlled clinical trials documenting their benefits in small animals. The value of corticosteroids are associated with their immunosuppressive and anti-inflammatory effects.[27]

Other drugs utilised as adjunctive therapy in refractory or severe IBD cases include the antimetabolite azathioprine (currently not licensed for veterinary use[22]), which inhibits cellular proliferation and reduces natural killer cell cytotoxicity, and the alkylating agent chlorambucil.[53,54] Ciclosporine (Ciclosporine A form licensed for dogs and cats[22]) has also been described as beneficial to those canine patients presenting with IBD that is refractory to prednisone immunotherapy.[55]

Sulfasalazine (currently not licensed for veterinary use[22]) is a prodrug utilised in the management of colitis.[27,29] The aforementioned drug inhibits the degradation and formation of inflammatory mediators, including prostaglandins, thromboxane, leukotrienes, platelet activating factor, histamine, and some cytokines. Nonetheless, sulfasalazine has no value in managing cases of small intestinal IBD, considering that colonic bacterial metabolism is required in order to release the active moiety. In addition, sulfasalazine is contraindicated in cats. [27,29,56]

In situations (or cases) when the aetiology of the diarrhoea is not discovered and the other causes of diarrhoea have been excluded, including infectious agents, and when suitable conservative therapy, i.e. change in diet, corticosteroids and deworming has failed, then motility modifiers can be used as a last resort treatment.[27] Opiate and opioid narcotic analgesics such as loperamide (currently not licensed for veterinary use[22]) are effective motility modifiers in managing diarrhoea. Anticholinergic agents are contraindicated, as they might cause the generalised suppression of all motility and potentiate ileus.[29]

Faecal microbiota transplantation has been used in human treatments, particularly in *C. difficile* infections.[57] In dogs, faecal microbiota transplantation can be considered in different clinical circumstances. It has been advised that after the diarrhoea aetiology is identified, cases of parasitic infections, dietary-associated diarrhoea, atypical hypoadrenocorticism and antibiotic-associated diarrhoea can be considered for faecal microbiota transplantation.[57] In addition, in parvoviral infections, faecal microbiota transplantation has been significantly associated with a more rapid resolution of diarrhoea and a shorter hospitalisation length.[58]

In dogs with AHDS, faecal microbiota transplantation showed a decrease in dysbiosis index when compared to oral metronidazole treatment, whereas oral metronidazole treatment was significantly associated with an increase of dysbiosis index at day seven and day twenty-eight, comparing to faecal microbiota transplantation. Moreover, dogs treated with faecal microbiota transplantation clustered with the healthy-dogs control group, which was not the case for dogs treated with metronidazole.[59] These findings have highlighted the negative impact on faecal flora that metronidazole has in AHDS cases, and warrant further studies to explore the utility of faecal microbiota transplantation in dogs presenting AHDS.

In chronic enteropathies such as IBD, there are clinical reports highlighting that faecal microbiota transplantation can help to normalise faecal microbiome and can help to reduce clinical signs associated with IBD.[60] In addition, a recent study has demonstrated that clinical

activity index of dogs suffering from chronic enteropathy improved in many of the participating dogs.[61] Nonetheless, the evidence around the benefits of faecal microbiota transplantation in chronic conditions remain unclear, considering that confounding effects such as distinct clinical presentations and other therapies provided to canine patients with chronic conditions make it difficult to assess the cause of any apparent improvement.[57]

1.2.3. Antibiotic-responsive diarrhoea

Antibiotic-responsive diarrhoea (ARD) has been described as a syndrome recognised in dogs, particularly in young large-breed dogs, particularly German shepherds.[51] Dogs present with GI signs without known cause, albeit these signs can be managed with antimicrobial therapy.[62,63] Historically, ARD was designated small intestine bacterial overgrowth (SIBO); nonetheless discussions around whether a genuine increase in bacterial numbers was found in dogs, in contrast with cases of SIBO in humans, have resulted in the alternative designation of ARD.[51]

Different theories have been presented to explain the cause of ARD throughout the years, with current hypotheses tending to focus on host-bacterial interactions. It has been suggested that ARD possibly develops as a secondary response to defects in the mucosal barrier, atypical local immune responses and qualitative modifications in the enteric bacterial flora, or a combination of these aspects.[51]

Definitive diagnosis of ARD is difficult to achieve, thus presumptive diagnosis of idiopathic ARD is often achieved by excluding other conditions and showing a positive response to antimicrobial therapy. Other conditions to be ruled out include exocrine pancreatic insufficiency, which can also affect German shepherds, presenting similar clinical signs. Exocrine pancreatic insufficiency can be excluded if the results of a serum trypsin-like immunoreactivity assay are normal.[51] In addition, biochemical tests, such as folate, cobalamin, and bacterial culture methods have limited diagnostic value in identifying cases of ARD.[51,62] Therefore, four recommended criteria have been described to reach a diagnosis of idiopathic ARD, namely: a positive response to trial antimicrobial therapy, associated with resolution of relevant clinical signs; immediate or delayed reversion of signs on withdrawal of treatment; remission of clinical signs after reintroducing antimicrobial therapy, after relapse; and elimination of other possible aetiologies, considering the results of diagnostic tests including histopathologic exams.[51]

Antimicrobial therapy for management of idiopathic ADR is advised, using a broad-spectrum antimicrobial. Indicated choices include oxytetracycline, metronidazole (both licensed for dogs and cats[22]), and tylosin (currently not licensed for dogs and cats[22]), with an initial course of 4 to 6 weeks duration, regardless of the elected antimicrobial. In the case of a suboptimal response, changing the chosen antimicrobial after two weeks has been recommended.[51,64] Debate around the use of oxytetracycline has been described, considering that oxytetracycline

is associated with plasmid-mediated AMR.[65] In view of AMR concerns, it has also been advised to revaluate periodically the implemented therapy, with stopping periods to assess whether antimicrobial therapy is still required. Moreover, dietary options with highly digestible low-fat feeding might be beneficial, especially in mild cases of idiopathic ARD, where diet itself can help to manage ADR.[51]

1.3. Enteropathogenic bacteria in small animals

When a veterinary practitioner uses antimicrobial therapy, they are responding to a belief, either consciously or subconsciously, that bacteria may be playing a role in the disease. This could be as primary pathogens, or legitimately addressing a case of ARD, as previously described. The bacteria most commonly implicated cases of diarrhoea in small animals include *Clostridium perfringens*, *Clostridium difficile*, *Campylobacter* spp., *Escherichia coli* and *Salmonella* spp.[66] Although faecal cultures are commonly requested in humans presenting diarrhoea, their helpfulness has been questioned as the diagnostic return of such cultures is considered to be quite low. [67,68] In the small animal veterinary setting, a study evaluating faecal bacteriology in 260 dogs with diarrhoea only yielded 28 (10.8%) results considered to be of likely clinical significance.[69] Nonetheless, these findings can also include false positives, as causality was not described.[70] Contemporary developments in real-time polymerase chain reaction (PCR) assays for small animals presenting with diarrhoea have been useful to provide a rapid and sensitive finding of toxin genes or organisms associated with disease.[70] Nevertheless, the clinical significance of enteropathogenic bacteria in dogs and cats as a cause of diarrhoea remains under debate.[66–69] Thus, the problem of determining aetiologies, in cases of GI clinical presentations associated with bacteria, is amplified by the challenges of defining what exactly constitutes a pathogen.[70]

Importantly, raw meat-based diets (RMBDs) are an increasing diet choice for both cats and dogs, with a recent study reporting that feeding non-commercial/unconventional foods, such as RMBDs, have become more prevalent nowadays in comparison to reports from the previous ten years.[71] Benefits of RMBDs remains under debate, with different worldwide veterinary and health organisations, such as the World Small Animal Veterinary Association and the US Centre for Disease Control and Prevention advising against the use of RMBDs.[72] Potential risks of feeding RMBDs include the risk of increased spreading of multidrug resistance (MDR) bacteria, as it has been reported that RMBDs often fall below hygiene standards for microorganism counts of Enterobacteriaceae, which can carry resistance genes to HPCIA, such as third-generation cephalosporins.[73] Different zoonotic pathogens were identified in commercially available RMBDs, including extended-spectrum β-lactamases (ESBL) *Escherichia coli*, *Listeria monocytogenes* and *Salmonella* spp.[74] These findings have been raising the discussion about the risk of RMBDs representing a source of bacterial infections in both dogs and cats, and potentially shedding and transmitting zoonotic and/or MDR bacteria to people.[73] This can be potentially dangerous for human health, particularly of

susceptible individuals such as young children, the elderly, and adults with compromised immune system.[72]

The exact role of enteropathogenic bacteria as causal agents of diarrhoea in companion animals remains unclear, and these agents have been associated with self-limiting diarrhoea. Therefore, with few exceptions, there is no clinical evidence supporting the wide use of antimicrobials as a beneficial management choice.[70] Several different initiatives have been trying to provide means to encourage responsible antimicrobial use, such as widely disseminated veterinary practice-level guidance.[10] However, it has been reported that systemic antimicrobials are prescribed in approximately 38% of dogs and 30% of cats presenting with GI clinical signs, suggesting a lack of compliance with current clinical evidence and guidelines in many cases.[3] Here, we will summarise the epidemiology, diagnostic features, and management options for the bacterial agents commonly incriminated in diarrhoeic cases in companion animals.

1.3.1. *Clostridium difficile:* epidemiology, diagnosis, and management

Clostridium difficile is a Gram-positive, spore-forming anaerobic bacillus, and it is a relevant pathogen especially in people.[70] The growing forms of *C. difficile,* named vegetative cells, are associated with intestinal disease. Spores of *C. difficile* are highly resistant in the environment and associated with transmission. The pathophysiology of *C. difficile* infection (CDI) is not yet fully understood, however it involves the development of toxin-producing strains of this pathogen in the intestinal tract, subsequently causing disease.[70] In humans, *C. difficile* has been associated with hospital-related infections and community-related disease.[75,76] In humans, treatment of CDI is only advised when clinical signs are present. Metronidazole has been described as first-line choice in mild presentations of CDI, with superior drugs such as vancomycin and fidaxomicin being reserved for severe CDI cases.[77]

In pets, the role of *C. difficile* remains under debate, with different studies identifying an association between *C. difficile* toxins in faecal samples and disease[69,78,79]; however causation of canine AHDS is yet to be established. Moreover, a recent study indicates that the key toxins of *C. difficile,* TcdA and TcdB, are not associated with AHDS, nor with clinical parameters, and therefore are not advised to be used to predict disease outcome.[80] In cats, CDI is rarely reported, with only one known report of suspected CDI in two cats from the same household.[81] Therefore, it is still unclear if *C. difficile* can cause concomitant disease in association with other pathogens, or if it is an incidental finding in pets.[70]

Risk factors for *C. difficile* colonisation include dogs living with an immunocompromised owner[82], antimicrobial administration to dogs[83], antimicrobial administration to the owner[84], contact with children[84], and visiting human hospitals[84]. However, *C. difficile* colonisation does not imply necessary disease development. In suspected cases of CDI in dogs and cats, presumptive diagnosis of *C. difficile* is made by combination of toxin detection by ELISA and simultaneous organism detection by culture, antigen ELISA, or PCR.[70]

Management strategies of CDI in small animals should generally be based on supportive therapy, similarly to other GI presentations. While metronidazole has been frequently used, there is still a lack of evidence for its relevance in treating CDI in small animals. Furthermore, metronidazole has been associated with modifications of duodenal commensal flora in healthy cats, thus actual benefits of metronidazole use remain unclear.[70] Although in severe CDI cases in humans, the use of highest priority critically important antimicrobial (HPCIA)[23] drugs, such as vancomycin and fidaxomin, are described[77], concerns about AMR bacteria together with lack of evidence of its actual need in small animals are reasons for not recommending their use.[41,70] Probiotic use in human CDI cases have been reported, however with inconsistent results.[85,86] Faecal transplantation has been reported useful in humans, when recurrent CDI is common.[87] Nonetheless, in small animals, recurrence of CDI is not described as a major concern. Due to *C. difficile* significance for human health, zoonotic potential of *C. difficile* should be considered.[70,82,88]

1.3.2. *Clostridium perfringens*: epidemiology, diagnosis, and management

Clostridium perfringens is a Gram-positive spore-forming anaerobic bacillus, and it is a widespread pathogen for both humans and animals. *Clostridium perfringens* is classified into biotypes, from A to E, according the presence of one or more of four major toxin genes: alpha, beta, iota, and epsilon.[70] The enterotoxigenic *C. perfringens* type A has been linked with human food poisoning and diarrhoea, canine acute and chronic large and small bowel diarrhoea, and AHDS.[69,79,89,90] Moreover, different studies have reported a link between the immunodetection of C. perfringens enterotoxin in faecal samples and canine diarrhoea. Nonetheless, the role of *C. perfringens* in diarrhoea in dogs and cats is still under debate, as it has also been found in non-diarrhoeic dogs, integrating with the indigenous canine intestinal microflora.[78,79] *C. perfringens* enterotoxin (CPE) is believed to play a role in diarrhoea in dogs, considering that fluid accumulation and diarrhoea can be induced when administered orally or directly into the intestinal lumen; however the importance of CPE in the development of clinical diarrhoea remains unclear.[70,91] Whilst one study has previously indicated a link between the detection of CPE in dogs and AHDS, a more recent publication has suggested that CPE does not play a significant role in canine AHDS. In the latter study, CPE was not found to be associated with clinical parameters in affected dogs, and thereby it was advocated not to use CPE to predict disease outcome.[69,80] In addition, the role of *C. perfringens* in cats is similarly uncertain, thus the incidence of diarrhoea caused by *C. perfringens* in small animal populations is still not well-known.[70]

Regarding diagnosis of suspected *C. perfringens* involvement in diarrhoea cases, a gold standard test is not described. Therefore, the diagnostic approach for diarrhoea associated with *C. perfringens* should be based on ELISA to detect CPE in combination with PCR aiming to detect enterotoxigenic strains.[70,79]

Management of *C. perfringens* infection in small animals with antimicrobial therapy in mild cases is not recommended, although different antimicrobials have been advised in the past for the treatment of diarrhoea associated with *C. perfringens* in dogs, including ampicillin, erythromycin, metronidazole, tylosin, and tetracyclines.[70,92] Considering documented *in vitro* resistance to tetracyclines[93] and best antimicrobial usage practices, HPCIAs in particular should be avoided.

1.3.3. *Salmonella* spp.: epidemiology, diagnosis, and management

The salmonellae belong to Enterobacteriaceae family and are Gram-negative motile non-spore-forming facultative anaerobic bacilli.[70] There are two species in the genus *Salmonella*, namely: *Salmonella enterica* and *Salmonella bongori*. *S. enterica* is divided into six subspecies: *S. enterica ssp. enterica*, *S. enterica ssp. salamae*, *S. enterica ssp. arizonae*, *S. enterica ssp. diarizonae*, *S. enterica ssp. houtenae*, and *S. enterica ssp. indica*.[94] In addition, *S. enterica ssp. enterica* has a wide range of serovars, including *Salmonella enterica ssp. Typhimurium, and Salmonella enterica ssp. enterica* serovar *Enteritidis* (SE), which have been associated with infection originating in mince[95]. However, not all Salmonella strains can cause disease, and therefore the pathogenesis of *Salmonella* in small animals is not yet fully understood.[96] Indeed, *Salmonella* spp. can be present or cause infection in a wide range of vertebrate animals and insects.[70] In small animals, Salmonella spp. have been isolated with diarrhoeic and healthy animals, with prevalence being similar in healthy and diarrhoeic animals[97–101], therefore limiting the use of bacterial isolation as an effective diagnostic tool.[88]Nonetheless, in certain environments such as shelters, the prevalence of *Salmonella* spp. in shelter animals can be around 50%.[103–105]

Moreover, *Salmonella* spp. have been isolated from RMBDs, with one recent study in the Netherlands isolating Salmonella spp. in 20 per cent (n=7) of 35 analysed commercially available RMBDs.[74] In addition, different studies in North America have also isolated Salmonella *spp.* from RMBDs, with prevalence ranging between 7.1% and 21%.[73,106–108] In the UK, the Animal and Plant Health Agency (APHA) have reported *Salmonella* spp. isolation ratios from RMBDs *versus* processed food of 6 to 1 in 2015, and alarmingly 20 to 1 in 2016.[109] *Salmonella spp.* serovars isolated from RMBDs have been reported to be of concern for human salmonellosis.[73] The possible routes of infection for owners include raw food preparation and handling, direct contact with their animal, and possible contact with *Salmonella* spp. in the environment resulting from faecal shedding from pets.[73] Indeed, a correlation was found between *Salmonella* spp. shed by dogs fed with RMBDs and *Salmonella* spp. isolated from their pet food.[110,111]. Additionally, different studies in canine populations have reported an association between the ingestion of contaminated pet food and the higher frequency of shedding of *Salmonella* spp.[112,113] These findings have been highlighting the risk associated RMBDs and faecal shedding of *Salmonella* spp., which potentially increase the risk of human infection, particularly in cases of poor hygiene or carelessness around pets, for instance, with young children, or in adults with a compromised immune system.[73,114]

The diagnostic approach for suspect salmonellosis in small animals should consider concurrently the clinical signs and risk factors, such as hospitalisation, age and potential environment exposure, and the isolation of *Salmonella* spp. by bacterial culture. Clinical signs can vary, and despite salmonellosis being primarily an acute disease, it can also be considered in chronic gastrointestinal cases. Although most dogs can shed *Salmonella* spp. without presenting clinical sings, some patients can present signs of sepsis.[70,96,115]

To manage *Salmonella* spp. infection in small animals, antimicrobials are usually not needed in mild cases, and therefore supportive therapy alone is recommended. Nonetheless, in the event of systemic illness and/or an immunocompromised patient, antimicrobial use may be needed. In addition, the zoonotic potential of *Salmonella* spp. should be considered.[70]

1.3.4. *Campylobacter* spp.: epidemiology, diagnosis and management

Campylobacter spp. are Gram-negative, microaerophilic, curved, motile rods. Pathogenic *Campylobacter spp.* include *C. jejuni, C. upsaliensis* and *C. helveticus*.[70] *Campylobacter* spp. prevalence in faeces of healthy and diarrhoeic dogs is similar [116], therefore establishing causation of diarrhoea is difficult.[117,118] Nonetheless, it is described that in young dogs (less than 1 year of age), *C. jejuni* and *C. upsaliensis* were twice as common in diarrhoeic animals compared with non-diarrhoeic dogs.[70,119] Animal factors such as stress levels, crowding (such as shelters), or other concurrent diseases may play a role in the development of campylobacteriosis.[120] Moreover, RMBD feeding and home-cooked based diet, feeding human leftovers and living with other dogs that carry *C. upsaliensis* have all been identified as risk factors for *Campylobacter* spp. carriage.[70,74,121,122] Seasonality of *Campylobacter* spp. has also been described, with spring and autumn months having increased isolation rates. [118,121,123] In both dogs and cats, prevalence of *Campylobacter* spp. is highly variable[123,124125], with felines having associated the same risk factors of crowded/intensive housing conditions, such as shelters, for increased shedding of *Campylobacter* spp.[117–119]

Diagnostic approaches often include a direct Gram-stained smear of faeces, allowing the identification of *Campylobacter*-like organisms (CLOs). However, this method in isolation does not differentiate between organisms of similar morphology, such as Arcobacter or non-pathogenic campylobacters, and therefore selective bacterial culture is advised.[70] In addition, real-time PCR with faecal sample as a template has been described to detect and differentiate *Campylobacter* spp.[116,125–127]

Mild cases of diarrhoea associated with *Campylobacter* spp. might be managed with supportive therapy. As it happens with other enteropathogens, in severe cases with systemic clinical disease antimicrobial treatment may be dispensed.[70] However, resistance to enrofloxacin and ciprofloxacin has been reported in samples from small animals[117], which is in line with human studies finding *Campylobacter* spp. isolates resistant to fluoroquinolones.[128]

In humans, relevant *Campylobacter* spp. that are associated with diarrhoea include *C. jejuni*, *C. coli* and *C. upsaliensis*.[129] Thus, the zoonotic potential of *Campylobacter* spp. from dogs to

humans should be considered. Indeed an association between *C. jejuni* diarrhoea in humans and the presence of a dog in the same household has been established, particularly young dogs (less than 6 months of age)[130]. Other studies have also demonstrated associations between small animals and *C. jejuni* diarrhoea in humans.[131,132]

1.3.5. Enteric *Escherichia coli: epidemiology, diagnosis and management*

Escherichia coli are part of Enterobacteriaceae family. These bacteria are Gram-negative, non-spore-forming pleomorphic rods. Although *E. coli* are commensal to enteric microflora, they have been linked with GI clinical presentations, in the existence of bacterial virulence factors and compromised local or systemic immunity.[70] There are seven pathotypes of *E. coli* classified as diarrhoeagenic, characterised for virulence features acquired by horizontal gene transfer, and which are related with clinical, pathologic, and epidemiological features of the associated disease each pathotype can cause.[133–135] Similarly to other enteropathogens, different strains of *E.coli* have been isolated from canine samples – both in healthy circumstances and when diarrhoea is present. Therefore, causation of diarrhoeic presentation in dogs and cats is not well described. Nonetheless, adherent-invasive *E. coli* (AIEC) infection has been associated with susceptible dog breeds, specifically the French Bulldog, Boxer and Border Collie.[70]

Isolation of *E. coli* alone is again not synonymous of a role in disease, as it is not possible to distinguish between pathogenic and non-pathogenic *E. coli* strains. Nonetheless, bacterial culture and isolation is relevant to apply subsequent biochemical testing to differentiate *E. coli* strains. [70] In addition, PCR can also be used for detecting and distinguishing pathogenic strains of *E. coli*.[136]

Similar to therapeutic management strategies for other enteropathogens, patients with mild clinical presentations are eligible for support therapy. Resistance to antimicrobials associated with the *E. coli* Gram-negative cell wall, and with prevalence of conjugative transfer of resistance determinants related are described.[66] Additionally, antimicrobials can act as enhancers of toxin synthesis, or stimulate their release from the bacteria, causing a subsequent amplified haemorrhagic colitis. Therefore, antimicrobial therapy should only be considered in severe presentations, such as in septicaemia.[66,70]

1.3.5.1. *Escherichia coli* associated with granulomatous colitis

Granulomatous colitis (GC) was first described as histiocytic ulcerative colitis of Boxer dogs by Van Kruiningen in 1965.[137] It is characterised by pathognomonic histopathological lesions including mucosal infiltration with large amount of periodic acid-Schiff (PAS)-positive macrophages, with further signals of mucosal ulceration and damage of goblet cells.[137,138] The identification of Gram-negative coccobacilli inside macrophages can be confirmed using fluorescence *in situ* hybridization (FISH) probes.[138] Besides Boxers, French Bulldogs and Border Collie can also be affected. The clinical history often includes severe large bowel diarrhoea, concomitant with obvious weight loss. Results of blood tests are frequently mild

and/or non-specific.[70] Published evidence has shown improvement in both clinical signs and histologic lesions in canine patients treated with enrofloxacin.[70,138–140] Tissue samples collected from the colon of affected animals can be useful to isolate *E. coli* and adjust antimicrobial therapy, considering AMR.[138] Recent genetic analysis of dogs with GC has indicated a region on chromosome 38 that is linked with detecting and killing of *E. coli* in other species. Therefore, it is believed that *E. coli*-associated GC in breeds such as Boxers is likely a heritable genetic defect in sensing or killing intra-cellular *E. coli*. In 2017, a case report described *E coli*-associated GC in a feline patient, therefore highlighting that GC should be considered in the differential diagnosis of chronic haematochezia in this species. Evaluating molecular, genetic and immune mechanisms of this condition in cats is needed.[138,141]

Concerns about AMR were highlighted in one study which found 50% of dogs diagnosed with GC harboured mucosal *E. coli* resistant to at least one antimicrobial agent, with resistance to fluoroquinolones found in more than 40% of dogs.[140] Different factors have been indicated for such levels of resistance, including the lack of clinical response in animals treated previously with antimicrobial agents with *in vitro* efficacy against the *E. coli* strains, such as amikacin and amoxicillin-clavulanic acid. Other factors, such as drug distribution may also affect eradication of AIEC.[70] However, fluoroquinolones have been associated with resolution of clinical signs, having a positive effect in cellular infiltration typical of this disease. [70,139]

1.4. Antimicrobials: mechanisms of action and classification

Although the isolation of bacteria is not synonymous with a specific need for therapy, antimicrobials have become a mainstay in treatment. Since their first description, they have been frequently used in small animal practice.[3] Understanding their mechanism of action and their mechanisms of antimicrobial resistance is essential to their most rational use. Thus, in this section, we will begin by summarising the mechanisms of action of antimicrobial agents, followed by providing an insight into AMR mechanisms and context in companion animals, highlighting the efforts developed by antimicrobial categorisation and prescribing guidance, in an attempt to promote responsible antimicrobial use in the veterinary sector.

1.4.1. Basic anatomy of bacterial cell

The Gram-positive bacterial cell comprises a cytoplasmic membrane surrounded by a rigid mesh named the cell wall. Gram-negative bacteria in contrast comprise a thin cell wall surrounded by the outer lipid membrane (OM),[142] separated by the periplasm. The OM acts as an extra protective layer preventing many substances from entering Gram-negative bacteria . Nevertheless, this membrane includes porin channels which may allow various drugs to enter. The cell wall is a rigid layer giving a bacterium its shape and protecting it from mechanical and osmotic stresses. The cytoplasmic membrane prevents ions flowing out or into the bacterium, maintaining the bacterial and cytoplasmic components in a confined space.[142]

1.4.2. Cell wall synthesis inhibition

The bacterial cell wall is composed of long sugar polymers of peptidoglycan. These undergo cross-linking of the glycan strands via the action of transglycosidases, with the peptide chains extending from the sugars in the polymers and forming cross links from one peptide to another.[143] The D-alanyl-alanine portion of a peptide chain is cross-linked by glycine residues in the presence of penicillin-binding proteins (PBPs).[144] Such cross-linking strengthens the cell wall. The glycopeptides and β-lactams inhibit cell wall synthesis.[142]

1.4.2.1. β-lactams

The primary targets of the β-lactam agents are PBPs. It has been hypothesised that the β-lactam ring mimics the D-alanyl-D-alanine portion of a peptide chain, which is typically bound by PBPs.[142] The PBPs interact with the β-lactam ring, becoming unavailable for new peptidoglycan synthesis, thus ensuing disruption of the peptidoglycan layer leading to lysis of the bacterium.[145] This large antimicrobial class includes cephamycins, oxapenams, carbapenems, cephalosporins and penicillins. Several molecular modifications have produced different subclasses of β-lactams, e.g. the cephalosporin subclass, presently consisting of five generations, of increased broad-spectrum action.[146] Different antimicrobial agents belonging to β-lactams class are licensed for dogs and cats.[22]

1.4.2.2. Glycopeptides

Glycopeptides inhibit the late stages of cell wall synthesis, binding to D-alanyl-D-alanine in peptidoglycan subunit precursors, preventing binding to PBPs and, therefore, preventing cell wall synthesis.[144,145,147] In humans, glycopeptides are last-resort antimicrobials for the most severe infections caused by Gram-positive bacteria, including *S. aureus*, *C. difficile*, and *Enterococcus* spp.[148] Glycopeptides are not currently licensed for veterinary use.[149]

1.4.3. Disruption of the cell membrane

1.4.3.1. Polymyxins

The most important polymyxins utilised therapeutically are colistin (i.e. polymyxin E) and polymyxin B (licensed for dogs and cats).[149,150] The spectrum of activity of polymyxins is generally considered to be narrow, mainly targeting Gram-negative bacteria. These polypeptides interact with lipopolysaccharide molecules in the OM of Gram-negative bacteria, thereby causing disruptions in the cell membrane and increasing cell envelope permeability, resulting in loss of osmotic control culminating in cell death.[151] In the 1970s, their clinical use fell out of favour because of renal- and neurotoxicity.[150] Nowadays however, they are increasingly being used to treat multidrug-resistant Gram-negative bacterial infections, wherein they are considered to be last-line therapies.

1.4.4. Inhibitors of DNA replication

1.4.4.1. Fluoroquinolones

Fluoroquinolones are broad-spectrum bactericidal agents, possessing activity against many Gram-negative and Gram-positive bacteria; their structure is based upon nalidixic acid, the

first quinolone described.[152] Fluoroquinolones work by inhibiting both DNA gyrase and topoisomerase IV, both of which are enzymes involved in DNA replication and necessary for bacterial viability. Manipulating the structure of fluoroquinolones has led to the generation of newer molecules with which to treat a range of important bacterial infections, including Gram-positive cocci and anaerobes.[152,153] Pradofloxacin is an example of a fluoroquinolone licenced for dogs and cats[149].

1.4.5. DNA degradation and synthesis inhibition

1.4.5.1. Nitroimidazoles

Nitroimidazoles are bactericidal agents that have been extensively utilised against a wide range of anaerobic bacteria and protozoa since their introduction in 1959.[154] Nitroimidazoles cause extensive breakage in DNA strands and inhibition of the DNA repair enzyme via an oxidation process after entering the cell via passive diffusion.[155] These lipophilic agents penetrate tissues well and can be detected in bone, synovial and peritoneal fluid, abscesses, and the central nervous system after systemic administration.[156] Metronidazole (nitroimidazole family) is licensed for dogs and cats[22].

1.4.5.2. Nitrofurans

The synthetic antimicrobials nitrofurantoin and nitrofurazone are the two members of the nitrofurans class that have clinical use at the present time. Following decades of use, nitrofurans have remained clinically useful against a wide range of Gram-negative and Gram-positive bacteria, particularly urinary tract pathogens. Thus, the primary use of nitrofurantoin is as an oral antimicrobial treatment for genitourinary infections. However, it is not licensed for veterinary use.[157] In a similar manner to nitroimidazoles, nitrofurans are reduced intracellularly to toxic intermediate compounds, which interfere with the enzymes involved in RNA, DNA, and protein synthesis.[158]

1.4.6. RNA synthesis inhibition

1.4.6.1. Rifamycins

The rifamycin class mainly comprises rifampicin, and display a broad spectrum of antimicrobial activity against Gram-positive and, to a minor extent, Gram-negative bacteria.[159] Rifamycins bind to and inhibit DNA-dependent RNA polymerase.[160] The lipid-soluble rifampicin possesses excellent oral bioavailability and retains more pronounced activity against Gram-positive bacteria, especially mycobacteria, thus becoming one of the mainstay agents in the treatment of tuberculosis in humans. Agents of the rifamycin class are not currently licensed for veterinary use.[159]

1.4.7. Inhibitors of protein biosynthesis

Protein biosynthesis is catalysed by cytoplasmic factors and ribosomes. The bacterial 70S ribosome is composed of two ribonucleoprotein subunits, namely 30S and 50S.[161] Antimicrobials inhibit protein biosynthesis by targeting the 30S or 50S subunit of the bacterial ribosome, and can be classified accordingly.[162,163]

1.4.7.1. Inhibitors of 30S subunit

1.4.7.1.1. Aminoglycosides

Aminoglycosides (licensed for dogs and cats)[22] are one of the oldest classes of antimicrobials and exhibit antimicrobial activity against a wide spectrum of different microorganisms, including both Gram-negative and Gram-positive bacteria. These concentration-dependent bactericidal agents are transported across the cytoplasmic membrane in an oxygen-dependent manner, thus demonstrating no activity against anaerobes.[164] They exert their activity further by binding to a specific site of 16S rRNA within the 30S ribosomal subunit, causing misreading and premature termination of the translation of mRNA, therefore inhibiting cell protein synthesis.[142] Aminoglycosides possess synergistic activity with β-lactams and other cell wall-active agents allowing greater penetration of aminoglycosides within the cell and at low dosages.[164,165]

1.4.7.1.2. Tetracyclines

Tetracyclines (licensed for dogs and cats)[22] are broad-spectrum agents that exhibit activity against a large amount of Gram-negative and Gram-positive bacteria, including such atypical organisms as chlamydiae and mycoplasmas.[166] This bacteriostatic class of antimicrobials penetrate moderately well into bodily fluids and achieve high concentrations in sputum, being principally useful in the treatment of respiratory tract infections.[166] Tetracyclines act on the conserved sequences of the 16S r-RNA of the 30S ribosomal subunit to prevent binding of t-RNA to the A site, whereby causing the inhibition of protein biosynthesis.[142,161]

1.4.7.2. Inhibitors of 50S subunit

1.4.7.2.1. Macrolides and lincosamides

Macrolides (licensed in veterinary medicine for large species)[22] and lincosamides (licensed for dogs and cats)[22] are bacteriostatic and generally utilised in the treatment of Gram-positive bacterial infections, though lincosamides can also be used to treat anaerobic infections.[167,168] They act on protein translocation, targeting the peptidyl transferase centre of the 23S r-RNA of the 50S ribosomal subunit, which results in the early detachment of truncated peptides.[142,161]

1.4.7.2.2. Amphenicols

Amphenicols (licensed in veterinary medicine for large species)[22] possess the same mechanism of action as that described for lincosamides and macrolides, targeting the 23S portion of the 50S ribosomal subunit, inhibiting peptidyl transferase and, thus, polypeptide elongation.[165,169] This class possesses a broad spectrum of activity, including against anaerobic bacteria.[169]

1.4.7.2.3. Oxazolidinones

Oxazolidinones (not currently licensed for veterinary use)[22] are a relatively new class of antimicrobials, with linezolid being the first oxazolidinone to become available. These synthetic agents are active against a large spectrum of Gram-positive bacteria, including methicillin and vancomycin-resistant staphylococci, as well as penicillin-resistant pneumococci.[170] It is

described that oxazolidinones interfere with several stages in the synthesis of proteins, by binding the 23S r-RNA of the 50S subunit, and they seem to inhibit 70S ribosome formation. Additionally, oxazolidinones interact with the peptidyl-tRNA.[142] Considering linezolid's good penetration and accumulation in tissues, its utilisation has been described in the treatment of osteomyelitis, sepsis, endocarditis, meningitis, and surgical infections.[170]

1.4.7.2.4. Fusidic acid

Fusidic acid (licensed for dogs and cats)[22] is a narrow-spectrum antimicrobial derived from *Fusidium coccineum* that has been used for over 40 years.[171] Its principal activity is against staphylococci, including multi-resistant strains.[172] The action of fusidic acid is largely bacteriostatic, but the effect may be bactericidal at high concentrations. The elongation factor G is a bacterial protein required for translocation on the bacterial ribosome following peptide bond formation. Binding of fusidic acid to elongation factor G and the ribosome inhibits further bacterial protein synthesis.[171]

1.4.8. Folic acid metabolism inhibitors

1.4.8.1. Sulphonamides and trimethoprim

Sulphonamides and trimethoprim (not currently licensed for dogs and cats)[22] are bacteriostatic drugs that inhibit distinct phases in folic acid metabolism. These agents act at distinct steps on the same biosynthetic pathway.[142] While sulphonamides inhibit dihydropteroate synthase in a competitive manner, trimethoprim acts at a later stage of folic acid synthesis, as well as inhibiting the enzyme dihydrofolate reductase.[161] A combination of sulphonamides and trimethoprim has a mutually synergistic potentiating action, which results in a concentration-dependent bactericidal action.[173]

1.4.9. Antimicrobial resistance: mechanisms and context in small animals

AMR is a complex and multifactorial problem that involves distinct bacterial species, resistance mechanisms, transfer mechanisms, and reservoirs. It is assumed that bacterial selection pressure associated with antimicrobial use is one of the most significant factors responsible for increased AMR.[1,2] Dogs and cats represent potential sources of the spreading of AMR because of the extensive use of antimicrobial agents in these animals and their close contact with humans.[174]

Bacterial resistance can occur through acquired or intrinsic mechanisms. Intrinsic mechanisms are those associated with genes naturally found on the chromosome of the host, e.g. AmpC β-lactamase of Gram-negative bacteria and many multidrug resistance (MDR) efflux systems.[175,176] Meanwhile, acquired resistance is the result of mutations in genes targeted by the antimicrobial and their transfer on transposons, bacteriophages, plasmids, and other mobile genetic material.[161,177] This exchange is generally achieved through different processes, namely: transduction (via bacteriophages), conjugation (via conjugative transposons and plasmids), and transformation (via incorporation into plasmids, chromosomal DNA and other DNAs from dying organisms).[175,178]

Over the years, continued selective pressure from different drugs has resulted in organisms bearing additional kinds of resistance mechanisms, and leading to multidrug resistance (MDR), including mechanisms such as novel PBPs, enhanced efflux pump expression, mutated drug targets, enzymatic mechanisms of drug modification, and altered membrane permeability.[175] Some of the most problematic MDR organisms encountered in the GI tract of companion animals include *Salmonella* spp., vancomycin-resistant enterococci (VRE), *and Escherichia coli* bearing extended-spectrum β-lactamases (ESBL).[24,179]

Enterococci are opportunistic Gram-positive pathogens usually found in the GI tract of a wide range of animal species. The species that are most frequently involved in disease are *Enterococcus faecalis* and *Enterococcus faecium*. Enterococci are characteristically resistant to a diverse range of antimicrobials, including penicilins, cephalosporins, trimethoprim, and clindamycin, potentiating the consequences of acquired resistance. In humans, VRE are a serious problem, especially *E. faecium* and *E. faecalis* strains that carry transferable vanA and vanB genes. VRE have been described as infrequent in companion animals; nonetheless, there have been some reports of colonisation or infection in household companion animals.[179,180]

E. coli is a relevant pathogen and is commonly present in the commensal intestinal microflora. Indeed, the intestinal *E. coli* reservoir has been characterised as a potential pool of AMR. The wide diversity in *E. coli* together with inherent biases associated with clinical specimen-based reporting make particularly challenging to understand AMR in *E. coli* at the population level. The central focus with regard to AMR in *E. coli* is associated with production of β-lactamase, because of the relevance of β-lactam antimicrobials in the treatment of infections in both humans and animals, and concerns surrounding resistant strains transmission between humans and animals.[179] Indeed, particularly relevant for resistance are ESBLs, which hydrolyse a broad range of β-lactam antimicrobials. Studies on integrons and associated resistance genes have identified several genes involving aminoglycoside resistance, trimethoprim resistance, streptothricin resistance, chloramphenicol resistance, and sulphonamide resistance from isolates of companion animals.[179] Additionally, genes encoding tetracycline resistance have been found in isolates from companion animals.[181] Studies on resistance determinants have been frequently focused on bacterial populations isolates with present a particular resistance phenotype, for example cephalosporin resistance; therefore, population prevalence is poorly understood.

Nonetheless, it is clear that MDR *E. coli*, including various combinations of β-lactamase and other resistance determinants, can be found in isolates from both clinical cases and healthy animals. Furthermore, it has been highlighted that the issue of AMR in *E. coli* in companion animals may have public health significance due to the risk of interspecies transmission.[179,182]

As stated previously, salmonellosis can be an important disease in different small animals, having zoonotic potential. MDR *Salmonella* spp. have been commonly reported in horses, including outbreaks;[183] they can also be problematic in companion animals, with sporadic

cases and outbreaks amongst humans and pets in veterinary practices and households.[184,185] As with *E. coli*, ESBL-producing strains of *Salmonella* have been described. Several AMR genes have been identified, including isolates that are resistant to third-generation cephalosporins in companion animals.[179,186,187]

1.4.10. Antimicrobial categorisation in the context of AMR: promoting responsible use

It is clear AMR is increasing amongst different species, and also causing infections in companion animals. The selection pressure associated with the use of antimicrobials, both in human and in veterinary medicine, largely contributes to this issue.[2] Thus, eliminating inappropriate use and promoting responsible use of antimicrobials is vital in both veterinary and human medical fields in order to preserve the efficacy of treatment.[23]

The WHO has classified distinct antimicrobial classes as "Highest Priority Critically Important Antimicrobials" (HPCIA) for human medicine.[23] The WHO's list of Critically Important Antimicrobials for Human Medicine (WHO's CIA List) was first developed in 2005 and was updated in 2018. The WHO CIA List is planned to be used by public health and animal health authorities, practising veterinarians and medics, as well as other stakeholders that are involved in managing AMR so as to ensure that all antimicrobials, particularly HPCIAs, are used cautiously in both humans and animals.[23] Indeed, the WHO's CIA List can be used as a guide to help to formulate and prioritise risk assessment and risk management strategies around AMR, particularly in relation to animal antimicrobial use.[23] Two criteria are used to categorise antimicrobial classes utilised in human medicine as 'Critically Important', 'Highly Important' or 'Important'. In the latest version of the WHO's CIA List (2018), a further distinction is made with critically important antimicrobials classified as high-priority. HPCIA are: quinolones, third- and higher-generation cephalosporins, ketolides and macrolides, polymyxins, and glycopeptides.[23]

Other international initiatives have classified antimicrobial classes that aim to promote judicious antimicrobial use. For instance, the recently published European-level *'categorisation of antibiotics for use in animals for prudent and responsible use'* by the European Medicines Agency (EMA) has ranked antimicrobials according to the risk of AMR development in both public and animal health, and the need of antimicrobial use in the veterinary sector. Overall, this classification consists of four categories of antimicrobials: Avoid, Restrict, Caution and Prudence.[188]

In the veterinary sector, different international groups have collaborated to develop clinical guidance and raise awareness with regard to antimicrobial use. The International Society for Companion Animal Infectious Diseases (ISCAID) have worked to develop and disseminate guidelines that contain recommendations for antimicrobial choice and dosing for specific diseases in companion animals, including guidelines for the treatment of urinary tract infections and for the diagnosis and therapy of canine superficial bacterial folliculitis.[189] Additionally, the American Association of Feline Practitioners and the American Animal

Hospital Association have disseminated the *'Basic Guidelines of Judicious Therapeutic Use of Antimicrobials'*.[190] In 2015 the American College of Veterinary Internal Medicine (ACVIM) and the European College of Equine Internal Medicine (ECEIM) published the Consensus Statement on Therapeutic Antimicrobial Use in Animals and Antimicrobial Resistance, aiming to offer a reference for therapeutic use of antimicrobials in veterinary patients, considering the necessity of an effective therapy whilst minimising AMR development in bacterial populations from both humans and animals.[191]

Other worldwide-disseminated initiatives on appropriate antimicrobial use, to be applied at a practical level, include the Federation of Companion Animal Veterinary Associations' (FECAVA) *'Advice on Responsible Use of Antimicrobials'* and the FECAVA's *'Recommendations for Appropriate Antimicrobial Therapy'*.[192] The latest clearly provides guidance with respect to the therapeutics of GI clinical cases, mentioning the frequent self-limiting characteristics of GI disease, with antimicrobial use and empirical therapy not being indicated. Furthermore, it advises on bacterial culture and antimicrobial susceptibility testing upon suspicion of *Campylobacte*r spp., *Salmonella* spp., and toxigenic Clostridia. Moreover, considering GI disease, these guidelines also suggest the usefulness of dietary modification and the possible benefit for recovery times and the target of intestinal dysbiosis by dispensing probiotics.[193]

In the UK, initiatives such as the British Veterinary Association's (BVA) *'responsible use of antimicrobials in practice seven-point plan'* and *'Are you antibiotic aware?'* have been raising awareness with regard to the need for judicious use of antimicrobials in veterinary practices.[194,195] What is more, the recently updated BSAVA *'PROTECT ME'* guidelines have provided guidance surrounding antimicrobial use in a wide range of clinical presentations in companion animals, including GI disease. Here it is clearly advised that dogs and cats presenting with acute GI signs, including dogs suffering from haemorrhagic diarrhoea, that are systemically well do not require antibacterial therapy.[10] Additionally, for chronic enteropathy in small animals it is indicated that diet manipulation (hydrolysed or novel protein source diets) can alleviate signs in 60–80% of food-responsive patients, therefore avoiding the need for empirical antimicrobial use in these patients.[10]

Nevertheless, and in spite of these initiatives in the UK and worldwide that have provided awareness and clinical guidance for encouraging effective antimicrobial stewardship in veterinary practice, antimicrobials are still frequently prescribed in GI cases in companion animals, making GI disease one of the most common syndromes for which antimicrobials are prescribed in small animal first-opinion practice.[3]

1.5. Approaches and surveillance for investigating antimicrobial prescription in small animals

The emergence and dissemination of AMR in small animals will certainly continue to be a challenge in veterinary medicine from both public health and patient health perspectives.[179] Though several widespread initiatives that aim to raise awareness and provide clinical

guidance surrounding responsible antimicrobial use have been published, analyses of data from veterinary practices have shown that antimicrobials are still frequently used in different clinical presentations, including in GI disease.[3] Thus, organised surveillance is required in order to better understand the scope of the problem and identify factors that are associated with antimicrobial prescription, which, ultimately, may be used to reduce the impact of this global problem.[179]

1.5.1. The Small Animal Veterinary Surveillance Network (SAVSNET)

An EHR is defined as a secure digital longitudinal repository of patient data provided in a standardised format, whose purpose is to expand accessibility to include several of authorised users, thereby improving the efficiency of care.[196] The content of EHRs may vary and can include information relating to the direct clinical history and/or diagnostic test results held by a diagnostic laboratory.[197] EHR data can range from structured data, as signalment information, e.g. age and sex, or closed-ended questionnaire responses, to semi-structured data (e.g. animal breed and prescribed medications) and largely unstructured data (e.g. clinical free text).[8,198,199]

In spite of the estimated UK population of 10.1 million cats and 11.6 million dogs in 2011, small companion animal populations largely lack coordinated disease surveillance.[199,200] For this reason, the Small Animal Veterinary Surveillance Network (SAVSNET) was developed in order to improve pet disease surveillance at local, regional and national levels.[199] SAVSNET harnesses the increasing volumes of patient EHRs in near-real time, which are available from volunteer sentinel small animal practices using compatible practice management software.[201] In addition, SAVSNET collects complementary data from diagnostic laboratories, thus aiming to improve human and animal health by means of enhanced surveillance and research.[199]

Owners attending practices participating in SAVSNET are given the option to opt out at the time of their consultation, thus excluding their data from research. For those who participate, data are collected on a consultation-by-consultation basis. Apart from the animal signalment data, e.g. species, breed, sex, and neuter status, collected data include the clinical notes written by the attending veterinary professional, as well as the owner's postcode.[199]

At the end of each consultation, the attending veterinary professional categorises the main reason for the animal's presentation, which is further described as the Main Presenting Complaint (MPC). Currently the MPC function is organised into syndromes (respiratory, gastrointestinal, pruritus tumour, and renal) and other veterinary interventions (e.g. trauma and vaccination) (Figure 3).[199] Additionally, a short syndrome-specific questionnaire is randomly assigned to around 10% of consultations, allowing the collection of additional information on each syndrome (e.g. duration of illness and diagnostic plans).[199]

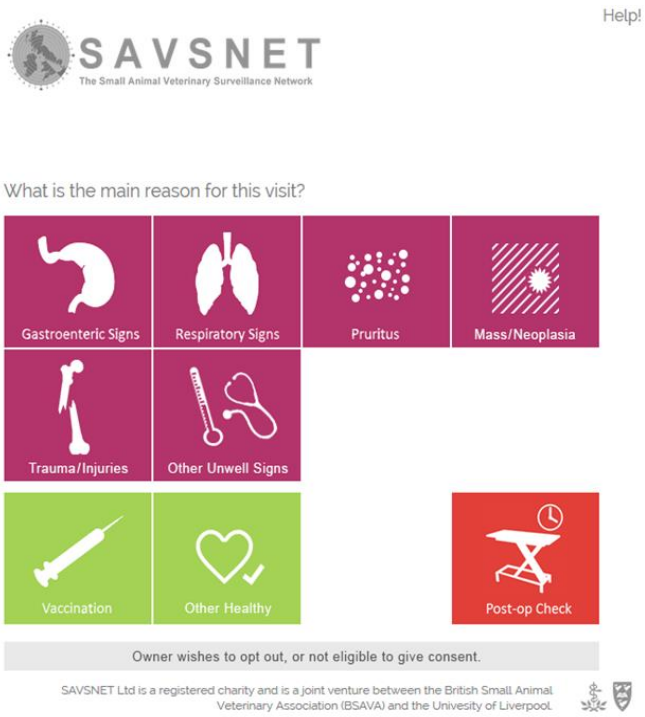

Figure 3. The 'SAVSNET window', which appears at the conclusion of every consultation. This inline frame contains a range of options that mandatorily requires the attending veterinary professional to provide a main reason the animal presented for examination in the relevant consultation. (Source: SAVSNET)

1.5.2. Characterising antimicrobial prescription

Different approaches have been adopted in order to characterise antimicrobial prescription in the veterinary sector. These include survey approaches at the European level, with a recent study identifying penicillins as the most prescribed antimicrobial class in cats and dogs (37% and 33%, respectively).[202] 'Critically important antimicrobials', e.g. third-generation cephalosporins and fluoroquinolones, were still commonly prescribed in small animals, especially in cats, wherein 30% of antimicrobials used were critically important agents, in comparison to 16% of critically important antimicrobials used in dogs.[202]

In the UK, the Veterinary Medicines Directorate (VMD) collates data on antimicrobial sales, producing the Veterinary Antibiotic Resistance and Sales Surveillance (VARSS) report.[203] Considering the quantities of antimicrobial active ingredients by antimicrobial class sold between 2014 and 2018 for use in cats and dogs, β-lactams were the most sold antimicrobial class, comprising 76% of total sales for companion animals in 2018. Additionally, sales of HPCIA in cats and dogs accounted for 9% of total HPCIA sales for all animal species in 2018.[203] Although sales data can be useful in outlining the volumes of antimicrobials sold in the veterinary sector, they bear their own limitations. The data presently available cannot specifically recognise the antimicrobials administered under the cascade prescribing system, to which species they were prescribed, variability at practice-level prescription, or the reasons as to why individual antimicrobials were prescribed under which clinical conditions. Recent

advances in veterinary health informatics provide new opportunities to fill this gap, especially for companion animals where EHRs are most developed and accessible.[3]

Different studies and surveillance reports have been published in order to investigate antimicrobial prescription in small animals in the UK through the use of EHRs.[3,8,11,42] In 2011, an early SAVSNET study on antimicrobial prescription reported that 48.5% of feline consults and 35.1% of canine consults involved systemic antimicrobial prescription.[8] In this study, the β-lactam antimicrobial class was indicated as the most frequent antimicrobial choice, although in cats the HPCIA cefovecin represented 24% of feline consults involving antimicrobials.[8] Interestingly, a more recent study has identified third-generation cephalosporins, where cefovecin is included, as the most frequent choice for systemic antimicrobials in cats, whereas in dogs the clavulanic acid potentiated amoxicillin was still the most frequent choice.[3] The frequent choice of cefovecin in cats was highlighted by a recent study, wherein cefovecin prescription occurred in around 30.2% of antimicrobial prescription events in cats, in comparison to 1.31% of cefovecin prescription in canine antimicrobial prescription events.[9]

In fact, the use of cefovecin in cats has been further investigated using SAVSNET data, given its importance as an HPCIA in the global AMR context.[204] In this study, the reasons for prescribing cefovecin in cats were not commonly recorded within the EHR (12.0%), and when a justification was found, it was mostly related to the inability to orally medicate patients. Most notably, only a minority of consultation narratives recorded the use of suitable microbiological evaluation.[204] Importantly, cefovecin (licensed for dogs and cats)[22] is commercially available as a long-acting injectable formulation, which contributes to its popularity in small animal practice.

It has been repeatedly mentioned that GI clinical presentations are one of the most common reasons for antimicrobial prescription in small animal practice.[11] Indeed, a recent study that used SAVNET data reported that 28.9% of feline GI consultations and 38.2% of canine GI consultations involved recorded systemic antimicrobial prescription.[3] Such numbers are concerning, particularly as stated previously that recently updated national prescribing guidance states cats and dogs presenting with acute GI signs, including dogs with haemorrhagic diarrhoea that are systemically well, do not require antimicrobial therapy, and diet manipulation can alleviate clinical signs in 60–80% of food-responsive patients with chronic enteropathy.[10] Additionally, a recent longitudinal study that investigated pharmaceutical prescription in canine acute diarrhoea reported that clinical advice around dietary modification and GI nutraceuticals dispensing alone were positively, albeit mildly, associated with resolution of diarrhoeic clinical signs, whereas no association was found for other pharmaceutical agents, including antimicrobials, thus supporting the view that antimicrobials are avoidable in the majority of acute diarrhoea cases.[42]

Nonetheless, the pharmacological approach to GI disease appears to be evolving over time. Indeed, in a recent surveillance report of temporal trends in prescription showed a reduction in the frequency with which systemic antimicrobials were prescribed over a period of four to

five years.[205] The same decreasing trend was observed in systemic anti-inflammatories, contrasting with the opposite trend noted for GI nutraceuticals.[205]

To summarise, these studies have improved our understanding of antimicrobial prescription in GI disease, including temporal trends and identified risk factors that are associated with diarrhoea cases.[11,42,205] The majority of these publications have, however, been quantitative in nature and barely made use of the clinical data recorded in the free-text narrative of each EHR.

1.5.3. Qualitative research methods: understanding antimicrobial prescribing behaviour

The use of qualitative methodologies has increased in popularity in the field of human health in both general practice and primary care settings.[206–208] Qualitative research can offer detailed understandings into the real world experiences and perspectives of both patients and healthcare professionals with distinct, yet complementary lenses to the insights acquired by the use of quantitative methods.[209]

Qualitative approaches are incredibly diverse, nuanced and complex, and thematic analysis has been identified as a foundational method of qualitative analysis.[210] Thematic analysis is defined as a method with which to identify, analyse and report patterns (themes) within data. It minimally organises and describes a dataset in detail. Furthermore, thematic analysis allows further interpretation of different aspects of a research topic.[209,210] This flexible method can usefully summarise key features of a large body of data, allowing social interpretations of data at the same time. Ultimately, the method can be useful in producing qualitative analyses suited to informing policy development.[210]

This qualitative methodological approach has been utilised more recently in order to better understand veterinary behaviour in both companion animal and food animal studies, using in-depth interviews to explore themes and drivers associated with antimicrobial prescribing and AMR.[211–214] Drivers associated with antimicrobial use were previously classified into intrinsic and extrinsic factors.[213] Intrinsic factors are those that are directly linked to the veterinarian, e.g. their knowledge of infectious diseases. Meanwhile, extrinsic factors are those that are related to other “players” but which can also influence the decision-making process regarding antimicrobial prescription, e.g. the pet’s owner, characteristics of the animal/clinical presentation (e.g. species, behaviour, and clinical signs), or the antimicrobial agent (e.g. the formulation or route of administration).[213,214]

Previous reports highlighted that drivers other than the clinical need for an antimicrobial can play an important role in decision making with regard to prescription. These include adherence to medication at home (e.g. the difficulty of administering oral medication to cats and aggressive animals), topical optic pharmaceutical formulations in dogs, and long-term therapies, such as in deep pyoderma in dogs).[213] Consequently, to have owners be compliant with therapies at home, veterinary practitioners in different studies identified the value of long-acting injectable antimicrobial preparations, especially in cats, though the only currently

authorised formulation uses an HPCIA as its active substance.[213,214] Furthermore, in a qualitative study conducted by King C*. et al.*, veterinary practitioners were conflicted as to whether the use of such long-acting antimicrobial products was likely to increase or decrease AMR.[214] Nonetheless, the impact of pharmaceutical factors, e.g. the route of administration, as well as the effect of duration of the antimicrobial therapy, upon prescribing behaviours was highlighted in this study.[214] Other drivers related to the animal's owner, e.g. the cost and/or the willingness to pay for the treatment, were also recognised that could potentially shape the veterinary decision regarding antimicrobial prescription.[214] What is more, in a recent qualitative study it was highlighted that in cases in which owners refused or did not want to pay for any further diagnostic testing, veterinary practitioners were faced with a barrier to making an appropriate diagnosis, eventually shaping the decision making around antimicrobial prescription.[215]

1.6. Study aims

Gastrointestinal disease remains common in dogs and cats presenting to veterinary practices and is frequently treated with antimicrobials, often of the most critical types. The use of such products may hasten antimicrobial resistance and suggests a belief by the veterinary practitioner that bacteria are frequently contributing to the disease. A greater understanding of antimicrobial prescription at a population level is needed for the veterinary profession, especially for critically important antimicrobials such as fluoroquinolones and third generation cephalosporins. Whilst descriptive studies have helped quantify antibiotic use, they are not able to describe the key clinical drivers of antimicrobial prescription during consultations. The aims of this thesis were therefore twofold:

- Using a quantitative approach, to reappraise the use of antimicrobials and to explore risk factors associated with antimicrobial prescription in GI clinical presentations (chapter 2)
- Using a qualitative approach, to describe in a subset of these cases the recorded justification and/or reasoning around antimicrobial use, particularly associated with HPCIA prescription (chapter 3)

We used a mixed-methods approach to EHRs, aiming to provide new insight into antimicrobial choices made by veterinary practitioners for gastrointestinal clinical presentations. The results of this work can help inform targeted interventions aimed at preserving the most critical antimicrobials for those animals and cases where they are most needed.

Chapter Two:

Characterising canine and feline gastrointestinal disease and appraising antimicrobial prescription in veterinary primary care in the United Kingdom: a retrospective observational analysis using Electronic Health Records

2.1. Abstract

Canine and feline gastrointestinal presentations are often observed in first opinion veterinary practice, commonly resulting in antimicrobial prescription. Our retrospective observational study used 23,337 electronic health records (EHRs) from canine (n=18,829) and feline (n=4,508) gastrointestinal consultations complemented with questionnaire responses provided by the attending veterinary professional, collected from 225 volunteer veterinary practices across the United Kingdom, between April 2014 and September 2018. We characterised canine and feline gastrointestinal (GI) clinical presentations and management choices, appraising antimicrobial prescription in canine and feline gastrointestinal consultations. In addition, using multivariable mixed effects logistic regression models, we explored factors potentially associated with systemic antimicrobial prescription in canine and feline gastrointestinal presentations. The most commonly reported clinical signs were non-haemorrhagic diarrhoea, reported in 47.9% (95% confidence interval, CI, 47.1-48.7) of canine consultations and in 44.9% of feline consultations (95% CI, 43.3-46.6); and non-haemorrhagic vomiting, which was reported in 43.0% (95% CI, 42.1-43.9) of canine consultations and in 49.4% of feline consultations (95% CI, 47.7-51.1). Most GI presentations were recorded as mild, in 83,4% of canine presentations (95% CI, 82.6-84.3), and 81.6% of feline presentations (95% CI, 80.3-82.9). However, systemic antimicrobials were prescribed in 28.6% of canine gastrointestinal consultations (95% confidence interval, CI, 26.9-30.3), and in 22.4% (95% CI, 20.4-24.4) of feline consultations. Systemic Highest Priority Critically Important Antimicrobials, recommended for human use alone, were prescribed in 0.9% of canine gastrointestinal consultations (95% CI, 0.4-1.3) and in 5.0% of feline gastrointestinal consultations (95% CI, 4.1-5.9). However, bacteriological and/or parasitological diagnostic tests were uncommonly used.

Results of multivariable modelling showed the presence of non- haemorrhagic diarrhoea (canine GI presentations OR 2.11, 95% CI 1.91-2.33, p<0.001; feline GI presentations OR 1.77, 95% CI 1.48-2.11, p<0.001) and haemorrhagic diarrhoea (canine GI presentations OR 4.22, 95% CI 3.80-4.68, p<0.001; feline GI presentations OR 3.05, 95% CI 2.44-3.82, p<0.001) were significantly associated with systemic antimicrobial prescription when compared with the absence of diarrhoea. In addition, moderate/severe GI presentations were also associated with significantly increased odds of receiving a systemic antimicrobial (canine GI presentations OR 1.85, 95% CI 1.65-2.07, p<0.001; feline GI presentations OR 2.03, 95% CI 1.68-2.46, p<0.001). Older dogs were more likely to receive an antimicrobial prescription.

This study successfully combined EHR-based data with structured questionnaire responses to profile canine and feline gastrointestinal presentations, and to explore factors associated with systemic antimicrobial prescription in canine and feline GI consultations in the veterinary primary care in the UK. Importantly, the present study highlights that antimicrobial prescription still represents a frequent management choice in canine and feline gastrointestinal presentations, commonly conflicting with practice-level prescribing guidance and international

recommendations to tackle antimicrobial resistance. Thus, the results of this study can be used to inform targeted interventions aiming to promote responsible veterinary antimicrobial prescription and compliance with current guidance in canine and feline gastrointestinal presentations.

2.2. Introduction

Gastrointestinal (GI) disease is a common reason for seeking veterinary care for small animals in the UK.[11] Multifactorial aetiology includes self-limiting factors (e.g. dietary modification) and life-threatening causes (e.g. canine and feline parvoviruses).[11,12,216] Bacteria are commonly implicated in canine and feline diarrhoea, including zoonotic pathogens such as *Clostridium perfringens, Clostridium difficile,* and *Campylobacter spp.*[70] Nonetheless, the exact role of these enteropathogens in companion animal GI cases remains under debate.[70,80] Dogs and cats presenting with GI signs are often diagnosed and treated by recognition of a set of clinical signs previously observed by the veterinary professional in similar cases, and diagnostic testing has been reported to be uncommonly used in GI cases.[12,42,217] This empirical approach often includes antimicrobial prescription as a management strategy.[42] Indeed, a recent study using SAVSNET data reported 38.2% of canine gastrointestinal consultations and 28.9% of feline gastrointestinal consultations involved recorded systemic antimicrobial prescription, therefore indicating GI disease as one of the most common syndromes for which antimicrobials are prescribed to companion animals.[3] It has been reported that antimicrobial prescription in canine acute diarrhoea cases was frequently associated with the clinical signs of haemorrhagic diarrhoea and pyrexia.[11,42] Additionally, it has been suggested these findings most likely reflect a perception of infectious process involvement and/or intestinal mucosal compromise, leading to increased risk of bacteria translocation and subsequently, sepsis.[42] Nonetheless, recently published evidence showed no difference in the incidence of bacterial translocation, and no improvement in disease severity and recovery parameters between patients with acute haemorrhagic diarrhoea receiving clavulanic acid potentiated amoxicillin *versus* a placebo, thus questioning the need of antimicrobials at all.[218,219]

Efforts to encourage responsible veterinary antimicrobial use have been developed, such as the recently published European-level *'categorisation of antibiotics for use in animals for prudent and responsible use'*, by the European Medicines Agency (EMA), and for small animals, the 'PROTECT ME' antimicrobial prescribing guidance.[10,188] Of note, the latter clearly states that dogs and cats presenting with acute gastrointestinal signs, including dogs with haemorrhagic diarrhoea that are systemically well, do not require antimicrobial therapy.[10] Despite recent clinical evidence and published guidance stating that systemic antimicrobials are largely unnecessary, there is still the need to understand whether such guidance is having an impact on antimicrobial prescribing choices in small animal practice in the UK. Therefore, the aim of this study was, firstly, to characterise GI presentations and management choices, appraising systemic antimicrobial prescription. Secondly, we aimed to explore factors

potentially associated with systemic antimicrobial prescription in both canine and feline GI cases, combining EHRs and questionnaire data collected from a large network of voluntary UK veterinary practices.

2.3. Materials and methods

2.3.1. Data collection

This retrospective observational study analysed electronic health records (EHRs) collected from 225 volunteer veterinary practices (502 sites) located in the United Kingdom (UK) that participate in the Small Animal Veterinary Surveillance Network (SAVSNET) and operate Robovet practice management software (Vet Solutions Ltd.). A veterinary practice was defined as a single business, while "sites" included all branches that comprised an individual veterinary practice, in accordance with previous SAVSNET research. Comprehensive data collection protocols were previously described.[42,199] Here, EHRs were collected from consultations where an appointment was made to see a veterinary professional (veterinary surgeon or veterinary nurse) between 1 April 2014 and 30 September 2018. As previously described in this dissertation (chapter 1, section 6.1.), each consultation is classified by the attending veterinary professional according to the main reason that the animal presented, defined as the main presenting complaint (MPC).[3] Moreover, a short questionnaire (Appendix 1) was completed by the attending veterinary professional in a random selection of consultations. Accordingly, consultations that had been classified into the GI MPC, which additionally had a completed questionnaire associated, were selected for inclusion in this study (n= 23,337).

Consultations from dogs or cats presenting primarily for investigation and/or treatment of GI clinical presentations, presenting diarrhoea and/or vomiting, where the episode of veterinary visit was clearly defined by the attending veterinary professional on the questionnaire answers were included in the study (*i.e.* one option selected to define the visit episode as *'first visit'* or *'revisit'*. Multiple answers and *'don't know'* category were excluded). Consultations were selected for presence of diarrhoea and/or vomiting but not at the exclusion of other clinical signs, *i.e.* clinical signs not limited to diarrhoea and/or vomiting (please refer to Appendix One, question one). In addition to the MPC and the associated questionnaire responses, each EHR also included signalment data, such as date of birth, sex, neutered status, insurance status, microchip status, owner's postcode, a text-based product description, and a vaccination history if relevant. Animals were defined as vaccinated if they had received a vaccination of any composition within 3.5 years before the consultation date, in accordance to previously published SAVSNET research.[42,220]

Pharmaceutical product prescription was described using five pharmaceutical families, in agreement with previous published reports, namely: antimicrobial agents authorised for systemic use (injectable or oral formulations, hence "systemic"); anti-inflammatory drugs authorised for systemic use; antiparasitic agents (endoparasiticides or endectocides); gastrointestinally active products, such as proton pump inhibitors; and products used for

euthanasia (hereafter “euthanasia”).[42,201] Gastrointestinal nutraceuticals were also included in the dispensed product analyses. Gastrointestinal nutraceuticalswere defined as products not listed as either authorised veterinary or human medicinal products, which contained a range of probiotics, prebiotics, and different kaolin formulations, which were dispensed with the purpose of assisting diarrhoea resolution.[42]

2.3.2. Statistical analyses

All analyses were carried out using R language (version 3.5.0). Descriptive proportions and associated 95% confidence intervals (95% CI) were calculated to adjust for clustering (bootstrap method, n=5,000 samples) within site, including a range of binary or categorical signalment, clinical sign, pharmaceutical agent prescription, and professional advice variables. Median and range were calculated for continuous variables. Following descriptive analyses, Univariable and multivariable mixed effects logistic regression models were fitted separately using the R package ‘lme4’ to model on a case-level the outcome variable ‘presence of systemic antimicrobial prescription’ against a number of categorical risk factors and one continuous variable was considered (age). Likelihood ratio tests (LRT), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), were used to examine presence of clustering within veterinary practice or site, and were subsequently included in each constructed model as random effects according to whether each individually, or both combined provided best fit.

Initial univariable mixed effects logistic regression considered categorical factors related to animal signalment (insurance status, vaccination status and neutered status) or questionnaire responses (consultation episode; faecal bacteriology/parasitology diagnostic testing; presence of diarrhoea and vomiting, including haemorrhagic and non-haemorrhagic; duration of the illness; and case severity). Considering case severity, due to a low number of severe cases, such cases were merged with moderate cases into a single category. For the continuous variable age, up to cubic polynomial terms were included if an LRT, AIC and BIC indicated significantly improved fit, compared to linear and lesser polynomial terms. The projected antimicrobial prescription probability and associated 95% confidence intervals were calculated from log odds using ‘sjPlot’. Explanatory variables were retained for multivariable analysis if an LRT indicated $P \leq 0.20$ against a null model. Multivariable models underwent manual step-wise backward elimination to minimise AIC and BIC. Confounding was accounted for via assessment of effect variation upon removal of variables. Two-way interaction terms between other explanatory variables were assessed via AIC, BIC and an LRT. The Variance Inflation Factor (VIF) was used to assess multicollinearity. Statistical significance was defined as $P<0.05$.

2.4. Results

2.4.1. Study population

A total of 29,140 EHRs were associated with a GI MPC and had a questionnaire completed, of which 26,988 fitted the gastrointestinal case definition (dog or cat, presenting diarrhoea and/or vomiting). EHRs containing a likely incorrect date of birth were removed (age range included for dogs: 0 to 29 years old; age range considered for cats: 0 to 38 years old), as were EHRs where spurious (multiple) questionnaire answers were given on the questions related with disease severity (e.g. answered mild, moderate and severe), episode of illness (e.g. answered first presentation, revisit and don't know) and duration of illness (e.g. responded up to two days and one month and over). Consequently, 23,337 GI consultations, collected from 225 volunteer veterinary practices (502 sites) were included in analyses. Of these retained consultations, 18,829 (80.7%) were canine GI consultations and 4,508 (19.1%) were feline GI consultations. Consultations were henceforth considered by species (canine and feline) for statistical analyses.

In canine GI consultations, 51.8% were recorded as male (95% CI, 51.0-52.6), and 48.2% were recorded as female (95% CI, 47.3-49.1). Overall, 26.7% of the dogs were insured (95% CI, 24.9-28.5), 68.1% were neutered (95% CI, 67.0-69.3). Additionally, 55.7% of the dogs were microchipped (95% CI, 54.1-57.3), and 75.2% has been vaccinated within the preceding 3.5 years (95% CI, 73.9-76.6). Median canine age was 5.1 years (rage 0.0-19.4).

In feline GI consultations, 50.5% were recorded as male (95% CI, 49.0-52.0), and 49.5% were recorded as female (95% CI, 48,0-51.1). Additionally, 18.0% of the cats were insured (95% CI, 16.1-19.8), 82.0% were neutered (95% CI, 80.5-83.4). Overall, 39.8% of the cats were microchipped (95% CI, 37.8% and 41.8%), and 59.2% has been vaccinated within the preceding 3.5 years (95% CI, 57.3-61.1). Median feline age was 7.8 years (rage 0.0-23.0).

2.4.2. Descriptive analyses

The majority of both canine and feline GI consultations were recorded as first visit consultations, representing 74.1% of canine consultations (95% CI, 73.0-75.1) and 66.1% of feline consultations (95% CI, 64.3-67.9). Most GI presentations were recorded as mild, in 83,4% of canine presentations (95% CI, 82.6-84.3), and 81.6% of feline presentations (95% CI, 80.3-82.9). Correspondingly, the most frequently reported clinical signs were non-haemorrhagic diarrhoea and non-haemorrhagic vomiting, followed by haemorrhagic diarrhoea in both canine and feline GI consultations (Table 1). Most of feline and canine GI presentations were of less than 2 days of duration (Table 2).

Table 1. Descriptive summary of reported clinical signs distributed by species.

	Dogs (*n* = 18,829 EHRs) % (95% CI) [a]	Cats (*n* = 4,508 EHRs) % (95% CI)
Clinical signs		
Non-haemorrhagic diarrhoea	47.9 (47.1-48.7)	44.9 (43.3-46.6)
Haemorrhagic diarrhoea	28.8 (28.1-29.5)	14.9 (13.9-16,0)
Non-haemorrhagic vomiting	43.0 (42.1-43.9)	49.4 (47.7-51.1)
Haemorrhagic vomiting	3.6 (3.3-3.8)	3.9 (3.3-4.5)
Poor appetite	13.3 (12.4-14.1)	11.8 (10.6-13.1)
Weight loss/fail to gain weight	3.4 (3.0-3.8)	10.0 (8.8-11.2)
Melaena	0.6 (0.5-0.8)	0.1 (0-0.3)
Other	1.8 (1.4-2.1)	1.9 (1.5-2.4)

[a] *Percentage of EHRs (95% confidence interval)*

Table 2. Descriptive summary of reported duration of GI presentation episode distributed by species.

	Dogs (*n* = 18,829 EHRs) % (95% CI) [a]	Cats (*n* = 4,508 EHRs) % (95% CI)
Duration		
≤ 2 days	53.7 (52.7-54.8)	40.1 (38.5-41.8)
≥ 3 days and < 2 weeks	35.6 (34.7-36.5)	32.9 (31.5-34.3)
≥ 2 weeks and < 1 month	3.9 (3.6-4.2)	7.3 (6.1-8.1)
≥ 1 month	6.2 (5.8-6.7)	18.8 (17.2-20.3)
Do not know	0.5 (0.4-0.6)	0.8 (0.6-1.1)

[a] *Percentage of EHRs (95% confidence interval)*

Diagnostic tests were uncommonly used (less than 13% of all diagnostic options for both canine and feline consultations), with faecal bacteriology and parasitology being used in only 7.9% of canine cases and in 7.8% of feline cases, as presented in Table 3. Dietary modification was the most commonly provided advice to dogs and cats owners (Table 4).

Table 3. Descriptive summary of diagnostic options distributed by species

	Dogs (*n* = 18,829 EHRs) % (95% CI) [a]	Cats (*n* = 4,508 EHRs) % (95% CI)
Diagnostic option		
Faecal bacteriology/parasitology	7.9 (7.1-8.7)	7.8 (6.8-8.7)
Faecal virology	0.2 (0.2-0.3)	0.2 (0.1-0.4)
Virus serology	0.1 (0.0-0.1)	0.3 (0.1-0.4)
Diagnostic Imaging	2.2 (2.0-2.5)	2.5 (2.1-3.0)
Haematology/Biochemistry	7.2 (6.7-7.7)	12.1 (10.8-13.3)
PLI (Specific Pancreatic Lipase)	2.1 (1.8-2.4)	2.8 (2.2-3.5)
Serum B12 and/or TLI	1.8 (1.6-2.1)	2.7 (2.1-3.3)
Urinalysis	0.6 (0.5-0.7)	1.3 (0.9-1.6)
Other	4.3 (3.8-4.8)	5.8 (4.8-6.7)

[a] *Percentage of EHRs (95% confidence interval)*

Table 4. Descriptive summary of reported advice given distributed by species.

	Dogs (*n* = 18,829 EHRs) % (95% CI) [a]	Cats (*n* = 4,508 EHRs) % (95% CI)
Advice		
Diet change	62.3 (60.5-64.0)	53.5 (51.3-55.7)
Check-up	25.3 (23.8-26.9)	29.4 (27.4-31.3)
Fast	12.4 (11.0-13.8)	5.3 (4.5-6.2)
Admit	3.1 (2.7-3.6)	3.1 (2.4-3.7)
Refer	0.3 (0.2-0.4)	0.5 (0.3-0.7)
Other	50.1 (48.2-52.1)	51.0 (48.9-53.1)

[a] *Percentage of EHRs (95% confidence interval)*

2.4.3. Pharmaceutical prescriptions and dispensing of nutraceutical products

Gastrointestinal active pharmaceutical products were prescribed in 40.4% of canine consultations and in 33.8% of feline consultations. In addition, systemic anti-inflammatories were prescribed in 9.8% of canine consultations, while in feline consultations systemic anti-inflammatories were prescribed in 16.8%. Moreover, endoparasiticides/endectocides were prescribed in 18.8% of canine presentations and in 19.1% of feline presentations. Interestingly, gastrointestinal nutraceuticals were commonly dispensed in canine consultations (41.7%), whereas in feline presentations, gastrointestinal nutraceuticals were less frequently dispensed (23.1%). Systemic antimicrobials were prescribed in 28.6% of canine consultations and in 22.4% of feline GI consultations. Overall, systemic HPCIA prescription was very low in canine presentations (0.9%) whereas in feline consultations, systemic HPCIA prescription occurred

in 5% of consults. Descriptive summary of pharmaceutical prescriptions and dispensing of nutraceutical products are presented in Table 5.

Metronidazole was the most commonly prescribed systemic antimicrobial in canine presentations (33.9% of antimicrobial prescribing canine cases), closely followed by clavulanic acid potentiated amoxicillin (33.1% of antimicrobial prescribing canine cases). Metronidazole combined with spiramycin, which belongs to the macrolide class, and therefore is considered a HPCIA, was the most commonly prescribed HPCIA formulation in canine consultations (5.6% of prescribing canine cases) followed by fluoroquinolones, which were prescribed in 1.4% of prescribing canine cases. In feline presentations, clavulanic acid potentiated amoxicillin represented the most commonly prescribed systemic antimicrobial (37.1% of antimicrobial prescribing cases). Third generation cephalosporins were the most commonly prescribed HPCIA in feline consultations (18.9% of antimicrobial prescribing in feline cases). Relative percentage of prescribed systemic antimicrobials are presented in Table 6.

Table 5. Descriptive summary of pharmaceutical prescriptions and dispensing of nutraceutical products distributed by species.

	Dogs (*n* = 18,829 EHRs)	**Cats (*n* = 4,508 EHRs)**
	% (95% CI) [a]	**% (95% CI)**
Therapy		
Gastrointestinal agent	40.4 (39.2-41.6)	33.8 (31.8-35.7)
Systemic antimicrobial	28.6 (26.9-30.3)	22.4 (20.4-24.4)
Systemic HPCIA	0.9 (0.4-1.3)	5.0 (4.1-5.9)
Systemic anti-inflammatory	9.8 (7.9-11.6)	16.8 (14.7-19.0)
Endoparasiticide and/or endectocide	18.8 (17.2-20.4)	19.1 (17.5-20.6)
Gastrointestinal nutraceutical	41.7 (39.9-43.5)	23.1 (21.5-24.7)
Euthanasia/death	0.2 (0.1-0.2)	0.3 (0.2-0.5)

[a] *Percentage of EHRs (95% confidence interval)*

Table 6. Relative percentage of pharmaceutical classes of systemic antimicrobials prescribed in canine and feline gastrointestinal consultations by species

	Dogs (*n* = 5,384 prescribing EHRs)	**Cats (*n* = 1,010 prescribing EHRs)**
	% prescription (95% CI) [a]	**% prescription (95% CI) [a]**
Systemic antimicrobial		
Amoxicillin	15.7 (11.5-19.8)	27.7 (23.1-32.3)
Other β-lactams [b]	0.1 (0-0.2)	-
1st generation Cephalosporin	0.3 (0.2-0.5)	-
2nd generation Cephalosporin	0.03 (0-0.08)	-
3rd generation Cephalosporin	0.5 (0.3-0.7)	19.0 (15.4-22.5)
Clavulanic acid potentiated amoxicillin	33.1 (29.9-36.2)	37.1 (32.8-41.3)
Penicillin	0.02 (0-0.05)	-
Metronidazole	33.9 (28.7-35.8)	5.4 (3.7-7.1)
Metronidazole and spiramycin (macrolide)	5.6 (3.3-8.0)	3.4 (1.9-5.0)
Macrolide (others)	0.9 (0.0-1.9)	0.8 (0.0-2.1)
Aminoglycoside	1.5 (1.14-1.8)	0.5 (0.07-0.9)
Amphenicol	0.2 (0.1-0.4)	0.3 (0-0.6)
Fluoroquinolone	1.4 (0.4-2.4)	1.1 (0.3-2.0)
Fusidic acid	3.0 (2.5-3.4)	2.4 (1.5-3.3)
Potentiated sulphonamide	0.8 (0.4-1.3)	0.09 (0.0-0.3)
Tetracycline	1.0 (0.5-1.5)	0.5 (0.1-0.9)
Clindamycin	0.3 (0.2-0.5)	0.8 (0-1.8)
Other Lincosamides	0.2 (0.0-0.3)	-
Other antimicrobial agents [c]	1.4 (0.4-2.5)	1.0 (0.1-2.0)

[a] *Percentage of total prescribing EHRs within antimicrobial group, 95% confidence interval*
[b] *Ampicillin and Cloxacillin*
[c] *Polymyxin b sulphate, mupirocin, novobiocin, thymol and bronopol*

2.4.4. Factors associated with systemic antimicrobial prescription

Univariable results are presented in Appendix Two, Table 11 for canine GI consultations, and Table 12 for feline GI consultations.

Results of multivariable mixed effect logistic regression models (Table 7 and 8) assessing the association between a number of categorical factors related to animal signalment, and questionnaire (Appendix One) responses and probability of systemic antimicrobial prescription, showed that in both species, presentations classified by the attending veterinary professional as moderate/severe were associated with significantly increased odds of systemic antimicrobial prescription when compared with mild GI presentations (canine GI presentations OR 1.85, 95% CI 1.65-2.07, p<0.001; feline GI presentations OR 2.03, 95% CI 1.68-2.46, p<0.001). In addition, the presence of diarrhoea, both non-haemorrhagic and haemorrhagic, were associated with significantly increased odds of systemic antimicrobial prescription when compared with the absence of diarrhoea in GI presentations. Particularly haemorrhagic diarrhoea was significantly associated with greatest odds of systemic antimicrobial prescription when compared with the absence of diarrhoea (canine GI presentations OR 4.22, 95% CI 3.80-4.68, p<0.001; feline GI presentations OR 3.05, 95% CI 2.44-3.82, p<0.001). GI presentations of between two weeks and one month of duration, and presentations of more than one month of duration were associated with significantly decreased odds of systemic antimicrobial prescription in both canine and feline GI consultations, compared with GI presentations of less than two days of duration. In canine GI consultations, presentations between three days and two weeks of duration were significantly associated with increased odds of systemic antimicrobial prescription.

In canine GI consultations, an interaction between consultation episode and severity provided best fit (Figure 4). Moderate/severe presentations were associated with decreased odds of systemic antimicrobial prescription in revisit consultations (OR 0.61; 95% CI, 0.50–0.73, p<0.001) when compared with first visit consultations. The predicted probability of systemic antimicrobial prescription for mild presentations in first visit GI consultations was approximately 13.2% (95% CI 11.7-14.9), similarly to mild presentations in revisit GI consultations where the predicted probability of systemic antimicrobial prescription was 13.0% (95% CI 11.3-15.0). Predicted probability of systemic antimicrobial prescription in moderate/severe presentations in first visit GI consultations was approximately 22.0% (95% CI, 19.2-24.9), whereas in moderate/severe presentations in revisit consultations, the predicted probability of systemic antimicrobial prescription was approximately 14.4% (95% CI 12.1-16.9) (Figure 3). In canine consultations, systemic antimicrobial prescription probability increased with age. A linear term provided the best fit for canine presentations (Figure 4).

Table 7. Results from a finalised multivariable mixed effects logistic regression model, modelling on a case-level the presence of systemic antimicrobial prescription against a series of risk factors in canine GI consultations.

Random effect	Variance	Standard Deviation	Variable	Category	β	SE [a]	OR [b]	Lower CI [c]	Upper CI	*P*
Practice	0.42	0.65		Intercept	-2.08	0.07	0.13	0.11	0.15	-
Site	0.19	0.43	**Consultation episode**	First visit			1.00	-	-	-
				Revisit	-0.15	0.05	0.99	0.89	1.09	0.76
			Severity	Mild	-	-	1.00	-	-	-
				Moderate/Severe	0.62	0.06	1.85	1.65	2.07	<0.001
			Diarrhoea	Absent	-	-	1.00	-	-	-
				Non-haemorrhagic	0.75	0.05	2.11	1.91	2.33	<0.001
				Haemorrhagic	1.44	0.05	4.22	3.80	4.68	<0.001
			Duration	≤ 2 days	-	-	1.00	-	-	-
				≥ 3 days and ≤ 2 weeks	0.14	0.04	1.15	1.07	1.24	<0.001
				> 2 weeks and < 1 month	-0.32	0.10	0.73	0.60	0.88	0.001
				≥ 1 month	-0.50	0.09	0.61	0.51	0.72	<0.001
				Do not know	-0.77	0.29	0.46	0.26	0.82	0.008
			Continuous factor							
			Age (years)	Age - linear	0.033	0.004	1.03	1.02	1.04	<0.001
			Interaction terms							
			Consultation episode : Severity	Revisit : Moderate/Severe	-0.50	0.097	0.61	0.50	0.73	<0.001

[a] Standard error

[b] Odds ratio

[c] 95% Confidence interval

Table 8. Results from a finalised multivariable mixed effects logistic regression model, modelling on a case-level the presence of systemic antimicrobial prescription against a series of risk factors in feline GI consultations.

Random effect	Variance	Standard Deviation	Variable	Category	β	SE [a]	OR [b]	Lower CI [c]	Upper CI	*P*
Practice	0.65	0.80		Intercept	-1.69	0.11	0.18	0.15	0.23	-
Site	0.23	0.48	**Severity**	Mild	-	-	1.00	-	-	-
				Moderate/Severe	0.71	0.10	2.03	1.68	2.46	<0.001
			Diarrhoea	Absent	-	-	1.00	-	-	-
				Non-haemorrhagic	0.57	0.09	1.77	1.48	2.11	<0.001
				Haemorrhagic	1.12	0.11	3.05	2.44	3.82	<0.001
			Duration	≤ 2 days	-	-	1.00	-	-	-
				≥ 3 days and ≤ 2 weeks	-0.12	0.09	0.89	0.75	1.06	0.199
				> 2 weeks and < 1 month	-0.72	0.17	0.49	0.35	0.68	<0.001
				≥ 1 month	-0.95	0.13	0.39	0.30	0.50	<0.001
				Do not know	-0.77	0.29	0.46	0.26	0.82	0.008

[a] Standard error

[b] Odds ratio

[c] 95% Confidence interval

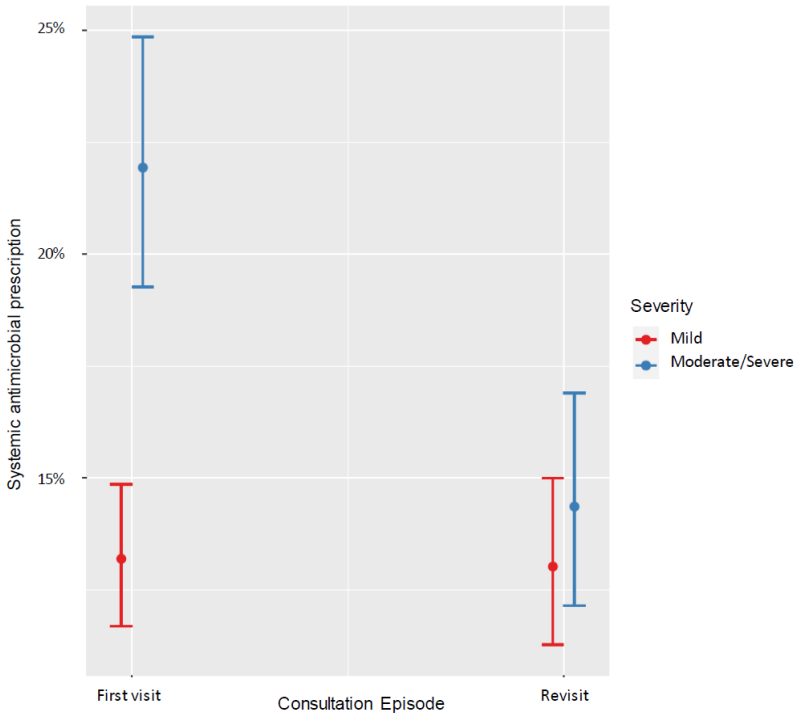

Figure 4. Results from a multivariable mixed effect logistic regression model, modelling predicted probability of systemic antimicrobial prescription in canine GI consultations, when an interaction between episode of consultation and severity is considered.

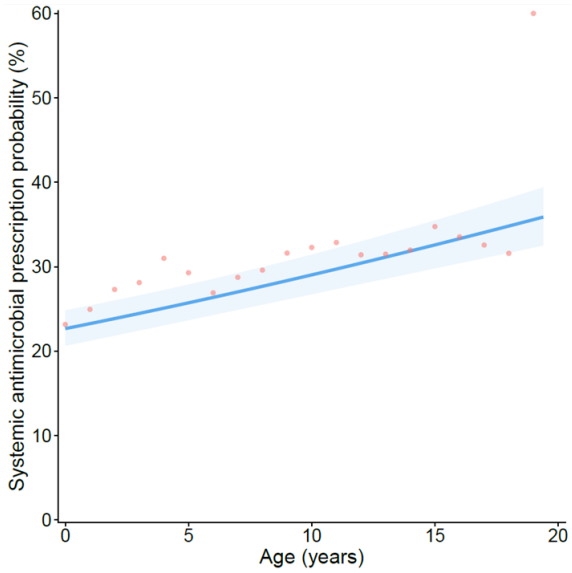

Figure 5. Projection of the probability of a systemic antimicrobial being prescribed in GI canine consultations, when considered against age at the consultation (in years). Line refers to predicted probability, with shading corresponding to 95% confidence interval. Points are plotted to show original data points expressing the percentage of consultations of each relevant age group (rounded to 0.5-year groups) in which were prescribed a systemic antimicrobial.

2.5. Discussion

The present study combined EHR-based data with structured questionnaire responses to profile canine and feline GI presentations, to describe common management and treatment strategies in GI veterinary consultations and to explore factors associated with systemic antimicrobial prescription in canine and feline GI consultations in veterinary primary care in the UK. Most veterinary-assessed cases were considered mild in severity, and the most commonly reported clinical signs were non-haemorrhagic diarrhoea and non-haemorrhagic vomiting. Mild nature in GI presentations and non-haemorrhagic vomiting and diarrhoea are also commonly described in previous studies of diarrhoeic dogs and on surveillance reports on GI presentations in companion animals.[3,11,205,221] Thus, this study further confirmed our early findings that suggested GI clinical presentations are generally a predominantly mild condition in both dog and cat populations[42]

In our study, systemic antimicrobials were prescribed in 28.6% of canine consultations and in 22.4% of feline consultations, which is consistent with previous studies that indicate a higher proportion of systemic antimicrobial prescription in canine consultations compared with feline consultations. Nonetheless, systemic antimicrobial prescriptions were lower compared with previous findings, particularly in canine GI consultations (36.2% and 38.9% for canine GI consultations; 25.7% and 28.9% for feline GI consultations).[3,205] The most commonly prescribed systemic antimicrobial in feline consultations was clavulanic acid potentiated amoxicillin, and in canine consultations, it was metronidazole, which is consistent with previous findings.[3,205] It has been described that the frequent use of metronidazole in canine GI presentations may be associated with the concern of anaerobic bacterial species involvement, such as *Clostridium perfringens*, albeit its role in causing gastrointestinal disease has been under debate.[42,80] Moreover, according to practice level guidance on antimicrobial use, metronidazole is recommended only for chronic diarrhoea/enteropathy treatment alone after all other diagnostic options and empirical therapy possibilities have been exhausted.[10,42] Therefore, the frequent use of metronidazole in canine GI presentations identified here suggests limited compliance with published guidelines.

Although HPCIAs are recommended to be reserved for human use only,[23] systemic HPCIA prescription was found in both canine and feline consultations. A relevant difference in the proportion of systemic HPCIA prescription was found between canine and feline cases. While in canine consultations, HPCIA were used in less than one percent, in feline consultations, HPCIAs were prescribed in five percent of GI presentations, with frequent use of third generation cephalosporins (Table 6). Nonetheless, other HPCIAs were found to have low use in feline GI consultations, such as fluoroquinolones. This may reflect that veterinary professionals are to some extent aware of responsible use of HPCIA, however they might be restricted by available formulations that use third-generation cephalosporins as active

ingredient. Indeed, the wide use of long-acting injectable third-generation cephalosporins in cats is described, with previous studies identifying the type of preparation (long-acting, 14 days) and ease of administration (injectable) as factors underpinning the extensive use of this veterinary licensed antimicrobial formulation, particularly in animals non-compliant with oral medication at home, as is descriptive of many felines.[204,213] Third-generation cephalosporins are used as last alternative treatment of serious conditions with multi-resistant pathogens involved, and excessively extended antimicrobial usage can cause selective pressure in bacterial populations, hence increasing the risk of carriage of resistant bacteria.[23,213,222,223] For these reasons, and although a veterinary formulation of third-generation cephalosporin (cefovecin) is authorised for use in small animals in the UK, its use should be carefully considered and supported by adequate bacterial culture and antimicrobial susceptibility testing. Hence, our study identifies the use of third generation cephalosporins in feline patients as particularly worrying. Identifying common prescription practices allows us to promote the reduction of antimicrobial classes considered critically important, which is vital for effective antimicrobial stewardship.[191] Thus, considering a 'One Health' approach and leading towards coordinated and cautious antimicrobial use, both in veterinary and human medicine, the present study highlights the need to intervene within the veterinary sector to safely promote the reduction of HPCIA use, particularly third-generation cephalosporins in feline patients.

Diagnostic tests were infrequently used in both canine and feline consultations, with faecal bacteriology/parasitology being used in less than 8% of consultations in both populations. In feline consultations, the most common diagnostic option was haematology/biochemistry (12.1% of feline consultations). This low frequency of diagnostic testing in consultations classified as GI presentations is not a novel finding; indeed, different longitudinal surveillance studies have revealed proportions of the same order of magnitude as observed here.[199,205,221] The mild nature of the reported disease and the majority of first-visit consultations may be reflected in the infrequent use of diagnostic testing options in both sub-populations. Thus, it can be reasonably assumed that most antimicrobial prescriptions described in these GI consultations were empirical. It has been described that the decision-making process around antimicrobial prescription can encompass a multitude of complex factors.[213] Indeed, a veterinary professional when presented in practice with non-specific GI clinical signs may suspect an ongoing disease process in another organ or system, which with limited use of diagnostic testing might not be promptly identified, subsequently leading to empirical antimicrobial prescription. In addition, factors such as client expectation from past antimicrobial prescribing, the veterinary desire to alleviate client anxiety and maintain an appropriate client relationship and the owner's resistance in consenting to diagnostic options can also influence the behaviour of the veterinary professional, acting as barriers to appropriate antimicrobial prescribing behaviour.[213,214,224] Strategies for mitigating these barriers are warranted in practice, aiming to provide tools to veterinary professionals for an evidence-based clinical decision around antimicrobial prescription in GI cases.

Multivariable mixed-effects logistic regression models allowed for the investigation of risk factors associated with systemic antimicrobial prescription. Here, we found that the presence of non-haemorrhagic diarrhoea was significantly associated with increased odds of receiving a systemic antimicrobial prescription in both canine and feline GI consultations. Previous findings state that diarrhoea increased the probability that antimicrobials would be prescribed to companion animals.[3,8,11] This likely reflects a perception of bacterial agent involvement, and may be associated with concerns about missing an infection. Although antimicrobial therapy is recommended for specific GI presentations, such as granulomatosis colitis (GC) cases, this should represent a minority of cases.[140,141] Moreover, antimicrobial prescriptions may also reflect a perception that animals presenting with diarrhoea can lose mucosal barrier function, increasing bacterial sepsis risk.[11] Evidence of this perception might be displayed here, as haemorrhagic diarrhoea was associated with significantly increasing the odds of receiving a systemic antimicrobial prescription, as were veterinary professional-classified moderate/severe consultations.[42] Whilst clinical evidence and published practice level guidance has established that systemic antimicrobial prescription is essentially avoidable, even in patients presenting with haemorrhagic diarrhoea that are otherwise systemically well, it has been indicated that establishing a consistent definition of sepsis risk might be important for effective antimicrobial stewardship.[10,205,218,219,225]

In addition, when an interaction between episode of consultation and severity is considered, predicted probability of systemic antimicrobial prescription in canine GI consultations were higher for moderate/severe presentations in first visit consultations (22.0% predicted probability, 95% CI, 19.2-24.9). This may reflect the attempt to address clinical concerns around the involvement of infectious agents, when an animal is presented for the first time with a moderate/severe GI presentation.

The effect of the age of the animal on the probability of systemic antimicrobial prescription was significant in canine GI consultations. In dogs, the probability of systemic antimicrobial prescription consistently increased with age. Different factors can be associated with an increased probability of systemic antimicrobial prescription in older animals. In fact, factors such as the knowledge of infectious/non-infectious diseases and the age of the animal were identified as prescribing factors in a qualitative study that investigated factors influencing the decision-making of antimicrobial usage in first-opinion small animal practices, which took into account 21 semi-structured interviews from veterinarians of seven different small animal first-opinion practices.[213] In this study, seven interviewees considered selecting antimicrobials for therapy of non-infectious gastritis if they were in the presence of an elderly animal (e.g., one with a compromised immune system) or if the owners were ‘particularly worried’.[213] Nonetheless, it was not possible for our study to take into account concomitant conditions, which may be present in cases in elderly animals, and could, therefore, influence the decision-making process around antimicrobial prescription in such cases. In addition, when an

interaction between episode of consultation and severity is considered, predicted probability of systemic antimicrobial prescription in canine GI consultations were higher for moderate/severe presentations in first visit consultations (22.0% predicted probability, 95% CI, 19.2-24.9). This may reflect the attempt to address clinical concerns around the involvement of infectious agents, when an animal is presented for the first time with a moderate/severe GI presentation.

Gastrointestinal nutraceuticals were frequently dispensed, particularly in canine GI consultations, which complies with previous longitudinal studies on diarrhoeic dogs.[42,217] Indeed, a recent longitudinal study in dogs showed that a combination of dietary modification and gastroenteric nutraceuticals without the prescription of pharmaceutical agents, such as antimicrobials and anti-inflammatories, was associated with slightly improved odds of resolution of diarrhoeic clinical signs.[42] Despite recent studies advocating that probiotics might be useful in aiding the resolution of infectious, non-infectious or idiopathic diarrhoea in dogs, further work is warranted in companion animals to better understand the complex interaction between probiotics and their host environment, mechanism of action, and potential clinical impact.[27,48] Providing more evidence defending the use of nutraceuticals in companion animal GI cases may be useful to support the use of a 'no harm' therapeutic option over an antimicrobial prescription, ultimately contributing to antimicrobial stewardship. Indeed, it has been suggested that clinical management strategies in GI presentations are changing, and they may be becoming more reliant on GI nutraceuticals rather than systemic antimicrobial prescriptions, which might suggest increased awareness of veterinary professionals on current guidelines, thus reserving antimicrobial therapy for only GI clinical presentations exhibiting, or at a perceived increased risk of, bacteraemia or sepsis. Nevertheless, it has also been recognised that a prospective cohort study is needed to more definitively confirm the observed trends.[42]

The observational approach of this study is valuable to characterise the profile of GI presentations in dogs and cats, as well as to describe the diagnostic approach, management strategies in practice, and to explore risk factors regarding antimicrobial use in GI presentations. Previous pilot analyses on temporal trends of systemic antimicrobial prescription, have demonstrated a reduction in the frequency of systemic antimicrobial prescription in GI consultations, over a period of more than four years.[205] Nonetheless, further temporal analyses would be useful to further characterise temporal trends in systemic antimicrobial prescription in GI consultations, particularly considering HPCIA prescription and potential inputs on practice from recently updated and distributed guidelines.[10] In addition, observational spatial analyses have demonstrated regions of increased GI disease prevalence in the UK and seasonal variation, reaffirming the different pattern of presentation for GI disease and suggesting that the relative risk for GI disease varies spatially and seasonally, particularly in dogs.[199,205,221] Nevertheless, zones of increased GI disease prevalence might not reveal

outbreak events; for that reason, further strategies that SAVSNET is currently developing would allow outbreaks to be identified in the future.[205,221]

In this study, EHRs that had an associated questionnaire completed by veterinary professionals were included to allow for the characterisation of GI clinical presentations in dogs and cats. These mandatory structured questionnaires are automatic and randomly assigned to veterinary consultations classified by the attending veterinary professional as GI, using the MPC function of the SAVSNET window. This strategy aims to overcome issues related to the lack and/or variability of recorded details on the clinical narrative of EHRs, as previously described, but without introducing bias.[42] Nonetheless, this proportion of records represents only a small proportion of available consultations within the SAVSNET database. Gathering this complementary questionnaire data to the EHR-based data allowed for further characterisation of veterinary-assessed parameters, such as case severity, and appraisal of parameters, such as veterinary advice provided, or the diagnostic options used consistently. In addition, individual variation in case of severity definitions due to self-defined questionnaire responses is possible and may have led to an over-simplification of the clinical severity scoring used in this study. Nonetheless, it is worth mentioning that the evaluation of other parameters that could help to better define case severity, such as recorded body temperature, has challenges due to veterinary professionals failing to record clinical parameters within the EHRs, as previous studies have identified.[42] Future work would allow for the development of novel text mining strategies to better identify and follow cases, un-tapping a greater number of cases within the SAVSNET database.[42,226]

2.6. Conclusion

This study successfully combined EHR-based data with structured questionnaire responses to profile canine and feline GI presentations, and to explore factors associated with systemic antimicrobial prescription in canine and feline GI consultations in veterinary primary care in the UK. Antimicrobial prescription still represents a frequent management choice in canine and feline GI presentations whilst bacteriological and/or parasitological diagnostic test options are uncommonly used, thereby suggesting that the use of current prescribing guidance and clinical evidence may be suboptimal and is commonly contradicted by actual prescription practices.

Using veterinary health informatics data to characterise common clinical presentations, such as gastroenteric cases, and to better understand factors associated with systemic antimicrobial prescription as demonstrated here, allows for a greater understanding of prescription choices made in veterinary first opinion practice. Ultimately, this allows the identification of opportunities to safely reduce the misuse of antimicrobials in the companion animal veterinary sector. Therefore, efforts should be made in veterinary training and practice-level interventions to raise awareness of current prescribing guidelines and to comply with the necessary ‘One Health’ approach towards effective antimicrobial stewardship, which is ultimately part of the veterinary professional’s responsibility.

Chapter Three

Exploring the reasoning and justification around antimicrobial prescription in canine and feline gastrointestinal disease: A qualitative study using clinical narratives from Electronic Health Records.

3.1. Abstract

Systemic antimicrobial agents are frequently prescribed to companion animals with gastroenteric clinical signs. To date, qualitative approaches to investigate prescribing in gastrointestinal (GI) clinical presentations have been lacking. This study took a qualitative approach to the clinical narrative of canine and feline consultations, classified as GI clinical presentations aiming (i) to investigate the content of the clinical narrative of electronic health records (EHRs) classified as GI cases by the attending veterinary professional, identifying the extent of discussion around reasoning for antimicrobial prescription; and (ii) to identify reasoning and attitudes within the clinical narrative around Highest Priority Critically Important Antimicrobials (HPCIA) prescription.

The first stage of the study (n=200 EHRs) showed that content related with reasoning around antimicrobial prescription was infrequently present in the clinical narrative of the analysed dataset, when compared with the amount of coding related to other themes. In the second stage of the study, which included 516 EHRs of GI cases prescribed a HPCIA, nine extrinsic factors underpinning reasoning for HPCIA prescription emerged from the thematic analysis, namely: perceived compliance; owner's behaviour; perceived risk of infection; clinical signs; recent clinical history; perceived (positive) previous response to antimicrobial therapy; geriatric patients and euthanasia; concomitant conditions; and diagnostic testing. Additionally, one intrinsic factor was identified as indirectly shaping the decision-making process around HPCIA prescription, namely the perceived veterinary-client relationship.

This study represented a novel approach to analysis of the clinical narrative of canine and feline consultations, allowing investigation of the discussion around antimicrobial prescription in GI clinical presentations. By understanding the content recorded in the clinical narrative, we can better understand the behaviours, concerns and challenges that the veterinary surgeon can face during consultations around the decision-making process of antimicrobial prescription, which can ultimately contribute towards effective antimicrobial stewardship in the small animal veterinary setting.

3.2. Introduction

Systemic antimicrobials are frequently prescribed to companion animals with gastroenteric clinical signs. Indeed, a previous study using a sentinel population of small animal practices in the United Kingdom, indicated that 38.2 per cent of dogs and 28.9 per cent of cats, in consultations classified by the attending veterinary professionals as GI clinical presentations, were prescribed with a systemic antimicrobial agent.[3] In addition, across different main presenting complaints, HPCIA, as defined by the World Health Organisation (WHO)[23] were 5.4 per cent in dogs and 39.2 per cent in cats of total antimicrobial prescriptions.[3]

Different studies using quantitative methodologies and EHRs have been invaluable for investigating patterns of antimicrobial agent prescription in small animal practice, and establishing the profile of diarrhoea clinical presentations, including diagnostic approach and management choices. [3,11] Additionally, a recent study explored the clinical factors associated with the decision to prescribe pharmaceutical agents, including antimicrobials, to dogs presenting with acute diarrhoea, thus providing an insight into the therapeutic diversity in gastrointestinal cases.[42]

However, to date, qualitative approaches to investigate prescribing in gastrointestinal clinical presentations are lacking. A qualitative approach using analysis of EHRs of consultations classified as gastrointestinal clinical cases may be particularly useful to better understand the decision-making process around antimicrobial prescription, especially considering the known use of HPCIAs in feline and canine gastroenteric clinical cases. Furthermore, current published guidelines set a “zero target” on antimicrobial prescription for dogs and cats with acute GI signs that are otherwise systemically well, and more generally advise careful consideration before veterinary use of HPCIAs for any clinical condition.[10]

In 2009, a survey in the UK reported that only 3.5% of the respondents (n=473) indicated that their veterinary practice had guidelines for antimicrobial use.[227] More recently, in 2014, a different survey indicated a contrasting level of guidelines awareness, 45% of practices had available guidelines for antimicrobial use, and 92.4% of the participants affirming that they were aware of published guidelines.[228] In spite of this apparent temporal change, available evidence indicates that veterinary practitioners appear to have limited awareness of current recommendations for judicious antimicrobial use (AMU) and antimicrobial choices may be subjective, considering social norms, amongst other intrinsic and extrinsic factors.[213,229]

An extensive body of qualitative studies around antimicrobial resistance (AMR) and antimicrobial usage has been published, particularly in human healthcare.[207,230] In the veterinary setting, qualitative studies have been used to understand perceptions and beliefs around AMU and AMR in food-producing animals.[211,212,231] More recently, qualitative studies using in-depth interviews exploring drivers associated with antimicrobial prescribing and AMR in small animal practices have been published.[213–215,224]

Drivers associated with AMU were previously classified into intrinsic and extrinsic factors.[213] Intrinsic factors are those directly linked to the veterinarian, such as their knowledge of infectious diseases and appropriate antimicrobial prescribing. Extrinsic factors are those related with other "players", but which can also influence the decision-making process around antimicrobial prescription, such as the pet's owner, characteristics of the animal/clinical presentation (such as species, behaviour, and clinical signs), or the antimicrobial agent (such as formulation or route of administration).[213,214]

In fact, a previous study reported that knowledge of infectious diseases influenced the clinical assessment made by veterinary practitioners and consequently their antimicrobial selection, as reported by a third of participants.[213] However, different participants considered selecting antimicrobials for therapy of non-infectious gastritis if the patient was an elderly animal (e.g. compromised immune system) or if the owners were "particularly worried", showing that different drivers other than the clinical need of an antimicrobial can play an important role on antimicrobial prescribing behaviours. In this previous study, short-term antimicrobial therapeutic courses were frequently administered (*i.e.* 2–3 days) using long-acting injectable preparations.[213]

Compliance is defined as the extent to which the patient's behaviour matches the prescriber's recommendations.[232] Reduced compliance was reported in a wide range of veterinary therapeutic options, such as the administration of oral formulations to cats and aggressive animals; and topical optic preparations in dogs.[213] Therefore, to have owners compliant with therapy at home, veterinary practitioners in different studies identified the value of long-acting injectable antimicrobial preparations, particularly in cats, although the only currently authorised formulation uses a HPCIA as its active substance.[213,214] In a qualitative study by King C*. et al.*, veterinary practitioners were conflicted about whether the use of such long-acting antimicrobial products was likely to increase or decrease AMR.[214] Regardless of considerations around AMR, the impact of pharmaceutical factors (such as route of administration, and effect duration of the antimicrobial therapy) was well articulated.[214]

It was identified in previous studies that owners' desires for their companion animal to recover could, at times, override the appropriate prescribing of antimicrobials.[213,214,224] Thus, perceived pressure from animal owners can influence the decision-making process around antimicrobial prescription.[214] Indeed, in a different study, which explored drivers of AMR and pet owner and veterinary practitioners interactions, the participant veterinary practitioners revealed that prescription was perceived as a measurable, visible action taken for the health of the animal, while a lack of prescription meant nothing was being done to help the pet.[224] In contrast to the veterinary practitioners' perspectives, in the same study, interviewed pet owners, overall, denied that they would be disappointed if their pets were not prescribed antimicrobials. In this study, the majority of pet owners stated that they would follow the veterinarian's recommendations because they perceived veterinarians to have expertise in an area where they had little to no knowledge.[224]

In addition, costs of, and the willingness to pay for, treatment were also identified as being influential to a veterinary practitioner's decision around AMU.[214] In a recent Dutch study, veterinarians identified cases where owners refused or did not want to pay for any further diagnostic testing, which limited the veterinary practitioners' options to make appropriate diagnosis.[215] Accordingly, in a recent UK study, almost all of the interviewed veterinary surgeons talked about not using diagnostic testing as much as they felt that they should to inform their prescribing, and expressed desire to use such tests more frequently. However the barriers of cost and time often influenced their decision-making around use of diagnostic tests.[214]

In the five-year UK Governmental Action Plans for AMR, developing interventions is one of the highlighted topics aiming to enhance antimicrobial stewardship by small animal veterinary practitioners..[233] It has also been described that for promoting stewardship behaviours, it would be desirable to minimise key barriers and maximising enablers in practice. Therefore, it is vital to identify relevant behavioural domains and the current barriers and enablers around the intended veterinary behaviour, which subsequently help to design better and effective interventions to the small animal veterinary sector.[229]

Consequently, this study aimed to use the clinical narrative of companion animals' EHRs to better understand drivers around antimicrobial prescription, and to investigate whether veterinary surgeons use their clinical notes associated with EHRs to record their reasoning for antimicrobial prescribing in companion animals. A qualitative approach was used (i) to investigate the content of the clinical narrative of EHRs classified as GI cases by the attending veterinary professional, identifying the extent of discussion around reasoning for antimicrobial prescription; and (ii) to identify reasoning and attitudes within the clinical narrative around HPCIA prescription.

3.3. Methods

This study took a qualitative approach to the clinical narrative of canine and feline consultations, classified as gastrointestinal clinical presentations.

3.3.1. Data collection and study design

An original dataset compromising EHRs collected from 225 volunteer veterinary practices located in the United Kingdom, between 1st April 2014 and 30th September 2018, resulting from dog and cat consultations mainly presenting for investigation and/or treatment of gastrointestinal (GI) disease. The Main Present Complaint (MPC) classifier function of the SAVSNET window, completed by the attending veterinary professional, was used to define such cases.[199] Cases were additionally required to have had a short questionnaire answered (Appendix 1) by the attending veterinary professional. Episode of illness in relation to the consultation had to be clearly defined by the attending veterinary professional in the questionnaire (*i.e.* only one option selected to define the consultation as 'first visit'; 'revisit/check-up'; or 'don't know').

The qualitative study was designed in two stages. In the stage 1, a sample of 200 EHRs from the initial dataset from canine and feline consultations were randomly selected according to three levels of antimicrobial prescription, namely: HPCIA-prescription (n=66), non-HPCIA prescription (n=66), and no-antimicrobial prescription (n=68).

Subsequently, a second stage of the study was conducted, which included all EHRs (including those from the original dataset), compromising canine and feline GI consultations where an HPCIA agent was prescribed (n=516).

3.3.2. Thematic data analysis

Anonymised clinical narratives were transferred into NVivo 12 (QSR) software for data management. A thematic approach was utilised.[234] Although thematic analysis is largely used in qualitative research, its approaches can be diverse and variable..[210,235,236] Hence, to ensure consistency of data analysis the six-phase approach to thematic analysis as defined by Braun & Clarke was adopted.[210] This approach has been extensively used and accepted as being robust across an extensive variety of disciplines, including human health research and previous studies regarding veterinary antimicrobial usage.[209,211,213]

A theoretical approach to thematic analysis was adopted in both stages of the study. In stage 1, the theoretical approach to thematic analysis was motivated by the standard structure of a generic veterinary consultation (*i.e.* categories such as clinical history, clinical examination, differential diagnosis, diagnostic testing, treatment plan, and advice given) and by the presence of content related to antimicrobial prescription. This initial coding process included all the content of each clinical narrative, regardless of the prescription of antimicrobials and/or HPCIAs. These initial codes were categorised into potential themes. Subsequently, the coded data extracts within each identified theme were reviewed and collated to detail the level of information, forming minor themes where relevant. In the second phase of the coding process, data extracts related with antimicrobial prescription were reviewed and coded, considering a theoretical approach motivated by previously published qualitative studies regarding drivers of AMU and AMR in the small animal veterinary set.[213,214,224,229] Thus, themes underpinning antimicrobial prescription and around reasoning for HPCIA prescription were collated.

Rigour in the analysis was ensured by a member of the supervisory team, who read a subset of EHRs and reviewed the coding map and emerging codes in both stages of the study. Divergences in coding, interpretation of findings and/or emerging themes were discussed and adjusted accordingly to reflect on the importance of the themes to the research questions.[237] Themes were subsequently refined to guarantee that each was meaningful and clear but distinct from other themes.[238] Minor themes were defined as associated by a communal topic, or which associated to an overall topic were gathered together, that were linked by a common topic area, or which related to an overall topic were grouped together, assuming a unique theme title and therefore accounted as major themes. Eventually, a thematic map was created

to review and summarise the relationships between minor and major themes around reasoning for antimicrobial prescription at the Stage 2 of the study.

3.4. Results

3.4.1. Study population

Stage 1 comprised a total of 200 randomly selected EHRs, where canine consultations represented 65.5% (131/200) of the dataset, and feline consultations represented 34.5% (69/200) of the dataset.

In the Stage 2, a randomly selected dataset of 516 EHRs of canine and feline patients which were prescribed with a HPCIA were considered. Feline consultations represented 64.7% (334/516) and canine consultations represented 35.3% (182/516) of total HPCIA-prescribing EHRs (n=516). Different HPCIA classes were prescribed in feline and canine consultations, hird generation cephalosporins where prescribed in 92.8% (n=310/334) of feline HPCIA-prescribing consultations and in 20.9% (n=38/182) of canine HPCIA-prescribing consultations. Fluoroquinolones were prescribed in 4.5% (n=15/334) of feline HPCIA-prescribing consultations and in 47.8% (n=87/182) of canine HPCIA-prescribing consultations. Macrolides were prescribed in only 2.7% (n=9/334) of feline HPCIA-prescribing consultations and in 31.3% (n=57/182) of canine HPCIA-prescribing consultations.

3.4.2. Thematic analysis of the clinical narrative of gastrointestinal presentations consultations: Stage 1

In the stage 1 of the study, the whole clinical narrative of each EHR was coded according to the standard structure of a veterinary consult, alongside coding reasoning underpinning antimicrobial prescription, allowing not only investigation of the general content of GI consultations, but also the extent of discussion and content around reasoning for antimicrobial prescription (Table 9). Using the amount of coding per theme arising from the narrative it was possible to infer which themes the veterinary professionals dedicate more content to in their clinical notes. The theme with the most coding was Clinical History, followed by the themes Treatment & Previous Drugs; Advice & Next Visit, and by Clinical Examination. Less coding was found associated with Diagnostic Testing, Differential Diagnosis and Owner-related Information. Content related with reasoning around antimicrobial prescription was infrequently present in the clinical narrative of the analysed dataset, when compared with the amount of coding of the other themes (Figure 6). Justification or reasoning related content was only found in 34.1% (45/132) of clinical narratives that had associated antimicrobial prescription (HPCIA-prescription and non-HPCIA prescription).

Table 9. Coding themes resulting from the thematic analysis of the 200 clinical narratives of 200 EHRs classified as gastrointestinal consults (Stage 1).

Coding themes
1. Owner-related information
2. Clinical History
2.1. Diarrhoea (positive)
2.2. Vomiting (positive)
3. Clinical Examination
4. Diagnostic Testing
4.1. Testing advised
4.2. Testing completed
5. Differential Diagnosis
6. Treatment & Previous Drugs
6.1. Antimicrobial Prescription
6.1.1. Reasoning-related
a) Perceived risk of infection (pyrexia and other clinical signs)
b) Perceived compliance
c) Animal's clinical history (duration of illness and others)
d) Attitudes of Pets' Owners
e) Perceived (good) previous response to Antimicrobials
f) No prescribing due to awareness for responsible usage
6.2. Nutraceuticals
6.3. Other Pharmaceutical Agents
6.1.2. Behaviour in trying Antimicrobials
7. Advice & Next Visit
7.1. Diet
8. Without clinical narrative
9. Excluded clinical narratives

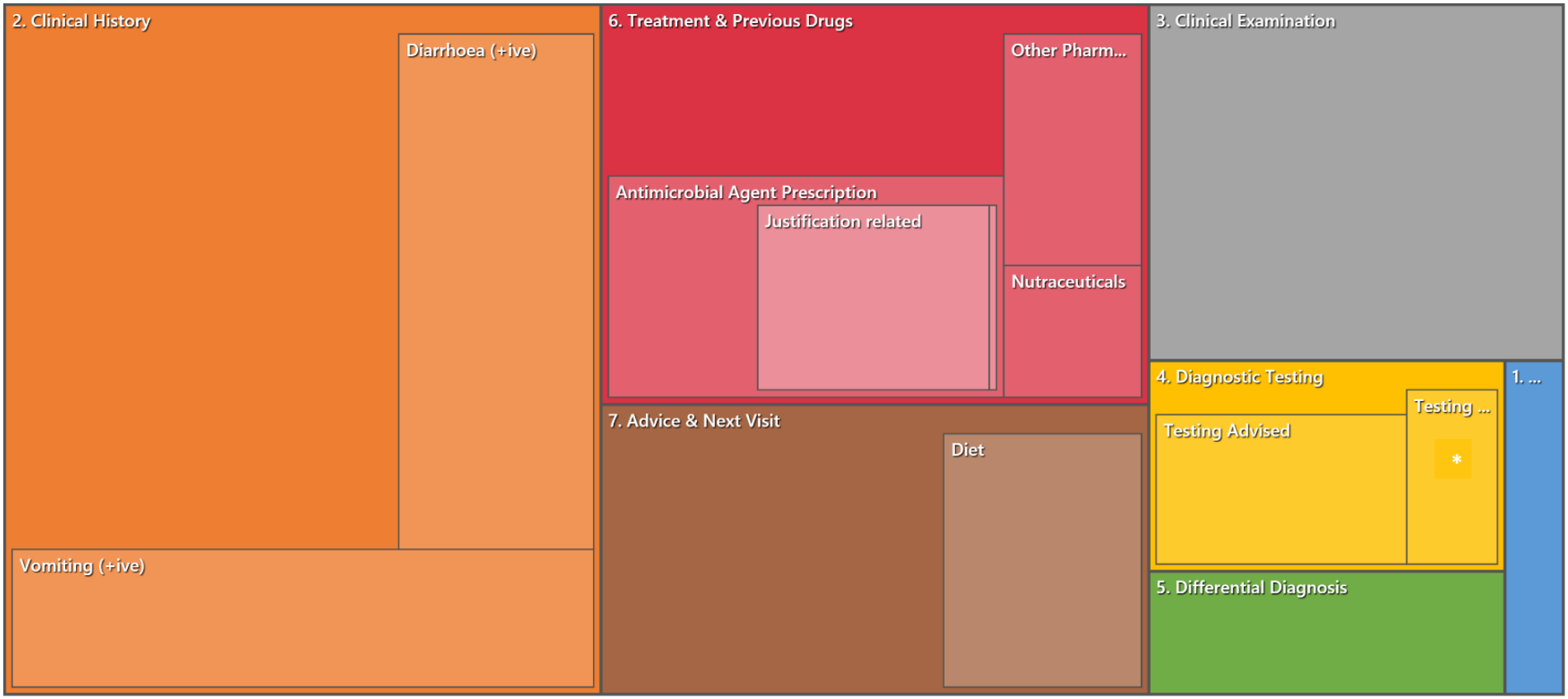

Figure 6. Hierarchy chart demonstrating the major themes and minor themes identified in the thematic analysis and the proportion of coding per each major and minor theme identified. Stage 1 (n=200 EHRs) (generated with NVivo© 12 QSR).
Notes: 1 - Owner-related information; *Testing Done

3.4.3. Factors underpinning reasoning for HPCIA antimicrobial prescription

Thematic analysis revealed ten major themes that were identified underpinning reasoning around HPCIA prescription within the 516 clinical narratives of feline and canine GI consultations where a HPCIA was prescribed. Major themes are shown in Table 10 and the thematic map (Figure 7) demonstrates the relationship between minor and major themes underpinning justification around HPCIA prescription. Quotes illustrating themes were directly extracted from the clinical narratives, with the anonymised consultation identification number (ID) and the species of the animal given between square brackets. When a typographical error is present in the quote, the correct spelling is presented after the misspelled word between square brackets. A list of abbreviations and clinical acronyms found throughout the clinical quotes is presented in Appendix Three.

Table 10. Identified intrinsic and extrinsic factors around reasoning for HPCIA antimicrobial prescription in 516 clinical narratives of GI consults.

Extrinsic factors (related with the owner, animal, or the antimicrobial therapy/formulation)	**Intrinsic factors** (related with the veterinary professional)
1. Perceived compliance **2.** Owner's behaviour: Decision-maker pressure and expectations **3.** Perceived risk of infection **4.** Clinical signs **5.** Recent clinical history **6.** Perceived (positive) previous response to antimicrobial therapy **7.** Geriatric patients and Euthanasia **8.** Concomitant conditions **9.** Diagnostic testing	**10.** Perceived veterinarian-client relationship

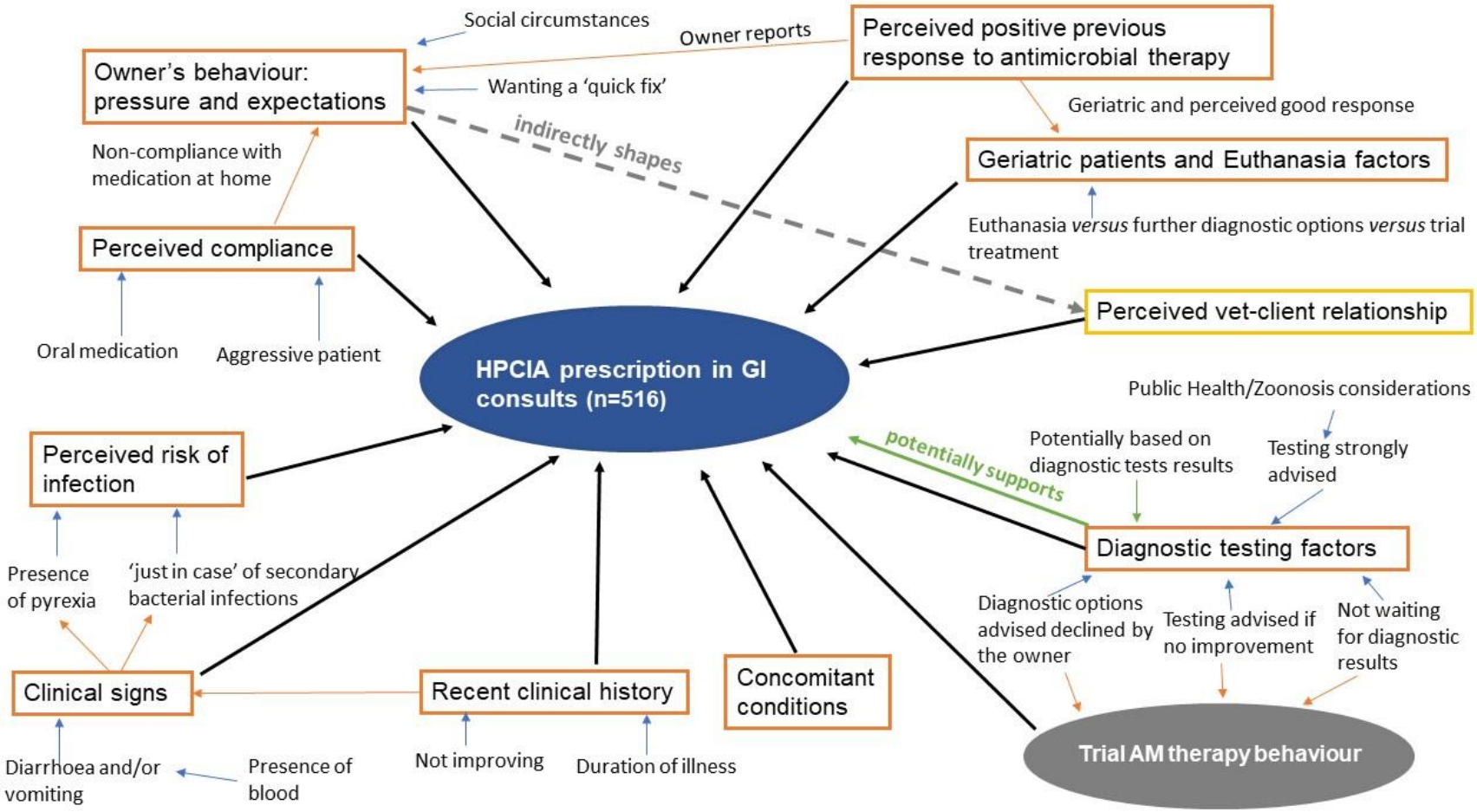

Figure 7. Thematic map demonstrating the relationship between minor and major themes around HPCIA antimicrobial prescription, resulting from the thematic analysis of 516 clinical narratives.
Notes: extrinsic factors are identified in orange boxes. The one intrinsic factor is identified in a yellow box. Behavioural trend identified in dark grey circle

3.4.3.1. Perceived compliance

Compliance is defined as the extent to which the behaviour of patients matches the prescribed recommendation.[232] Perceived animal compliance was frequently identified by veterinary professionals in the clinical narrative around antimicrobial prescription, commonly associated with expected owner difficulties with oral medication administration in feline and aggressive patients, although non-compliance with oral medication was also identified in dogs.

'leaking watery D+ on bed. dirty botton [bottom]. (…) owner unable to pill so given convenia' [ID 572650, feline]

'Dog not compliant for oral medication at home. Very little appetite and still passing mucoid diarrhoea.' [ID 849343, dog]

'As <<name>> is hard to handle (caretaker will have problem with tablets) and there maybe a problem to bring her in tomorrow I am givin [giving] her convenia.' [ID 4570886, cat]

Moreover, perceived ability or willingness of the owner to administer antimicrobial therapy was identified through the clinical narratives as influencing the antimicrobial formulation selected, and therefore, the substance. In some cases, the veterinary professional explicitly stated changing their first-choice antimicrobial based on perceived compliance. Thus, justification to change from a first line antimicrobial agent to a HPCIA was intrinsically linked with perceived owner compliance or ability, and the owner behaviour/pressure.

'Could not tablet, offered clavapet to be crushed but O preferred to try convenia.' [ID 881098, feline]

'O would be unable to give penicillin course orally so convenia injected' [ID 3251478, canine]

'O have not managed Synulox at all so offered CONVENIA instead.' [ID 3123584, cat]

3.4.3.2. Owner's behaviour: decision-maker pressure and expectations

Commonly recorded in the clinical narratives were contents of discussion about diagnostic testing and further investigation where the owner had declined this option, which lead the practitioner to prescribe a medical treatment empirically, including antimicrobial therapy.

'Discussed further investigation (feaces sample+bloods-FIV,FeLV+xray) vs treatment. O. elected 2nd option by now and will see after Christmas.' [ID 291923, cat]

Distinct pressure reasons were identified in the clinical narrative, potentially shaping prescribing behaviour. These included pressure by the owner related to non-compliance with oral medication administration at home, and the inability or unwillingness to pay for further investigations.

'The owner has money problems and <<identifier>> is not insurred [insured]. I offer the option of giving AB (no good with tablets so Convenia seems like only option) (…) The owner is aware that we are treating blind and that we may not be able to help her as much as we could because we do not know what the real problem is.' [ID 1489353, cat]

'Continuing problem with vomiting. (…) Ideally we would investigate eg BT, UA, scan/xray abdo etc. Unfortunately costs an issue so we have decided to postpone euth and try meds.' [ID 639391, cat]

'owner does not want cat to be put through a lot of diagniostics [diagnostics] etc and lots of treatmnent [treatment] at home eg tablets. (…) plan to trail [trial] antibiotics (convenia so owner does not have to give tablets at home)' [ID 3960188, cat]

Moreover, there was perceived expectation of pet owners on the outcome of the veterinary clinical consult (e.g. "quick fix" of the animal's condition), which can be conflicting with the intent of the veterinary professional. Occasionally, owners' social circumstances appeared to indirectly influence the outcome of the consultation and drive antimicrobial prescription (e.g.: owner going on holidays, therefore antimicrobial prescription happened).

'o's going away for 2 weeks tomorrow so advise cover ab's' [ID 348447, cat]

'O going on hols tomorrow for 5d, advised will give ab today, RV with f/s if no improvement.' [ID 2184052, cat]

In addition, owners' previous positive experience with antimicrobial therapy was identified in narratives, as pressure on the veterinary professional to prescribe the same antimicrobial agent.

'recheck re d+. No further v. D++ still, light brown, no blood/straining. O said only time really improved was after convenia injection prev!! (…) O keen to try convenia again but warned may not help/could make d+ worse. (…) bloods/faecal sample but o declined this for now.' [ID 935909, dog, female]

'Ddx gastroenteritis - could be same cause as last time - offered bloods and further testing i.e. scanning - owner declined. Would like to trial previous treatment initially at home but aware may need to come in again - given one off cerenia and course of marbocyl and omeprazole.' [ID 1328552, dog]

Owner pressure resulting from a combination of causes, such as owner's social circumstances, wanting a 'quick fix' of the animal's condition, together with previous perceived positive experience with antimicrobial therapy was encountered. In some clinical narratives,

the veterinary professional expressed that the decision in prescribing an antimicrobial agent was against his/her intent of action, yielding to the owner's expectations.

'O going away on Monday so wants to get sorted. (…) offered bloods but O would rather try treating first - if no better by tomorrow then recheck and would advise bloods + IVFT if dog has become dehydrated. Other dog had a bout of this recently and O felt that she only improved with Abs so wanted me to give convenia. Did explain that gastroenteritis is often viral but she still wanted Abs.' [ID 4202133, dog]

3.4.3.3. Perceived risk of infection

The perceived risk of infection was a common influence on prescribing an antimicrobial, often associated with the presence of pyrexia.

'Plan - given pyrexia I have given Convenia.' [ID 819187, cat]

'Ddx: GE (infxn), IBD, neoplasia, hepatopathy, GI parasitism. cover w/ abx as pyrexic' [ID 1278404, cat]

'This evening both episodes came with some fresh blood in the vomit and directly after. (…) Has muild [mild] pyrexia so susp infectious cause leading to oesophagitis or pharyngitis. Plan Abs' [ID 3998583, cat]

'temp 39.5. otherwise nad on clinical exam. suspect colitis? discussed could be due to stress/change of diet whilst in cattery? could be bacterial infection? given marbocyl injection and advised course of antirobe' [ID 389609, cat]

'nad on clinical exam. suspect viral? can trial on antibiotics in case there's any secondary' infection?' [ID 394387, cat]

'temperature 39, checked twice. Abdominal palpation limited. Gave convenia to cover possible infections...' [ID 547447, cat]

'T 39.2. P: Ab course as T slightly high and no stressed.' [ID 4838152, cat, female]

Some veterinary professionals expressed apparent doubts about the aetiology of the pyrexia and/or the need to prescribe antimicrobials (e.g.: *'could be bacterial infection?'*; *'can trial on antibiotics in case there's any secondary' infection?'*).

'cover convenia as precaution.' [ID 827378, cat]

'Antibs in case bact component.' [ID 959600, cat]

In one clinical narrative, the veterinary professional justified antimicrobial prescription with the perception associated with the perceived risk of bacterial translocation in the gastrointestinal tract, implying a possible intestinal mucosal compromise and/or an infectious process involvement in the GI clinical presentation.

'convenia (to reduce risk of bacterial translocation)' [ID 3480096, cat]

3.4.3.4. Clinical signs

The prescription of an antimicrobial agent was also justified in association with other clinical signs that the animal presented with, including diarrhoea. This justification could be associated with the belief that antimicrobials can empirically help to alleviate clinical signs in diarrhoea cases, which may be indirectly related with the perceived risk of infection, and it can additionally underline the assumption that the presence of blood in diarrhoea or vomiting make the clinical signs more severe and therefore antimicrobial prescription potentially beneficial.

'diarrhoea 2 days, definitely some with blood this am, no vom, still (…) As blood given abios. T 38.4' [ID 1046791, cat]

'and convenia for diarrhoea.' [ID 494854, cat]

'*Convenia given as mild high temperature and blood in faces.'* [ID 1575408, cat]

'probind and convenia.to clear up diarrhoea.' [ID 5067161, cat]

3.4.3.5. Recent Clinical History

Factors related with the recent clinical history, such as the duration of the clinical signs were also given as justification for antimicrobial prescription, such as illustrated below.

'Since has been going on a while advise cover with Abs also.' [ID 317835, cat]

'Given duration of signs I have decided to start Baytril.' [ID 878687, cat]

The end of a previously prescribed antimicrobial therapy associated with recurrence of GI clinical signs, also prompted antimicrobial prescription a second time, regardless of further diagnostic testing advised by the veterinary professional. In some cases, faecal sampling was accepted by the owner, however it is clear that antimicrobial prescription happened before results of the diagnostic test results, therefore resulting in empirical antimicrobial therapy.

'so advise f+ sample but treat in meantime.' [ID 532355, dog]

'D+ recurred soon after end of AB's (…) initially prolonged ab course if recurs despite this will require further investigation' [ID 1518459, dog]

'?appetite reduced since stopping omeprazole and baytril, send home back on trip antibiotics' [ID 5111356, dog]

'still ongoing diarrhoea and dripping fresh blood. (…) still waiting for faecal sample.' [ID 509315, dog]

3.4.3.6. Perceived positive previous response to antimicrobial therapy

In different clinical narratives from dogs and cats that were prescribed a HPCIA, veterinary professionals mentioned previous response to antimicrobial therapy, explicitly affirming a perceived positive response to a previous antimicrobial therapy. This previous response may also be used by the owner as an attempt to compel the veterinary professional to prescribe an antimicrobial agent, thus linking to owner pressure.

'History of D+ and good response to antibiotics all the way back to 2012.' [ID 829312, cat]

'Has improved w/ antibiotics, so seven days more' [ID 139734, cat]

'Vomiting + and off food is a bit depressed and does this every so often sometimes quick recovery and other times like 2014 slow TREATMENT PLAN. 1/ injection convenia / dexf low dose as worked before.' [ID 555881, cat]

3.4.3.7. Geriatric Patients and Euthanasia

A link between geriatric patients and euthanasia and underpinning HPCIA antimicrobial prescription was also uncovered. In one clinical narrative, the geriatric condition of the patient, together with a perceived positive response to previous antimicrobial therapies in GI clinical presentations of the patient underpinned antimicrobial prescription in that consultation.

'V+/D+. Often has episodes of gastroeneteritis [gastroenteritis] (…) O takes her to a differemnt [different] vets where she usually responds to cernia [cerenia] and convenia. This time she has v+ 2-3 times and also has d+. No blood in d+. (…) Is an old girl and as has recurrent episodes that are ab responsive given convenia as well today.' [ID 2979128, dog]

Additionally, the geriatric condition of patients was mentioned and linked with the possibility of euthanasia. Frequently, concomitant conditions were mentioned, and antimicrobial prescription was perceived as an empirical medical treatment, to reduce the perceived risk of infection, in cases where the owner declines further investigation or whilst the owner considers treatment options, or euthanasia. Thus, in this context, antimicrobial usage appeared to be an empirical treatment approach in either trying to postpone euthanasia or waiting for a decision.

'Continuing problem with vomiting. (…) She is polydipsic but has been for years and has been investigated for this. (…) Ideally we would investigate eg BT, UA, scan/xray abdo etc. Unfortunately costs an issue so we have decided to postpone euth and try meds.' [ID 630391, cat]

'Various issues (…) had some d+. Lost 0.5kg. (…) O not sure whether time to euthanasia or no. Cat seems bright and comfortable. Discuss full workup, bloods, imaging wvt bladder surgery, O not keen. Opt for medical manage with antibiotics and nsaid for now, O aware palliative.' [ID 1341013, cat]

'Re/ex - GI Issues. (…) Has lost further weight (40g) and still d+ which owner is noting in garden. (…) Recommended repeat abdo ultrasound today to reassess small bowel and look

for fluid but owner declines. As had been vomiting quite severely prior to the last vitbee injection, advise convenia to reduce risk of e.coli reflux into b.duct, p.duct and some concerns about feel of abdo. (…) O considering put to sleep if not improving.' [ID 1526856, cat]

'weight loss and soft f+ with blood. owner reports has been gradually losing weight. was v+ regularly (…) owner does not want cat to be put through a lot of diagnostics etc and lots of treatmnent [treatment] at home eg tablets. owner is starting to think that cat could need to be put to sleep (…) plan to trail [trial] antibiotics (convenia so owner does not have to give tablets at home). (…) if no improvement then owner may wish to put to sleep rather than do diagnostics/further meds.' [ID 3960188, cat]

3.4.3.8. Concomitant conditions

Concomitant conditions were commonly mentioned in the clinical narrative of GI consultations, which combined with other factors may influence the prescription of antimicrobial agents. In the majority of narratives, it was difficult to establish which clinical signs predominantly led to antimicrobial prescription. Nonetheless, the existence of other clinical signs or concomitant conditions (e.g., dermatitis) often resulted in empirical HPCIA prescription, with advice for further investigation in case of no improvement or recurrence.

"Liquid faeces for 2d. (…) Clinical exam unremarkable except peri-anal dermatitis. (…) Antibs given for both GIT and skin - would have preferred metronid for GIT but cat will not take oral meds. Recheck by 48h if no better or sooner if worsening or other signs eg vomiting." [ID 2845333, cat]

'sick thursday and friday last week and runny diarrhoea (…) o noticed blood in urine once last time (…) Has had urine crystals before so cannt [cannot] rule out but sounds like general infection Start antibiotics rx 5 days If urination worse phone us asap and try to get a urine sample.' [ID 2533734, dog]

'Recheck right ear (…) Colitis signs (…) frequent passage of small vols of faeces for last month. Temp normal today 38.5 but mucus on thermometer. Treat pro-bind and antibiotics.' [ID 3251478, canine]

'd+ (yellow and watery) (…) skin bad again especially shoulders; seems irritated by it - looks like superficial dermatitis again. from history had similar episode in July this year. (…) start antibiotics (mainly for skin), bland food. owner not been able to get tablets into her recently' [ID 2325500, dog]

3.4.3.9. Diagnostic testing

Clinical narratives mentioning diagnostic testing, such as haematology, imaging (ultrasound) and bacterial culture were identified. When diagnostic testing options were mentioned, they

were often related to advising faecal sampling in the near future, with HPCIA prescription happening in the current consultation. Thus, HPCIAs were prescribed before any faecal culture results were available. This included clinical narratives where the veterinary professional clearly stated that the antimicrobial therapy might be adjusted considering faecal culture results. In one clinical record, the slow turnaround of results is mentioned implying justification for starting antimicrobial therapy empirically. Moreover, Public Health considerations regarding concerns about zoonotic agents were identified in two narratives.

'Presented as still d+ watery and frequent and now v+ again. (…) Poss inf, recommend f+ sample but results are slow so start meds in meantime.' [ID 3698681, cat]

"Re/ex - Anal Glands and Recurrent D+++. Non-resolving diarrhoea now - mucoid, tenesmus and unable to hold overnight. (…) No antirobe as this may promote loose motions, so metronidazole and baytril at least 14 days. O also has d++ and is has been on meds that have dropped her WBC - STRONGLY advised a faecal analysis to r/o zoonotic causes (campylobacter/salmonella)." [ID 839561, dog]

'Gets an odd motion every few months in her crate overnight -always runny, brown without blood, slight mucus, lasts for two or three nights. (…) In light of the faecal results, start a three-week course of a/b. ADVICE: Request three faecal samples on three consecutive days for pooling in two weeks.' [ID 3220616, canine]

Only three clinical narratives mentioned previous results from faecal samples that could potentially have led to appropriate antimicrobial prescription, albeit exact sensitivity results from Antimicrobial Susceptibility Testing (AST) were not mentioned in the clinical narrative, therefore in most cases it was not possible to conclude that the bacterial culture results/mentioned pathogen(s) supported the HPCIA prescription or whether the prescription was in agreement with current guidelines.

'Recheck colitis. Prelim results isospora/Clostridia/Camp. (…) treatment as young [young] children & immunosupressed [immunosuppressed] adult in household as a precaution. Adv cannot say if pathogenic strain.' [ID 162130, dog]

'DAIRRHOEA [DIARRHOEA], WELL IN SELF. (…) Pro-bind to help restore the flora. Asked for bringing a faecal sample (comprehensive Faecal) for testing again to see if Cryptosporidium still on. NOTE: O is advanced pregnant and it's a zoonotic disease. Warned O about this.' [ID 4838152, cat]

'Recheck d+. 2 month history of v+d+ with weight loss. (…) Various investigations done so far: - low albumin (14) on 24th October. Low cholesterol too. - B12 low, TLI normal, folate normal. – 'Camp identified in f+ 2 weeks ago. - renal enzymes normal 1w ago. - liver enzymes normal 1 w ago. - radiographs didn't show any Fb/intussusception (…) Main remaining differentials are inflammation, lymphangiecastasia [lymphangiectasia], neoplasia. (…) Tx now with

erythromycin. Unlikely that campy causing problems but dog has d+ and campy so needs tx.' [ID 2384442, dog]

'Well in self but stools getting loose again can be on ywllow [yellow] end no mucus. (…) Been off tylan about a month so probably best to restart this once collected [collected] faecal samples. (…) Send faecal off for analysis to <<identifier>> - collect 3 samples and send to be pooled. Start tylan after collected.' [ID 1380692, dog]

Diagnostic results from imaging (ultrasound) and haematology were mentioned with discussion around differential diagnosis, however exact sensitivity results from AST were not mentioned in these clinical narratives, hence these appeared to lead to empirical antimicrobial prescription. Perceived risk of infection was also identified as a driver underpinning HPCIA prescription when diagnostic testing results were mentioned in the clinical narrative.

'still same and bloods indicate either infection/inflammation/neoplasia will send off for electriophoresis [electrophoresis] and treat in meantimne [meantime].' [ID 28509, cat]

"3 days with metronidazole, and concenia [convenia] due to v high wbc , ? coccy cysts ? incidental or immunocompromised ? poss chk felv status' [ID 368591, cat]

'Bloods suggestive of bacterial overgrowth or a shunt, therefore admitted for ultrasound investigation. Full scan - NORMAL renal size, NORMAL Liver size. (…) Pancreas normal. Intestinal content fluid, therefore suggests chronic malabsorption/bacterial overgrowth, therefore started treatment for this.' [consult ID 122039, dog]

'has had diarrhoea repeatedly over the w/e. bg 6mmol. scanned abd=nsf. injection for infection.' [ID 393749, cat]

3.4.3.10. Perceived Veterinarian-Client relationship

Particularly in clinical narratives where owner pressure was found, there was often additional narrative potentially highlighting a complex interaction between pet owners and the attending veterinarians, regarding the use of diagnostics, the treatment choices and the owner's expectations. In some cases, these pressures and expectations on the veterinarian's decision-making process around antimicrobial prescription, seemed to play a role on the veterinarian's clinical approach to the GI case.

'Discussed blood test and did adv FPLi quite strongly. For now O wants symptomatic. Must recheck tomorrow if not 100% for bloods+FPli in house. O understands this' [ID 1064693, cat]

'O did not want to do bloods, wanted quick fix before goes away at weekend, cannot give tabs so wanted injections. Was going to trial mtz but instead gave injection convenia' [ID 352216, cat]

'adv a number of ddx. plan: adv bloods, o prefer to trial tx first as responded to ab previously. [I was] not keen to give ab but as has improved previously and o reluctant to investigate felt was best to cover' [ID 892045, dog]

These examples not only illustrate the owner's pressure in the clinical decision-making process of the veterinary professional, but also the veterinarian's behaviour in matching to the client expectation (e.g. owner wanting a 'quick' fix and injections, therefore prescribing accordingly) without any further record of discussion with the owner about the true clinical need and relevance of implementing an antimicrobial therapy. This reveals that the pressure from the owner can shape the veterinarian-client interaction, with the veterinary professional yielding to the owner's expectations, in order to keep the client satisfied, even when the decision for prescribing is against his/her clinical judgement, or when the veterinarian would prefer other options to be implemented.

3.4.4. Behaviour associated with Antimicrobial Usage: Trialling antimicrobial therapy first

A common behavioural trend apparently led by the veterinary professional, was to implement an empirical therapy, prescribing antimicrobials as a first line treatment. Veterinary professionals often recorded advising faecal sampling if the introduced therapy failed to solve the clinical signs associated with the gastrointestinal presentation. This is in contrast with cases where pressure to prescribe antimicrobials seemed to come from the owner, despite the veterinary professional recommending other options.

"O reports frequent V+ with quantities of blood. (…) Adv medical tx for now, given cerenia and conveinia [convenia] to try to see if improves, adv re-ex tomorrow.' [ID 3549345, cat]

'Responded to metronidazole but now recurred. (…) Plan 10 days course erythromycin but submit faecal sample if not resolved by end, or recurs a third time.' [ID 63702, dog]

'Start erythromycin and asses response before anything else done. Then prob repeat vom profile to assess the liver and Ca+ and prob another faecal sample before referral .' [ID 1018004, dog]

'V+, not eating much for the last three days. This morning has been sick 5 times, bile content. (…) Treatment support for gastroenteritis. Inj of antbs, ranitidine and cerenia given. Disc if still sick or deteriorates for the next hours to bring her back for further investigation.' [ID 1133239, cat]'

'v+. o reports been v+ after eating over past 24/48 hrs. (…) possible gastroenteritis ? given convenia injection. (…) if doesn't settle or v+ reoccurs phone and may take bloods.' [ID 303831, cat]

'D+ for last week or so. (…) As in good condition at the moment ok to try symptomatical [symptomatic] treatment for now, advise if no improvement in 3-4 days to come back, sooner if any deterioration. In any of those cases warned lady might need blood test owner faecal sample as old boy now and something else could be causing D+. Lady unsure about tableting him so conv injection given. (…) Lady happy with plan' [ID 2126815, cat]

'Weight loss - was plump. Diarrhoea. Both signs only noticed in the last few days. (…)Tx as non-specific diarrhoea but may be MUCH more serious so come back in a few days if not improving quickly. Light diet - ow will feed cooked fish.' [ID 1309596, cat]

'CHRONIC DIARRHOEA. Diarrhoea been going on for a few months now. (…) Advised owner no obvious cause on clinical exam. differential diagnosis - infectious, ibd, liver, neoplasia (not high on list currently). Plan – can't tablet so convenia given and pro-bind. If no response owner will bring in faecal sample to determine if infectious, if not infectious can rule out and consider B12 injections. If infectious treat appropriately.' [ID 2412818, cat]

3.5. Discussion

This structured qualitative study represented a new approach to EHRs and to the clinical narrative of canine and feline consultations, allowing investigation of the discussion around antimicrobial prescription in gastrointestinal clinical presentations. Here, we found that content underpinning reasoning for antimicrobial prescription is infrequently recorded in the clinical narrative of feline and canine GI consultations, when compared with other themes approached in a standard veterinary consult (e.g. physical exam, clinical history). Nonetheless, the thematic analysis of the clinical narrative of canine and feline GI consultations where a HPCIA was prescribed suggested a number of important themes underpinning reasoning behaviours around antimicrobial prescription, including a novel insight about prescribing behaviour and postponing euthanasia. Further qualitative approaches, such as in-depth interviews to veterinary practitioners and owners, about HPCIA prescription in canine and feline GI presentations would allow further exploration of the themes identified in this study. Moreover, ethnographic observational methodologies could be beneficial to explore in-depth veterinary GI consultations.

In this study, perceived compliance was a justification particularly around the choice of HPCIA prescription in GI clinical presentations. Perceived compliance related to different circumstances, namely non-compliance by the owner and/or the animal with oral medication at home, or with aggressive and/or difficult to handle patients. HPCIA prescription was commonly justified based on non-compliance with oral medication at home in feline consultations, though was also identified in canine consultations. Indeed, this study supports previous findings, as poor compliance has been reported in the administration of oral medication to cats and aggressive animals, in long-term therapies and in therapies with higher dosing frequencies.[213] A common finding reported in a previous qualitative study was the use of long-acting third generation cephalosporins to treat common clinical presentations in cats.

Most of the veterinary participants mentioned that they were more likely to use long-acting injectable preparations with owners that were not able to administer oral medication at home to ensure that animals would complete the therapeuthic.[213] In fact, in a recent study using EHRs to describe the use of cefovecin, a third-generation long-acting injectable antimicrobial, in a UK population of cats attending first-opinion practices, the most cited reason for prescribing cefovecin over alternative antimicrobials was inability to orally medicate cats.[204]

Indeed, considering the use of a long-acting injectable third-generation cephalosporin preparation, veterinary participants in a qualitative study reported that the marketing of this pharmaceutical product was seen as an opportunity to address the challenges around the administration of antimicrobial agents. [214] This currently appears to be influencing prescribing behaviour towards HPCIA in the absence of other long-acting formulations being authorised for use in cats in the UK. Moreover, veterinary participants on this study were conflicted about whether the use of this pharmaceutical product was likely to increase or decrease AMR[214], despite recently published evidence demonstrating an association between third-generation cephalosporin use and increased risk of detection of AmpC-producing faecal *Escherichia coli*.[239] Irrespective of the nature of the impact on AMR, the influence of compliance and this pharmaceutical formulation on prescribing behaviours was articulated by veterinarian participants in this qualitative study.[214]

It seems issues relating to owner compliance do not just apply to cats but likely to dogs as well. In a previous study with dog owners, compliance was estimated to be higher for short-term oral antimicrobial therapies with dosing frequencies of one to two times a day, compared to long-term therapies and higher dosing frequencies.[240] It was reported that to deal with non-compliance, veterinary practitioners should consider changing their first-choice antimicrobial agent.[213] In the present study, the perceived ability and/or preparedness of the owner to administer antimicrobial oral therapy in dogs influenced the antimicrobial formulation selected, and therefore, the substance. As with cats, this is likely driving the prescription of a HPCIA instead of a first-line antimicrobial in some canine cases.

In the present study, the owner's behaviour manifested by recorded evidence of pressure and expectations was also identified as an important factor around prescription. Examples included wanting a 'quick fix' of the animal's condition, declining diagnostic options, social circumstances such as going on holidays, or difficulty affording further clinical investigations. However, these may not be drivers specific to HPCIA prescription but of prescribing any antimicrobial. Further analysis is warranted to assess if similar themes are recorded in clinical narratives associated with non-HPCIA-prescribing consultations. Veterinary practitioners from a previous qualitative study affirmed feeling pressure from owners to prescribe antimicrobials during consultations, although most veterinary practitioners attested that they did not yield to owner's expectation. Nonetheless, if the owner expressed inability or unwillingness to pay, veterinary practitioners affirmed they would consider changing their first choice of substance.[213]

It was described in a previous study that if pet owners reported previous negative experiences with antimicrobials associated with adverse reactions, the veterinary practitioner was less likely to select the same substance again.[213] Moreover, another recent study, which explored the drivers of AMR amongst pet owners and veterinary practitioners also described the extent of perceived owner's influence on the decision-making around antimicrobial prescription, which was dependent on distinct factors beyond the appropriate use of an antimicrobial.[224] These related to clinical need, such as previous experiences with receiving antimicrobials for their pets, ease of treatment administration, and the expectation of active treatment. It was commonly reported by veterinary practitioners that they prescribe 'just in case' in response to the perceptions of client anxiety about their pet's health and welfare.[224]

Here, owners' reporting a previous positive experience with a specific antimicrobial therapy with a HPCIA was perceived as pressure by the veterinary professional to prescribe the same antimicrobial agent previously used. Owner pressure is complex and may result from a combination of causes, which may lead to behaviour in some circumstances against the veterinary practitioners intent of action based on beliefs, scientific knowledge, training, or current guidelines.[213,214,224] This behaviour was expressed by veterinary professionals in the clinical narrative. Attending veterinary professionals reflected on the actual need for antimicrobial therapy, sometimes considering differential diagnoses that might not need antimicrobial therapy and describing that the HPCIA prescription was in fact empirical (e.g., *'felt was best to cover'*) or recognising that owner expectation and pressure for a certain antimicrobial therapy had eventually influenced their prescribing behaviour (e.g. *'O felt that she only improved with Abs so wanted me to give convenia'*)..

In a recent qualitative study that explored interactions between veterinary practitioners and pet owners, dissonance between the pet owner and veterinarian was reported between their perceptions of where the accountability/responsibility around antimicrobial prescription and use should be..[224] Although pet owners were shown to be aware of negative consequences of inappropriate antimicrobial use, the study reported low levels of knowledge and understanding of AMR and interspecies transmission between pet owners..[224] This identified lack of knowledge has the potential to limit antimicrobial stewardship. Nonetheless, pet owners considered veterinary practitioners as being essentially responsible for prescribing decisions, attaching accountability to their professional know-how; they did not report having extraordinary expectations of receiving antimicrobial prescription.[224] In this previous qualitative study, veterinary practitioners attributed over-prescribing to the complexity of different drivers, such as the perceived client satisfaction, commercial pressures to retain clients, and the symbolic value of giving treatment. Indeed, in a recently published expert consensus, barriers associated with the owners were perceived to be the veterinarian's belief that their clients both expected and wanted to receive antimicrobials, and would go elsewhere if they were not prescribed them, in addition to the lack of sufficient time in a consultation for client education.[224,229] Our study supports this perception that pet owners sometimes expect to

receive antimicrobial prescription for their pet, and it was clearly articulated by some attending veterinary professionals in the clinical narrative. Interestingly, this perceived pressure to prescribe an antimicrobial agent is also described in the literature exploring prescribing behaviours of medical doctors and registered nurses, with a survey of 1000 UK general practitioners, reporting that 90 per cent felt pressure from patients to prescribe antimicrobials.[241,242]

Thus, veterinary practitioners should be trained and supported in communication and managing client expectations around antimicrobial use.[224,229] Any attempt to change behaviours of veterinary practitioners will need support from clients; therefore, it has been highlighted that interventions designed for veterinary practitioners should be run simultaneously with complementary interventions for owners. Involving pet owners in antimicrobial stewardship has been described as essential to facilitate more effective and dynamic interactions between veterinary practitioners and owners around appropriate antimicrobial prescription.[224] It has been described in the literature that if negative consequences of over-prescription were outlined on the interventions in terms of side effects for the animal (diminished future efficacy of antimicrobial agents) it might be particularly effective.[224] In this regard, interventions destined to increase self-efficacy and pro-activeness of pet owners by teaching skills to participate in consultations might be useful. Nonetheless, there are some possible barriers reported in the literature to enhancing antimicrobial stewardship.[213,224,229] Research in other areas has shown that awareness *per se* is insufficient to modify individual behaviours[243], particularly for topics such as AMR, which are multifaceted and seen to have a relatively distant and vague risk.[224]

Thus, standardised guidelines and protocols could help pet owners and veterinary professionals to better manage their interactions. It has been suggested coinciding with the development of guidelines, mandatory legislation could be developed. Nonetheless, this type of measure would be dependent on political will and identifying appropriate bodies to legislate and implement these procedures.[224] Additionally, it has been highlighted that standardisation and regulation of prescribing could be rejected by veterinary practitioners, perceiving these as potential impositions on their autonomy and management approaches.[244] In addition, pharmaceutical companies can also play an important role related to the type of products they develop and commercialise, particularly when considering HPCIA importance and antimicrobial stewardship. In this regard, national and international regulatory bodies of pharmaceutical industry could also potentially play a more active role in promoting and establishing regulatory standards, for antimicrobial formulations where HPCIAs, and/or CIAs identified by WHO are the active substance of a proposed pharmaceutical formulation. This could include standards not only on the antimicrobial agent used, but also on the type of formulation and availability of the pharmaceutical product (wider availability versus reserved use: to use when appropriately documented and justified).

To address the particular challenges identified in this study, training sessions and webinars could be developed to teach the owner to administer oral therapy at home, particularly in feline patients. Training in managing canine and feline behaviour and stress could also be useful to overcome the issues around perceived compliance, which often shapes a justification around HPCIA prescription, due to its formulation characteristics (injectable and long-acting). Thus, veterinary professionals should have an active role in educating pet owners to comply with prescribed therapy in order to reduce the occurrence of therapeutic failure and potentially AMR.[204,213,245]

The perceived risk of infection often associated with the presence of pyrexia was one of the main recorded factors to justify prescribing HPCIAs in feline and canine GI consultations. Indeed, previous studies have reported the presence of pyrexia, perceived as an indicator of infection, can influence antimicrobial prescription, both in companion animals and in human medicine, in a different set of clinical conditions.[213,246] Nonetheless, pyrexia can be non-bacterial in origin, being observed in animals with viral, parasitic, mycotic, immune-mediated, neoplastic, or metabolic conditions, as well as sometimes being idiopathic. Indeed it can also occur due to antimicrobial therapy itself.[247] Mitigation of the perceived risk of secondary infection and the behaviour of 'cover with antimicrobials just in case' were captured in several clinical narratives. This behaviour was previously described[224] as a key driver of inappropriate prescribing related with feelings of fear of missing an infection that could have negative consequences for both the animal and for the professional reputation of the veterinary practitioner. Although veterinary surgeons seem aware of AMR, the fear of not diagnosing/missing an infection could still act as an over-riding pressure on their antimicrobial prescribing behaviour.[214] Other clinical signs, such as haematochezia, haematemesis, and the presence of diarrhoea itself, were identified as content around justification for prescribing in the clinical narrative. Considering the myriad of different and non-specific clinical signs that an animal can present, the veterinary practitioner cannot always exclude infection outside the GI tract (e.g., biliary tract: kidneys), especially considering the low uptake of complementary diagnostic tests, even when the veterinary practitioner advises for further investigation and options are declined by the owner, as identified in several narratives. Ultimately, this set of circumstances can also underpin antimicrobial prescription, when suspicion of associated infection outside the GI tract is present, however not confirmed.

In addition, it was possible to identify in one clinical narrative antimicrobial prescription clearly associated with perceived risk of bacterial translocation across the gastrointestinal tract. In haemorrhagic gastroenteritis, the presence of blood in the faeces might reflect a breach of intestinal integrity.[248] This has been identified as the reason of different authors advising empirical prophylactic antimicrobial use in such patients.[248] In parvoviral enteritis it is described that intestinal tract damage secondary to viral infection increases the risk of bacterial translocation, and subsequently the risk of coliform septicaemia, which may cause a systemic inflammatory response that can subsequently progress to septic shock and, ultimately,

death.[38] Nonetheless, whilst bacterial translocation in veterinary patients has been documented, further studies are needed to establish its specific role and mechanisms in critical illness and in the development of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS).[37] Moreover, further studies are necessary to investigate the existence of bacterial translocation and whether these patients are at an increased risk for septic complications.[37] Additionally, recent evidence showed no difference in the incidence of bacterial translocation, and no improvement in several parameters, including disease severity indices, laboratory parameters, length of hospitalisation, or mortality rates between patients with acute haemorrhagic diarrhoea receiving amoxicillin-clavulanic acid versus placebo.[219,248] Thus, the use of antimicrobials had no effect on bacterial translocation when compared with placebo.[37] Moreover, antimicrobial use has also been shown to induce translocation from native commensal bacteria and promote an inflammatory response.[37,39] In addition, metronidazole should be prescribed carefully, with a recent report highlighting a decrease in aerobic and anaerobic bacterial duodenal populations in healthy cats, with the emergence of *Streptococcus* and *Corynebacterium*, thus modifying intestinal commensal flora.[37,41]

As well as perceived compliance, perceived risk of infection, or with the behaviour of the owner in establishing pressure for AMU, we also identified circumstances related to the recent clinical history including duration or recurrence of clinical signs as justification for antimicrobial prescription. Concomitant conditions were also found to be linked to justification for antimicrobial usage. However, in the majority of these clinical narratives it was difficult to establish which clinical signs predominantly led to antimicrobial prescription. In addition, the geriatric condition of patients and decision making around euthanasia also appeared to sometimes result in an empirical treatment approach in trying to postpone euthanasia.

Public Health concerns regarding zoonotic infections were identified in two clinical narratives, illustrating the role of the veterinarian in advising the owner and raising awareness regarding the importance of appropriate diagnostic testing, with impact both on the individual patient and on human health. In addition, it would have been ideal if information related with diet were recorded within the clinical narrative, especially in cases where suspicion of involvement of zoonotic bacterial and/or parasitic agents was described. Indeed, raw meat-based diets have become gradually more popular as a diet choice for both dogs and cats[73,249] and a variety of concerns have been raised regarding raw meat-based feeding practices, with potential implications to both animal and human health. These include the potential risk of presenting antimicrobial-resistant bacteria, considering that raw meat-based diets often fall below standard hygiene thresholds for Enterobacteriaceae, which are frequently implicated in antimicrobial resistance to HPCIA, such as third-generation cephalosporins, thus increasing the risk of shedding such resistant bacteria.[73] Different zoonotic bacterial agents have been identified in commercially available raw meat-based diets, including ESBL *Escherichia coli*,

Salmonella species, *Listeria monocytogenes*, and zoonotic parasitic agents such as *Toxoplasma gondii*.[74]

In the present study, the behaviour of prescribing an empirical antimicrobial therapy without results of further diagnostic testing was a common theme throughout the analysis. Such AMU seemed to occur frequently without any recorded evidence of this being based on pressure from the owner, suggesting that sometimes antimicrobial therapy was a primary clinical approach to a case presenting with gastrointestinal signs. However, the absence of content in the clinical narrative of other factors underpinning this behaviour, such as pressure from the owner, does not necessarily mean that the veterinary professional did not offer diagnostic options during the consultation or that the owner did not influence the veterinary decision. It may be the case that information related to the owner's pressure and/or expectations, and related to the decision-making process together with the owner was not recorded in the clinical narrative.

Indeed, one limitation of an approach such as this is the reliance in the clinical narratives itself. Clearly, for any action in the consulting room, there are three possible states – did not happen in the consult; happened but it was not recorded; or happened and it was recorded. Best practice using EHRs would lead to significant events and decision-making processes around these always being recorded in the clinical narrative. Due to the current significance of HPCIA prescription, particularly for effective antimicrobial stewardship, we would argue that this information regarding antimicrobial prescription and the reasoning underpinning should always be recorded within the clinical narrative. This assumes particular importance where it is not possible for the same veterinary professional to see an animal at follow-up visits such that practitioners have to rely on the written recorded clinical narrative. In addition, it appears from this study that narratives are sometimes incomplete regarding the decision-making process around HPCIA prescription. Nonetheless, it is unclear if this is due to lack of consideration or lack of recording.

To analyse these data in this study, a six-phase thematic analysis approach as defined by Braun & Clarke was adopted, focused on the overall descriptive analysis of the process of interest and providing an interpretation of the findings in the context of current scientific evidence.[210] Previous studies around AMR and AMU in the small animal veterinary setting have used qualitative research and thematic analysis in the context of in-depth interviews both with veterinary practitioners and pet owners aiming to explore intrinsic and extrinsic factors around antimicrobial resistance and usage.[213–215,224] The findings of this study supported most of the pre-defined themes based on current scientific literature. Moreover, these analyses allowed the identification of different themes inherent to the clinical context in which HPCIA's are prescribed, such as a link between postponing euthanasia as reasoning to prescribe antimicrobials, in this case, HPCIA. Associations as such might not easily emerge in interview-based studies, where the veterinary practitioner is not in the moment of the decision-making, and therefore has to reflect in different clinical circumstances to provide context, potentially

not approaching in-depth challenging clinical decisions, or pressure from owners. This feature is a strength of this study, as it allowed better understanding of the clinical context of pre-established and new factors that are used by veterinary professionals to underpin HPCIA prescription decisions in feline and canine gastrointestinal clinical presentations (Figure 3).

The present study allowed analyses of what the veterinary professional effectively recorded in EHRs at the time of the decision-making process around antimicrobial prescription, revealing consultation-level content that may not have emerged in a different qualitative research setting, such as in a semi-structured interview context. Nonetheless, in-depth interviews are likely to be a robust and complementary qualitative methodology to better understand the drivers around small animal veterinary AMU, to explore intrinsic factors, and take into account the professional experience of small animal veterinary practitioners. This would allow exploration of themes such as workplace factors, influence of staff and relationship between senior and junior veterinary practitioners around AMU, and to better understand the vet-client relationship from the veterinarian perspective. Thus, a limitation of this study is the decreased possibility to explore intrinsic factors in depth such as social norms established in the workplace. Social norms are defined as rules that govern ordinary or non-contractual interactions among members of a community,[250] and in this context of AMU could be represented by verbal protocols for prescription agreed between colleagues. Therefore, the resultant themes are limited to the information recorded in the clinical narrative, which *per se* is self-limiting to explore undertones, or to take into account existing knowledge around AMR and current guidelines, or verbal protocols in place.

Observational research, using for example an ethnographic approach for in-depth observation of interactions in consultations, could be beneficial to complement this study, allowing the collection of impressions in a systematic and purposeful way to learn about a phenomenon of interest[251] in the clinical context. This would give complementary insight into the subtleties of client pressure and the veterinarian-client communication process, it would allow investigation of factors, circumstances, and discussion around antimicrobial prescription with pet owners that effectively happen in small animal veterinary consultations, and it would allow better understanding of the extent to which these are reflected in the clinical narrative content. This approach could also be useful to gain more knowledge around the intrinsic factors that could act as barriers for appropriate prescribing behaviour in a veterinary practice environment, such as social norms in the work environment and business perception. In addition, further qualitative approaches to clinical narratives of other common clinical presentations where antimicrobials are frequently used, such as in respiratory presentations, could be beneficial to validate common themes around AMU reasoning in different clinical presentations using EHRs.

Although the stage 1 of the study (n=200) encompassed clinical narratives including a 'no-antimicrobial prescription' dataset, no themes emerged around the justification for not prescribing. Only one clinical narrative from the no-antimicrobial prescription set (n=68)

included content related with antimicrobial therapy, where the attending veterinary professional stated that in case of no improvement, they would consider implementing antimicrobial therapy. As such, this study does not clearly illustrate the decision-making process or drivers for not prescribing. The veterinary professional could have an appropriate prescribing behaviour, according to current guidelines, but failed to record factors around the justification for no-prescription in the clinical narrative. Moreover, stage 1 of the study (n=200) included both HPCIA-prescription (n=66) and non-HPCIA prescription (n=66), however reasoning around antimicrobial prescription was only found in 34.1% (45/132) of clinical narratives that had associated antimicrobial prescription (HPCIA-prescription and non-HPCIA prescription). Several factors could contribute to the low percentage of recorded justification around antimicrobial prescription found here. Such recording may simply not be part of some veterinary practitioners' routine around clinical decisions made during consultations. In addition, the veterinary practitioner could feel the need to only record any reasoning when feeling unsure about the clinical decision (e.g., in a *'just in case'* situation) or feeling pressure to prescribe (e.g., owner expectations). This can create a potential bias, as we are only able to analyse the cases where the veterinary practitioner felt the need to record a justification/reasoning within the clinical narrative. Nonetheless, absence of reasoning for antimicrobial prescription, absence of AMR awareness-related content, and the absence of content that could be identified as drivers for appropriate prescribing behaviour were expected, as in general, clinical narratives are brief, containing summarised information related to the animal (clinical history, physical examination, diagnostic testing, differential diagnosis), owner, treatment, and advice given on the consultation. Nonetheless, previous studies have shown that UK veterinary practitioners have a low uptake of antimicrobial use guidelines, limited awareness of their details and are prone to social norms and verbally agreed practice protocols.[213,227,229] Conversely, in the human health setting, a systematic review around the antimicrobial prescribing behaviours of medical nurse prescribers, it was reported that the education and training around prescribing in medical nurses is fundamentally protocol driven. Therefore, nurses are most likely to underpin their prescribing practices on both national guidelines and local protocols, which highlights the importance of these decision support tools in shaping prescribing behaviour.[241] As a result, it has been suggested that the current challenge for veterinary practitioners is to facilitate and improve engagement and adherence with available guidance.[229]

This is perhaps one area for future education; highlighting the important clinical decision processes required to not prescribe antimicrobials and encouraging these to be articulated to owners and recorded in the EHR could help redefine the importance and value of such a decision, and empower more veterinary practitioners to follow this course of action in appropriate cases. Shifting pre-established practice norms will likely require a variety of tactics. Different suggestions have been described, including group education, changes to professional regulation as well as incentives to reward intended behaviours.[224,229]

Previous studies demonstrated that discussion of clinical cases with peers, and effectiveness meetings in the clinical context are effective tools for veterinary practitioners to learn and share clinical knowledge, and generating agreement on protocols for clinical conditions and surgical procedures.[213,227] These should be evidence-based, following available up-to-date guidelines and take into account the resources available in the workplace. Therefore, targeted training of veterinary practitioners in practice together with peer support around compliance with guidelines has been described as strategy to stimulate responsible effective antimicrobial stewardship.[229]

3.6. Conclusion

The present study presents an original piece of work using a qualitative approach to the clinical narrative in EHRs to better understand justification content around antimicrobial prescription, particularly related with HPCIA prescription in feline and canine GI clinical presentations. By understanding what is recorded in the clinical narrative, we can better understand the behaviours, concerns and challenges that the veterinary practitioner can face during consultations around the decision-making process of antimicrobial prescription. In addition, it contributes to a wider understanding of the content of the clinical narrative, which could be used to feed into novel targeted text-mining approaches considering specific content around antimicrobial prescription, HPCIA usage, and canine and feline gastrointestinal clinical presentations. The results presented here should help inform the further development of current guidelines for appropriate antimicrobial prescription.

Chapter Four:

General discussion and future work

4.1. General discussion and future work

This project builds on previous work on antimicrobial prescription surveillance in companion animals using electronic health records (EHRs).[3,8,11,42] Here, we focused on gastrointestinal (GI) presentations in dogs and cats, characterising antimicrobial use and exploring risk factors associated with their prescription in GI consultations (Chapter Two). Additionally, we investigated reasoning and justification underpinning Highest Priority Critically Important Antimicrobials (HPCIA) prescription using thematic analysis applied to clinical narratives of canine and feline GI consultations where HPCIA prescription occurred (Chapter Three). This mixed methods approach provides new opportunities to understand antimicrobial use and decision making in consultations for GI disease, for which antimicrobials are frequently prescribed. In addition, we propose such an approach can unlock previously untapped data recorded within EHRs which can be used to promote antimicrobial stewardship at individual and population levels.

Antimicrobial resistance (AMR) is a significant worldwide concern.[3] Transmission of AMR isolates between human beings and pets, as well as evidence for the development of resistance in response to treatment have all been described.[6,252,253] All of these issues highlight the need to preserve antimicrobial efficacy, which requires identification of opportunities to safely reduce antimicrobial prescriptions.[3,4] Antimicrobials are frequently prescribed in dogs and cats, and GI presentations are one of the most common clinical presentations for which they are systemically prescribed.[3,8,9] In the present study, we have therefore focused on antimicrobial use in GI presentations.

Quantitative findings highlighted that the vast majority of canine and feline GI presentations in the studied population were considered by the attending veterinary professional as being mild in severity, and the use of diagnostic test options, including bacteriological and/or parasitological tests, was uncommon. Thus, it seems likely that many of the observed antimicrobial prescriptions were empirical in the studied population, occurring in the absence of clinical evidence support. This further suggests that use of current prescribing guidelines and clinical evidence may be suboptimal in the studied population, and in some cases contradicted by the observed prescription practices[10] In addition, the presence of diarrhoea (haemorrhagic and non-haemorrhagic) and GI presentations considered moderate/severe by the attending veterinary professional were significantly associated with increased odds of systemic antimicrobials prescription in both species. This may suggest a perceived increased risk of bacterial translocation at the intestinal level, as well as concerns with other concomitant diseases in these animals outside the GI tract (such as in the liver or urinary tract), which the veterinary practitioner felt the need to cover empirically in the absence of fuller diagnostic investigations.

In relation to the qualitative analysis of clinical narratives, to the author's knowledge this project represents the first attempt to utilise structured thematic analysis of EHR content as a novel way to better understand motivations underlying HPCIA prescription. Such a qualitative

approach identified ten major themes underpinning HPCIA prescription in GI consultations. Perceived (increased) risk of infection was stated by attending veterinary professionals in several clinical narratives of canine and feline diarrhoeic cases as justification for the prescription of HPCIAs. Similarly, so too was geriatric animals, often linked to the possibility of euthanasia; this was consistent with both our quantitative analyses and work from previous studies, which found that older animals had increased systemic antimicrobial prescription probability.[11,42] Frequently, concomitant conditions were mentioned as a reason for prescribing HPCIAs, and there was recorded evidence that antimicrobial prescription was also perceived as an empirical medical treatment, to reduce the perceived risk of infection in elderly patients and in cases where the owner declined further investigation. Antimicrobial therapy via HPCIA prescription also occurred whilst the owner considered other treatment/diagnostic options, or euthanasia. Thus, in this context, HPCIA prescription appeared to be an empirical treatment approach, to either try and postpone euthanasia or whilst waiting for a decision. This example illustrates the complexity and the wide range of clinical and non-clinical elements that can shape the decision-making process to prescribe a systemic antimicrobial in each individual patient. Extrinsic factors such as age of the animal, concomitant conditions, owner's availability to move forward with diagnostic test options, or to consider euthanasia, can clearly profoundly shape the veterinary decision-making process around antimicrobial prescription.

Whilst several factors, such as the presence of certain clinical signs (e.g., haemorrhagic diarrhoea) and the age of the animal can be easily evaluated through the application of quantitative methodologies to EHRs datasets, extrinsic factors shaping antimicrobial prescription would hardly be captured using such approaches, or by the syndromic surveillance questionnaires currently implemented in SAVSNET alone. Hence, by using the mixed-methods approach described here, we can reach a more holistic understanding of antimicrobial prescription trends in canine and feline GI presentations, its underpinning motivations and reasoning, which frequently are not exclusively clinical or evidence-based. The mixed-methods approach employed here provides a template that could be applied to clinical narratives of other common clinical presentations where antimicrobials are frequently used, such as in respiratory presentations, and would further validate common themes around antimicrobial prescription in different clinical presentations.

Projects such as the present mixed-methods approach represent an innovative early step forward to better harness the information contained in EHRs in the small animal veterinary setting. However, there are challenges associated with the use of both quantitative and qualitative approaches in a relatively short period of time, and when relying on fixed resources such as EHRs, where a more interactive discussion such as occurs more typically in in-depth interviews and focus groups is not possible. Whilst this project is undoubtedly valuable in monitoring and surveillance terms, allowing us to understand more widely antimicrobial prescription and its underpinned reasoning in a defined clinical presentation, a duration of one year limits the extent and depth of analysis achievable with these distinct yet complementary

research lenses. In addition, qualitative themes can only be identified where they are recorded in the health narrative. Nonetheless, the findings presented by this mixed-methods study highlight the current need, in the veterinary sector, to address antimicrobial prescribing behaviour with holistic and integrated research strategies. Moreover, it is likely that the information recorded in EHRs by practitioners, recorded as it is at or close to the time of the clinical decision to prescribe in the consulting room, reflects well the factors deemed most important to the decision-making process. The findings we present can reliably and actively inform the design of interventions, which target the small animal veterinary sector and its own intricacies.

A recurring theme of our studies was that veterinary professionals often emphasised within the clinical narrative a role for the owner in choices around antimicrobial prescription. This included perceived prescribing pressure from pet owners, directly or indirectly related with social circumstances, previous perceived positive response to antimicrobial therapy, and refusing a diagnostic testing approach opting instead to pursue a more therapeutic approach. The lack of compliance with oral medication at home may also lead the veterinary professional to opt for a long-acting injectable HPCIA formulation, particularly in feline patients. These owner-related drivers have been described in previously published studies[213,214] , giving external validation to our results based on qualitative study of clinical narratives. To the author's knowledge, studies exploring pet owner and veterinary professionals' interactions around antimicrobial prescription and AMR are scarce.[224] This use of EHRs data could therefore represent an additional opportunity for future work. In addition, further work using in-depth interviews or focus groups informed by the results presented here would allow greater understanding on antimicrobial prescribing factors considered to be intrinsic (related to the veterinary professional/prescriber) and to further expand our knowledge on extrinsic influences mediated by other important players, such as pet owners.

Such owner-derived data, potentially generated by more in-depth qualitative approaches, can help to characterise veterinary care-seeking behaviour and to explore beliefs and behaviours around antimicrobial use in pet owning communities, with the inclusion of variables such as socioeconomic factors. Moreover, development of symptom reporting systems may help to characterise how common clinical presentations, such as canine and feline GI presentations, are generally managed at home, and what proportion lead to veterinary consultations and antimicrobial use/antimicrobial-seeking behaviour. This approach could represent the development of a prospective community cohort study, as has been described in human healthcare.[254] Additionally, this would identify opportunities for raising awareness about antimicrobial stewardship in the pet owning community and veterinary practice, and ultimately integrate the development of interventions, focusing on all major players involved in companion animal care.

Previous studies have also indicated that interventions developed for the small animal veterinary sector aiming at behavioural change regarding antimicrobial prescription, should

also consider owners as a key-player. Moreover, it has been highlighted that better-informed owners in topics such as AMR, can facilitate the veterinary-owner dynamics and discussions around appropriate antimicrobial prescription, as owners can be less likely to expect antimicrobial prescriptions for their pets.[224] We therefore advocate that interventions in the veterinary sector are needed to outline a future that moves from passive data-driven surveillance approaches to the promotion of behaviour change around over and misuse of antimicrobials. Carrying out such interventions and exploring if and how they work may represent an exciting opportunity for further SAVSNET research and development under the antimicrobial stewardship framework.

Antimicrobial stewardship, defined as an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness, has become an increasingly important concept to approach the challenges associated with ensuring effective surveillance and judicious use of antimicrobials.[255,256] In the United Kingdom, the national action plan defines a wide range of approaches to tackle AMR.[257] Behaviour change is key to tackle AMR and to implement effective antimicrobial stewardship, in terms of appropriate prescribing, use of diagnostic testing, and to promote the use of practice-level published guidance to support the clinical decision around antimicrobial prescription.[4] Nonetheless, behavioural interventions in the companion animal veterinary sector have been scarce. Furthermore, design of interventions and stewardship programmes in human healthcare often fail to take advantage of more qualitative research outputs, including consideration of social influences and behavioural factors, instead being predominantly based on quantitative-driven data analysis, resulting in limited use of behaviour change techniques.[258,259] This limited use of a more behavioural lens may ultimately cause failure or lack of engagement, as has been described in human medicine.[9] Social approaches using ethnographic observation methods can be particularly valuable to gain a deeper understanding in complex settings, and can additionally help to target those areas that need adjustment, therefore facilitating change of behaviours. The application of such methodologies allows reflection on the details of effective interventions, considering that an intervention can work in a particular setting, but may be ineffective, or produce different results, in a different context.[9] Thus, an interdisciplinary approach should be taken in designing stewardship interventions, and it should be rigorously applied to the veterinary sector to encourage effective antimicrobial stewardship, in line with ongoing protocols for antimicrobial stewardship in human healthcare.[4,260]

Ongoing initiatives in the small animal veterinary setting, such as “mySavsnetAMR” have been delivering the opportunity of antimicrobial prescription benchmarking, allowing veterinary practices to benchmark their own antimicrobial prescription against other anonymised practices, thus providing a wider context for their own antimicrobial use.[261] Hence, the use of this benchmarking portal can help generate workplace discussions around antimicrobial use, ultimately providing a tool for reflection about their own decision-making processes around

prescription, and potentially leading to subsequent changes in established practices.[42,262] Nonetheless, future and expanded initiatives under the antimicrobial stewardship umbrella using population health data and a data intelligence background may be valuable to provide targeted awareness messages around antimicrobial use to veterinary professionals in real time, combining the knowledge gathered from research outputs about antimicrobial prescription trends and underpinning prescribing drivers, with practice-level prescription guidance.[10] This could be particularly relevant to veterinary professionals if it allows them to reflect on their own prescribing behaviour in real-time (for example, a targeted awareness message when prescribing an HPCIA without mentioning antimicrobial susceptibility testing results), and may also empower veterinary professionals to initiate a discussion with the owner about responsible antimicrobial use.

Other initiatives, such as the non-prescribing form[10,263] can be useful to provide a more formal output from the veterinary consultation, helping to communicate to owners the reasons why antimicrobial prescription may be unwarranted to a veterinary patient, including the risks carried by overuse of antimicrobials, and eventually contributing towards antimicrobial stewardship on a daily-basis in practice.[10,263] An online tool to support decisions on the responsible use of antimicrobials in the veterinary setting has been recently described.[264] This user-friendly comprehensive decision supporting tool includes search functions, allowing an efficient retrieval of information that is structured by animal species, organ systems and therapeutic indications, while providing access to current knowledge of rational antimicrobial prescription practices.[264] The development of evidence-based decision supporting tools aimed at practicing veterinary professionals can represent an opportunity for national collaborations to implement useful antimicrobial stewardship initiatives in the UK. The approaches described in this study provide a novel way to evaluate the implementation and effectiveness of such tools in practice.

In addition, pharmaceutical companies can also play a key role in antimicrobial stewardship in developing antimicrobial research and new antimicrobial drugs, often accelerated and motived by governmental financial incentives, known as ‘market entry rewards’.[265] Furthermore, there may be a role for new concepts for promoting stewardship in antimicrobial development, such as the concept of Antibiotic Susceptibility Bonus, which relies on the effectiveness of the antimicrobial drug for treating target pathogens, in the years subsequent to market entry. Antibiotic Susceptibility Bonus has been described as a future option directed to the ability of the product to stave off resistance, and therefore protecting long-term product efficacy whilst avoiding profit-driven product promotion, and reducing the reliance on high-volume sales.[265] The prescribing Cascade establishes the requirement for the veterinary practitioner to prescribe and use authorised veterinary medicines when available.[266,267] Although this general legislative provision is necessary, this can also create a perverse pressure to prescribe a product that is licensed but not consistent with the principals of responsible antimicrobial use, to the detriment of products that although un-licensed, are more aligned with responsible

antimicrobial use. This is particularly relevant when considering long-acting characteristics and the ease of administration of licensed veterinary formulations that have an HPCIA as active substance. Arguably, for promoting effective antimicrobial stewardship in the small animal veterinary sector, all stakeholders including licensing authorities, the pharmaceutical industry and veterinary practitioners, would need to work together to find strategies tailored for this specific part of the veterinary sector. This would potentially promote discussions where the principals of animal welfare are prioritised and safeguarded, as well as the needs of veterinary practitioners to have product formulations that meet the needs of their day-to-day practice, while developing and promoting marketed pharmaceutical products consistent with concepts such as Antibiotic Susceptibility Bonus, with the ultimate goal of preserving antimicrobial effectiveness.

Importantly, widespread professional training (e.g., workshops, seminars, and webinars) is needed to ensure that currently published guidelines are widely disseminated, and the veterinary professional has the necessary resources for an evidence-based decision around antimicrobial prescription, not only in canine and feline GI presentations, but also in other clinical presentations. The findings presented here can be used to inform the development of such training, ensuring it addresses the challenges identified here faced by practitioners. In addition, our observations can be incorporated into targeted interventions aimed at small animal veterinary practices to safely reduce unnecessary prescription of antimicrobials in GI presentations, particularly HPCIAs. In the future, continuous surveillance of antimicrobial prescribing trends and behaviours; development of well-balanced interventions for both veterinary professionals and pet owners, appropriately informed by interdisciplinary approaches; specific veterinary training; together with innovative data intelligence methodologies will together help ensure future effective antimicrobial stewardship for the companion animal veterinary sector.

4.2. Conclusion

The studies presented here highlight the value of quantitative approaches to better understand antimicrobial prescription practices in GI presentations, particularly to profile commonalities of canine and feline GI presentations, to characterise management strategies, and to investigate risk factors associated with systemic antimicrobial prescription. However, research to date has largely neglected the use of the clinical narrative as a research dataset. Hence, we advocate the continued integration of qualitative approaches to increase the potential of the unstructured text-derived data found in EHRs. Using such an approach provided novel insight into intrinsic and more extrinsic factors associated with the decision to prescribe HPCIAs. Such a holistic view of EHRs provide complementary evidence and insights to the veterinary decision-making process underpinning antimicrobial prescription in companion animals, that can be used to inform evidence-based policy making, development of targeted health messages and professional development, and contributing towards effective antimicrobial stewardship. Further interdisciplinary efforts are needed to ensure clinical compliance with currently published prescription guidance.

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Appendix One: SAVSNET Gastrointestinal questionnaire

Questions asked if the veterinary professional selects Gastroenteric signs option on first screen.

Definition in the box: "Signs including but not limited to: diarrhoea, vomiting, weight loss, poor appetite."

1. Please indicate the clinical signs present*

- Diarrhoea without blood
- Diarrhoea with blood
- Vomiting without blood.
- Vomiting with blood.
- Melaena.
- Weight loss/failure to gain weight.
- Poor appetite.
- Other.

2. If diarrhoea was present how would you describe it*

- No diarrhoea.
- Small intestinal diarrhoea.
- Large intestinal diarrhoea/colitis.
- Mixed pattern.
- Don't know.

3. Please indicate disease severity

- Mild illness i.e. normal apart from GI disease.
- Moderately ill.
- Severely ill/debilitated.

4. How does this consultation relate to this episode of illness

- First presentation.
- Revisit/check-up.
- Don't know.

5. How long approximately has the pet had this episode of illness?

- Up to 2 days.
- Between 3 days and 2 weeks
- More than 2 weeks – less than 1 month.
- 1 month and over.
- Don't know.

6. What diagnostic options will be used today for this episode of illness? *

- None.
- Faecal parasitology/bacteriology.
- Faecal virology.
- Virus serology.
- Diagnostic Imaging.
- Haematology/biochemistry.
- Serum B12/Folate and/or serum TLI.
- Canine/feline specific pancreatic lipase.
- Urinalysis.
- Other.

7. What advice did you give today? *

- Change of diet.
- Fasting.
- Admit patient for treatment.
- Refer patient.
- Check-up in near future.
- Other.

*indicates multiple options may be chosen

Appendix Two: Results from univariable mixed effects logistic regression models

Table 11. Systemic antimicrobials in canine consultations: Parameter estimates from a series of univariable mixed effects logistic regression models, modelling on a case-level the outcome variable 'presence of systemic antimicrobial prescription' against a number of categorical and continuous risk factors.

Random effect	Variance	Standard Deviation	Variable	Category	β	SE [a]	OR [b]	Lower CI [c]	Upper CI	*P*
Practice	0.39	0.63	**Insurance status**	Uninsured (Intercept)	-0.96	0.06	-	-	-	-
Site	0.16	0.40		Insured	-0.02	0.04	0.98	0.90	1.06	0.59
			Vaccination	Unvaccinated (Intercept)	-0.94	0.06	-	-	-	-
				Vaccinated	-0.04	0.04	0.96	0.89	1.04	0.33
			Neutered status	Un-neutered (Intercept)	-0.98	0.06	-	-	-	-
				Neutered	0.02	0.04	1.02	0.95	1.09	0.64
			Consultation episode	First visit (Intercept)	-0.94	0.05	-	-	-	-
				Revisit	-0.11	0.04	0.90	0.83	0.97	0.006
			Severity	Mild (Intercept)	-1.05	0.05	-	-	-	-
				Moderate/Severe	0.44	0.04	1.55	1.42	1.69	<0.001
			Faecal bacteriology/parasitology	Absent (Intercept)	-0.97	0.05	-	-	-	-
				Present	0.02	0.07	1.03	0.90	1.16	0.71
			Diarrhoea	Absent (Intercept)	-1.78	0.07	-	-	-	-
				Non-haemorrhagic	0.72	0.05	2.05	1.86	2.26	<0.001
				Haemorrhagic	1.43	0.05	4.17	3.77	4.62	<0.001
			Vomiting	Absent (Intercept)	-0.79	0.06	-	-	-	-
				Non-haemorrhagic	-0.42	0.04	0.66	0.61	0.70	<0.001
				Haemorrhagic	-0.31	0.09	0.73	0.61	0.88	0.001
			Duration	≤ 2 days (Intercept)	-1.01	0.06	-	-	-	-
				≥ 3 days and ≤ 2 weeks	0.22	0.04	1.24	1.16	1.33	<0.001
				> 2 weeks and < 1 month	-0.31	0.09	0.74	0.61	0.88	0.001
				≥ 1 month	-0.50	0.08	0.61	0.52	0.71	<0.001
				Do not know	-0.70	0.28	0.50	0.29	0.86	0.013
			Continuous risk factor							
			Age (years)	Intercept	-0.97	0.05	-	-	-	-
				Age – linear	0.14	0.02	1.15	1.12	1.19	<0.001

[a] *Standard error*
[b] *Odds ratio*
[c] *95% Confidence interval*

Table 12. Systemic antimicrobials in feline consultations: Parameter estimates from a series of univariable mixed effects logistic regression models, modelling on a case-level the outcome variable 'presence of systemic antimicrobial prescription' against a number of categorical and continuous risk factors.

Random effect	Variance	Standard Deviation	Variable	Category	β	SE [a]	OR [b]	Lower CI [c]	Upper CI	*P*
Practice	0.58	0.76	**Insurance status**	Uninsured (Intercept)	-1.32	0.08	-	-	-	-
Site	0.21	0.46		Insured	-0.07	0.11	0.93	0.76	1.15	0.51
			Vaccination	Unvaccinated (Intercept)	-1.29	0.09	-	-	-	-
				Vaccinated	-0.08	0.08	0.92	0.79	1.08	0.31
			Neutered status	Un-neutered (Intercept)	-1.21	0.11	-	-	-	-
				Neutered	-0.16	0.10	0.86	0.71	1.04	0.11
			Consultation episode	First visit (Intercept)	-1.25	0.08	-	-	-	-
				Revisit	-0.26	0.08	0.77	0.65	0.91	0.002
			Severity	Mild (Intercept)	-1.46	0.08	-	-	-	-
				Moderate/Severe	0.62	0.09	1.86	1.55	2.23	<0.001
			Faecal bacteriology/parasitology	Absent (Intercept)	-1.32	0.08	-	-	-	-
				Present	-0.19	0.15	0.83	0.61	1.11	0.21
			Diarrhoea	Absent (Intercept)	-1.73	0.10	-	-	-	-
				Non-haemorrhagic	0.47	0.09	1.61	1.35	1.91	<0.001
				Haemorrhagic	1.04	0.11	2.83	2.27	3.53	<0.001
			Vomiting	Absent (Intercept)	-1.12	0.09	-	-	-	-
				Non-haemorrhagic	-0.47	0.08	0.63	0.54	0.73	<0.001
				Haemorrhagic	0.01	0.19	1.01	0.69	1.48	0.95
			Duration	≤ 2 days (Intercept)	-1.16	0.09	-	-	-	-
				≥ 3 days and ≤ 2 weeks	-0.02	0.09	0.98	0.83	1.16	0.84
				> 2 weeks and < 1 month	-0.66	0.17	0.52	0.37	0.72	<0.001
				≥ 1 month	-0.77	0.12	0.46	0.37	0.58	<0.001
				Do not know	-1.21	0.55	0.30	0.10	0.88	0.03
			Continuous risk factor							
			Age (years)	Intercept	-1.45	0.09	-	-	-	-
				Age - linear	-0.11	0.04	0.90	0.83	0.97	0.006
				Age - quadratic	0.12	0.04	1.12	1.03	1.22	0.008

[a] *Standard error*

[b] *Odds ratio*

[c] *95% Confidence interval*

Appendix Three: List of abbreviations and clinical acronyms present in the analysed clinical narratives

a/b – antibiotics

Ab('s) – antibiotics

Abdo – abdomen

Abios – antibiotics

Abx – antibiotics

Adv – advised

Am – morning

Antibs – antibiotics

Asap – as soon as possible

B. duct – biliary duct

Bact – bacterial

BG – Blood Glucose

BT – Blood Test

Camp – *Campylobacter spp.*

Campy – *Campylobacter spp.*

Chk – check(ed)

D+(++) – Diarrhoea

Ddx – differential diagnosis

dexf – dexamethasone

Disc – discussed

E.coli – *Escherichia coli*

Euth - euthanasia

F/S – faecal sample

f+ – faeces/faecal

FeLV – Feline Leukaemia Virus

FIV – Feline Immunodeficiency Virus

FPLi – Feline Pancreatic Lipase Immunoreactivity

GE – gastroenteritis

GI – gastrointestinal

Hols – holidays

IBD – Inflammatory Bowel Disease

Inf – infection

Infxn – infection

Inj – injection

IVFT – intravenous fluid therapy

Meds – medication/medical treatment

Metronid – metronidazole

mmol – millimoles

Mtz – metronidazole

NAD – Nothing Abnormal Detected

NSAID – non-steroidal anti-inflammatory drug

NSF – No Significant Findings

O – Owner

Opt – opted

P – plan

P. duct – pancreatic duct

Poss – possible

Re – re-examination

Re/ex – re-examination

re-ex – re-examination

RV – revisit

Rx – prescribed medication/re-examine (depending on the context)

Susp – suspect(ed)

T – temperature

Temp – temperature

TLI - Trypsin-Like Immunoreactivity

Tx – treatment

UA – Urinalysis

V+ – vomiting

Vom – vomiting

W/ – with

W/e – weekend

WBC – White Blood Cells