

# Antibiotic therapy in dogs and cats in general practice in the United Kingdom prior to referral.

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## 4 ABSTRACT

5 Objectives: To describe antibiotic prescription by veterinarians in general practices in the

6 United Kingdom (UK) prior to referral and analyse if UK antibiotic stewardship guidelines were

7 followed.

8 Materials and methods: The clinical records from dogs and cats referred to the Internal

9 Medicine and Oncology departments of two referral hospitals were retrospectively reviewed.

10 Results: There were 917 cases included, of which 486 (53.0%) had been prescribed antibiotics

11 for the presentation they were subsequently referred for. Bacterial culture or cytology to guide

12 antibiotic prescription had been performed in 43/486 (8.8%) and 9/486 cases (1.8%)

13 respectively. In four cases, both cytology and culture were performed. For those animals who

14 had received antibiotics, 344/486 (70.8%) prescriptions did not comply with UK antibiotic

15 stewardship guidelines. Following investigations at a referral centre, a bacterial aetiology was

16 found or suspected in 17.9% of the cases that received antibiotics.

17 Clinical significance: Use of diagnostics, including culture and cytology, to prove or determine

- 18 the likelihood of a bacterial aetiology was infrequently performed prior to referral and may
- 19 have contributed to over prescription of antibiotics. Encouraging veterinarians to undertake
- 20 appropriate diagnostics, in combination with education around compliance with antibiotic

21 stewardship guidelines, might reduce antibiotic prescription.

22 Keywords: antibiotic, antimicrobial, prescription, resistance, responsible

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#### 24 INTRODUCTION

25 Antibiotic resistance has been observed since antibiotics were first discovered. Antibiotic 26 therapy contributes to the development of antibiotic resistance (AR) in both humans and 27 animals (Jernberg et al., 2010; Schmidt et al., 2018). Any use of antibiotics exposes bacterial 28 pathogens and commensal microbiota to a selection pressure that can result in the emergence 29 of antibiotic resistance or, if a resistant subpopulation is present, an increase in the abundance 30 of resistant bacteria (Weese *et al.*, 2015). This has increasingly become a problem in recent 31 decades where use of antibiotics has accelerated the rate at which resistance has developed 32 (Costelloe et al., 2010). Broad dissemination of AR amongst different bacterial populations has 33 resulted in treatment failures in both human and veterinary medicine (Huemer et al., 2020). 34 The concern regarding AR in veterinary medicine is further underpinned by studies 35 investigating the nature and frequency of the contacts that occur between pets and people, 36 which highlight the large number of opportunities that exist for the zoonotic transfer of 37 bacteria and that have provided evidence that bacteria can be transferred in both directions 38 (Westgarth et al., 2007; Wieler et al., 2011; Walther et al., 2012). This interspecies 39 transmission can further contribute to AR through a feedback loop of resistance reservoirs and 40 the evolution of generations of increasingly resistant bacteria (Manian, 2003; Guardabassi, 41 Loeber and Jacobson, 2004; Loeffler et al., 2005; Van Balen et al., 2017). 42 In the UK, many antibiotics are licensed for veterinary use and can only be prescribed by a 43 veterinary surgeon (UK Stationery Office, 2013). Responsible antibiotic use can be defined as 44 'an attitude to maximise therapeutic efficacy and minimise the selection of resistant 45 microorganisms' and should theoretically reduce the spread of antibiotic resistance (Duquette 46 and Nuttall, 2004). The Protect and ProtectMe guidelines (BSAVA/SAMSoc, 2013, 2018) 47 produced by the British Small Animal Veterinary Association (BSAVA) and Small Animal 48 Medicine Society (SAMSoc) were developed to promote responsible antibacterial prescribing

49 practises. However, it is unclear if these guidelines are widely followed in UK practice or if they

50 have had any widespread impact on antibiotic use (Hughes *et al.*, 2012).

51 The aim of this study was to assess prescription of antibiotics by veterinarians in general

- 52 practices in the UK prior to referral to Oncology and Internal Medicine departments for the
- 53 condition the patient was subsequently referred for. A secondary aim was to analyse whether
- 54 these prescriptions adhered to Protect and ProtectMe Guidelines.

55

## 56 MATERIALS AND METHODS

57 Medical records of dogs and cats who were referred to the Internal Medicine department of 58 the hospital A between the 1<sup>st</sup> of March of 2018 and the 28<sup>th</sup> of February of 2019 and to the 59 Internal Medicine and Oncology departments of hospital B between the 1<sup>st</sup> November 2016 60 and the 1<sup>st</sup> November 2017 were reviewed in a retrospective manner.

61 The following information was collected from each patient's medical record: signalment, 62 clinical signs which resulted in patient referral and length of time the patient had been 63 experiencing these clinical signs, whether or not antibiotics had been prescribed for these 64 clinical findings, and the final or presumptive diagnosis made at the referral centres. Only 65 information regarding antibiotics prescribed for the condition they were referred for were 66 recorded. If an antibiotic was prescribed for the condition the patient was referred for then 67 the following information was collected: antibiotic class, dose, route, duration and frequency 68 of administration, whether the animal was receiving the antibiotic(s) on the day they were 69 referred, and whether or not bacterial culture and sensitivity or cytology were performed to 70 guide antibiotic prescription. Where an animal received multiple antibiotics, but of the same 71 class, these were counted as different antibiotics. When the animal had received a long-acting 72 injection of cefovecin, 14 days was assumed for duration of the antibiotic (Stegemann et al., 73 2006; Stegemann, Sherington and Blanchflower, 2006). Where the clinical signs were reported 74 as chronic (lasting >4 weeks), clinical records were also analysed for antibiotic use up to three 75 months prior to referral. Animals receiving antibiotics to treat a condition independent of the 76 reason for their referral were excluded because the final diagnosis for these conditions could 77 not commonly be verified. Cats referred for radioiodine therapy for the treatment of 78 hyperthyroidism at one of the centres (hospital B) were also excluded. 79 If the patient had been prescribed an antibiotic / antibiotics for the condition they were 80 referred for then the patient heart rate, respiratory rate, body temperature and white blood 81 cell count at the time of antibiotic prescription were collected and used to determine if criteria 82 for systemic inflammatory response syndrome (SIRS) were met. When two or more (dogs) and 83 three or more (cats) of the following criteria were met, the patient was classified as following 84 SIRS criteria: hypothermia or fever, tachycardia or bradycardia (the latter only in cats), 85 tachypnoea, leukocytosis, leucopenia or increased band neutrophil count in animals with a 86 normal white blood cell count (Hauptman, Walshaw and Olivier, 1997; Brady et al., 2000). 87 Antibiotic use was analysed using UK veterinary antibiotic guidelines (BSAVA/SAMSoc, 2013, 88 2018). In particular, we evaluated four ways the guidelines were not followed which could be 89 objectively analysed: 1. evidence of underdosing, which included inferior absolute dose and 90 insufficient frequency of administration, and was assessed against the BSAVA Small Animal 91 Formulary 8<sup>th</sup> and 9<sup>th</sup> editions (Ramsey, 2014, 2018); 2. cycling antibiotics, defined as 92 successive use of antibiotics of different classes without supportive culture and sensitivity 93 results; 3. the inappropriate use of either fluoroquinolones or 3<sup>rd</sup> and 4<sup>th</sup> generation 94 cephalosporins defined using the aforementioned guidelines when an antibiotic better aligned 95 with prescribing guidelines is inappropriate and/or ineffective, and culture/sensitivity testing 96 indicates that they will be effective; 4. whether antibiotics were prescribed when not indicated by aforementioned UK guidelines. We assessed antibiotic prescription in the following settings: 97 98 acute vomiting (regurgitation was also included in this category), acute diarrhoea (including

99 haemorrhagic), chronic diarrhoea (cases that received a four week treatment were excluded as

100 antibiotic trials have been described for management of chronic diarrhoea and cases in which

101 *Giardia spp.* infection was diagnosed and metronidazole was prescribed were also excluded as

102 it is a recognised treatment) (Scorza V., 2012), canine sino-nasal disease, subclinical

103 bacteriuria, feline lower urinary tract disease, polyuria and polydipsia (unless pyogenic focus

suspected), weight loss and the use of prophylactic antibiotics except for a few specific medical

- 105 conditions (e.g. immunocompromised patients). If the patient met the SIRS/sepsis criteria at
- 106 the time the antibiotic was prescribed, they were not classified as inappropriate.
- 107 Cases were divided into subcategories depending on body system affected (i.e. respiratory,
- 108 gastrointestinal, multisystemic, hepatobiliary, endocrine, haematology/immunology,
- 109 urinary/reproductive and other). Oncological cases were categorised under the major body
- 110 system affected by the tumour, or where this was not possible then were classified as

111 multisystemic.

## 112 Statistics

113 Descriptive statistics were used. Data were tested for normal distribution using histograms and

114 Shapiro Wilk tests. Non-normally distributed data are presented as median and range. Chi-

square tests were used to compare antibiotic prescription between species. All analyses were

116 performed using commercial software (IBM<sup>®</sup> SPSS<sup>®</sup> v.28.0.1.1). Statistical significance was set

117 as  $P \le 0.05$ .

140 RESULTS

### 165 Study Population

- 166 A total of 917 animals met the inclusion criteria for the study, 265 were referred to hospital A
- and 652 were referred to the hospital B. Of these, 666 cases were referred to internal
- 168 medicine and 251 cases to oncology.
- 169 There were 739 dogs, with 405 (54.8%) being male and 326 (44.1%) were female, of which 307
- 170 (75.8%) of males and 261 (80.0%) of females were neutered. There were 178 cats with 96
- 171 (53.9%) being male and 79 (44.4%) female, of which 89 (92.7%) of males and 74 (93.6%) of
- 172 females were neutered. The sex was unknown in eight dogs and three cats. Median age of
- dogs at the time of referral was 7.4 years (range 1 month to 16 years) and cats was 9.3 years
- 174 (range 2 months to 19 years) (Supporting information S1).

#### 175 Antibiotic Prescription

176 There were 486 animals (53.0%), which compromised of 390/739 (52.8%) dogs and 96/178 177 (53.9%) cats, that had received antibiotics prior to referral for the clinical presentation they 178 were referred for. Of the dogs who had received antibiotics, there were 223 (57.2%) males and 179 166 (42.6%) females, of which 163 (73.1%) of the males and 132 (79.5%) of the females were 180 neutered. The gender was not reported in one dog. Of the cats receiving antibiotics, 52 (54.2%) 181 were male and 43 (44.8%) were female; 43/52 (82.7%) of males and 40/43 (93.0%) of females 182 were neutered. The gender was not reported in one cat. The median age of the dogs who 183 received antibiotics was 8 years (range 1 to 16 years) and for cats was 8 years (range 2 months to 19 years). 184

185 Three hundred and forty seven cases had been prescribed one antibiotic class. Two different

- antibiotic classes had been prescribed for 120/486 animals (24.7%), whilst 16 (3.3%) had
- 187 received three different antibiotic classes, three (0.6%) had received four antibiotic classes and

- 188 one animal received five different antibiotic classes. One hundred and sixty animals (32.9%)
- 189 were still receiving antibiotics at the time of referral.
- 190 Table 1 describes antibiotic classes prescribed. The antibiotic classes most commonly
- 191 prescribed in dogs were penicillins in 279/390 (71.5%) cases and nitroimidazoles (ie.
- 192 metronidazole) in 100/390 (25.6%) cases. For cats, the most common classes prescribed were
- 193 penicillins in 47/96 (49.0%) cases and third generation cephalosporins in 32/96 (33.3%). When
- antibiotics were prescribed, cats were significantly less likely to receive a penicillin antibiotic
- 195  $(X^2 (1, N = 486) = 17.8, p < 0.001)$  and more likely to be prescribed a 3<sup>rd</sup> generation
- 196 cephalosporin compared with dogs ( $X^2$  (1, N = 486) = 79.5, p<0.001). The only third generation
- 197 cephalosporin that was prescribed for both dogs and cats was cefovecin.
- 198 The data for the combination of antibiotic classes prescribed is presented in Figure 1 and 2. The
- 199 most commonly prescribed combination of antibiotics was a nitroimidazole and a penicillin in
- 200 both dogs (40/390; 10.2%) and cats (6/96; 6.3%). In dogs, the second most common
- 201 combination of antibiotics included a penicillin and a fluoroquinolone (9/390; 2.3%) and a
- 202 penicillin and a lincosamide (9/390; 2.3%), whilst in cats a penicillin and a 3<sup>rd</sup> generation
- 203 cephalosporin was the second most common combination (5/96; 5.2%).
- The data for the antibiotic classes prescribed for each body system is presented in Figure 3.
- 205 Penicillins were the most commonly prescribed antibiotic class for all body systems (endocrine
- 206 10/46; 21.7%, haematological/immunological 7/31; 22.6%, hepatobiliary 24/69; 34.8%,
- 207 multisystemic 108/320; 33.8%, respiratory 49/108; 45.4% and urinary/reproductive 43/86;
- 208 50%) apart from the gastrointestinal body system where it was nitroimidazoles (67/170;
- 209 39.4%). When lincosamides or second and third generation cephalosporines were prescribed,
- they were most commonly prescribed for multisystemic disease (lincosamides 17/320; 5.3%,
- second generation cephalosporines 15/320; 4.7% and third generation cephalosporines
- 212 19/320; 5.9%) (Supporting information S2).

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## 214 Use of culture and sensitivity and/or cytology to guide antibiotic prescription

- A bacterial culture and sensitivity had been performed in 43/486 (8.8%) animals that had been
- 216 prescribed antibiotics prior to referral. In 10/43 (23.3%), the antibiotic prescription was
- 217 considered inappropriate on the basis that results were obtained from nasal swabs, which
- 218 typically isolates microorganisms representative of colonisation rather than true infection
- 219 (Meler, Dunn and Lecuyer, 2008).

Nine (1.9%) patients underwent cytology testing to guide antibiotic prescription. The antibiotic prescription was considered questionable in one dog where extracellular bacteria were seen in an otherwise inactive urine sediment and in one cat where bacteria likely representing normal flora were seen in an upper respiratory secretion. In four cases, both cytology and culture were performed.

#### 225 SIRS/sepsis criteria

226 Out of 390 dogs that had received antibiotics, 85 dogs (21.8%) had data in the clinical records 227 available to assess for SIRS criteria at the time of antibiotics prescription. Of these, 10 (11.8) 228 dogs had all four criteria available (i.e., heart rate, respiratory rate, temperature and 229 haematology), 38 (44.7%) dogs had three criteria available and 37 (43.5%) had two criteria 230 available. Of the 10 dogs with four criteria available, eight were classified as following SIRS 231 criteria. Ten of 38 dogs with three criteria available were classified as following SIRS criteria 232 and six of 37 dogs with two criteria available were classified as following SIRS criteria. 233 Out of 96 cats that received antibiotics, 9 (9.4%) cats had data in the clinical records available 234 to assess for SIRS at the time of antibiotic prescription. One cat had all four criteria available 235 and 8 cats had three criteria available. The cat with the four criteria available was classified as 236 following SIRS criteria and six of nine cats with 3 criteria available were classified as following 237 SIRS criteria.

238	Therefore, only 27/94 (14.3%) animals with enough data available to assess SIRS met the	
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criteria for SIRS at the time they had been prescribed an antibiotic.

## 240 Antibiotic guidelines

- 241 When considering Protect/ProtectME guidelines, 344/486 (70.8%) cases did not have antibiotic
- 242 prescription in line with these guidelines in one way only (i.e. underdosing, cycling antibiotics,
- 243 inappropriate prescription of fluoroquinolones or third generation cephalosporins and use of
- antibiotics for clinical signs that were recommended against antibiotic use by the guidelines.)
- 245 One hundred and eleven (47.8%) cases did not adhere with the guidelines in two different
- 246 ways, 31 (17.7%) cases in three different ways and 8 (3.4%) cases in the four ways assessed.
- 247 Underdosing was recorded in 131/486 (26.9%) cases. Cycling antibiotics occurred in 97/467
- 248 (i.e. 20.8%, 19 patients were prescribed two antibiotics from the start of their treatment),
- following apparent failure of a first antibiotic, cases were prescribed a second antibiotic
- without supportive culture and sensitivity results.). There were 91/486 (18.7%) cases that were
- 251 prescribed a fluoroquinolone or third generation cephalosporin, and nappropriate prescription
- of these two classes of antibiotics occurred in 81/91 (89.0%) cases. A culture and sensitivity test
- had been performed in 1/91 cases that were prescribed these class of antibiotics.

254

- There were 232/486 (47.7%) cases that had been prescribed antibiotics for clinical signs where
- antibiotics are not recommended by the Protect/ProtectME guidelines.
- 257 Of the patients who received a prior antibiotics as indicated by UK guidelines, only clinical
- variables met SIRS/sepsis criteria, 13/20 dogs and 3/7 cats who met these criteria
- 259 subsequently received antibiotics which did not adhere to UK guidelines (Supporting
- information S3, S4 and S5).

#### 261 Bacterial infection documented

After investigations within a referral centre setting, a bacterial aetiology was found in 55/486

263 (11.3%) cases that received antibiotics, and was suspected in a further 32 (6.6%) cases.

264 Therefore, a bacterial aetiology was found or suspected in 17.9% of the cases that received

antibiotics. For one cat included here, *Helicobacter spp* was diagnosed within gastric biopsy

266 samples.**DISCUSSION** 

267 Our data demonstrates that substantial improvement on adherence to antibiotic guidelines in

268 general practice in the UK can be made as in 70.9% of the cases referred to internal medicine

269 or oncology the guidelines were not followed. It also demonstrates over-prescription of

antibiotics and infrequent use of appropriate tools to diagnose bacterial infection such as

culture or cytology.

Three general approaches have been recommended to help limit antibiotic resistance: a)
preventing disease occurrence, b) reducing overall antibiotic use and c) improved antibiotic
use (Weese *et al.*, 2015).

274 use (weese et ul., 2015).

Setting aside prevention of disease, which was not a focus of our study, and focusing on the approach of reducing overall antibiotic use, our data demonstrated an over-prescription of antibiotics in general practice in the UK relative to indication. This study reports that 17.9% of the cases who had received antibiotics and were referred to internal medicine and oncology services ultimately had a bacterial aetiology confirmed or suspected at the referral centre. In an attempt to limit an underestimation of cases with a bacterial aetiology, we included both confirmed and suspected bacterial aetiology as categories for analysis.

282 Various drivers have been attributed to the over-prescription of antibiotics in veterinary

283 practice. This includes client factors such as perceived client satisfaction, commercial pressures

to retain clients and the symbolic value of giving treatment (Smith *et al.*, 2018). Interestingly

- 285 however, this was not borne out in pet owner surveys, where pet owners reported a
- 286 perception of over-prescription by veterinarians (Smith *et al.*, 2018). Additional contributing

factors to consider may include time pressures and clinical and financial resources available toallow a definitive diagnosis.

289 Focusing on the approach to limit AR of improved antibiotic use, the Protect / ProtectMe 290 Guidelines attempt to guide veterinarians when antibiotics might be appropriate, and thereby 291 reduce unnecessary prescription. Our data demonstrates poor adherence to antibiotic 292 guidelines.. The most common way in which the Protect/ProtectMe guidelines were not 293 followed was the prescription of antibiotics for clinical signs for which the guidelines were 294 specifically advising veterinarians against, which happened in 47.7% of the cases that received 295 antibiotics. Of those, the most common were uncomplicated vomiting and/or diarrhoea. In 296 addition to breaking from the Protect / ProtectMe guidelines, this also goes against additional 297 antibiotic use guidelines, where recommendations around managing enteropathogenic 298 bacterial infections recommend reserving antibiotics for patients demonstrating signs of sepsis 299 (Marks et al., 2011). Furthermore, although a recent study suggests that metronidazole can 300 shorten duration of acute non-specific diarrhoea in some dogs (Langlois, Koenigshof and Mani, 301 2020), multiple other veterinary studies indicate a limited benefit (Jergens et al., 2010; 302 Shmalberg et al., 2019; Werner et al., 2020, Busch et al., 2015)). For chronic enteropathies, 303 current UK antibiotic guidelines consider appropriate a four-week trial of antibiotics for 304 determining if the clinical presentation is antibiotic-responsive. However, a recent publication 305 proposes antibiotic use is reserved until other therapeutic trials are proven unsuccessful, 306 including diet/pre-probiotics or immunosuppressive drugs (Cerquetella et al., 2020). 307 In our cohort, metronidazole was commonly prescribed to manage both acute and chronic 308 gastrointestinal disorders, similar to data collected across Europe (Hughes et al., 2012). Whilst 309 metronidazole is a popular choice to manage *Clostridial sp.* in people, the role of *Clostridial sp.* 310 in canine diarrhoea syndromes remains uncertain (Busch et al., 2015). Metronidazole also 311 disrupts the normal canine microbial flora, and is associated with an increased risk of

becoming a carrier for multi-drug-resistant *Escherichia coli* (Gibson *et al.*, 2011; Igarashi *et al.*,
2014). Further, it may increase the risk of bacterial translocation, which has been shown in
laboratory mice. (Wells *et al.*, 1987).

315 Another clinical sign in which antibiotics were frequently prescribed but which contradicted 316 Protect/ProtectMe guidance against their use was feline lower urinary tract signs. Similar to 317 recommendations within the ISCAID guidelines (Weese et al., 2011, 2019), Protect/ProtectMe 318 guidelines state that bacterial culture and susceptibility testing should be performed in all 319 cases of suspected bacterial cystitis. However, an update to those guidelines (Weese et al., 320 2019), was not available for use at the time of the study, with older guidelines (Weese et al., 321 2011) conflicting with Protect / ProtectMe guidance in that they supported empiric antibiotic 322 therapy while awaiting culture and susceptibility results to relieve patient discomfort. This 323 could have been one reason why antibiotics were prescribed in this setting. Current 324 recommendations are to confirm a diagnosis of bacterial cystitis, by culture, in all feline 325 patients due to the low likelihood of bacterial cystitis in cats. Further to this, clinical signs of 326 bacterial cystitis are frequently a result of inflammation and there is some evidence from 327 humans that analgesics alone may be as effective as antibiotics in uncomplicated cases 328 (Bleidorn *et al.*, 2016).

Both polyuria/polydipsia and canine sino-nasal disease were also associated with poor adherence to Protect / ProtectMe guidelines. Multiple aetiologies can result in polyuria and polydipsia in dogs and cats, with antibiotics only necessary where a septic focus is identified or strongly suspected. Primary bacterial rhinitis is an uncommon entity in dogs, with bacterial rhinitis more likely to occur as a sequela to inhaled foreign bodies or as a consequence of loss of turbinates resulting from mycotic disease, or trauma. In these cases, antibiotics might improve clinical signs but rarely permanently (Windsor *et al.*, 2006). 336 In human medicine sepsis guidelines, antibiotics are recommended within one hour of 337 recognition in patients with septic shock or high likelihood/confirmed of sepsis, given the 338 strong association of antibiotic timing and mortality (Evans et al., 2021). SIRS/sepsis criteria 339 were assessed as a possible reason why antibiotics may have been prescribed in these patients 340 in which assessing clinical signs alone, the prescription was considered inappropriate. Only 341 6.9% of the population met the criteria for SIRS/sepsis at the time they were prescribed with antibiotics. However, only 85 (21.8%) dogs and 9 (9.4%) cats had criteria available at the time 342 343 of antibiotic prescription to make some assessment for SIRS, with the vast majority not having 344 complete criteria available. Of those, 36.2% of the animals met the SIRS criteria, although a 345 significant proportion of these were classified based upon 2 or 3 criteria alone. It is difficult to 346 make robust conclusions around the incidence of SIRS in this cohort given the vast majority of 347 cases prescribed antibiotics had insufficient information available to make an assessment at 348 all. This could reflect those parameters were normal but were not documented, were not 349 assessed due to short consultation durations in general practise in the UK, or a lack of 350 emphasis regarding the importance of those factors in decision making around antibiotic use. 351 Failure to confirm a bacterial aetiology and evaluate antibiotic susceptibilities leads to the 352 misuse of antibiotics, and does not allow veterinarians to make adequate choices around 353 appropriate prescription (EMA, 2015; The Veterinary Medicines, 2015; Weese et al., 2015). The 354 data from our study demonstrates that antibiotic prescription was based on results of culture 355 and sensitivity in only 8.8% of cases, whilst cytology was used in only 1.8% of cases, with only a 356 very small number of cases having both. This is similar to data reported elsewhere, where only 357 approximately half of veterinarians surveyed considered bacterial culture and sensitivity as 358 important prior to prescribing antibiotics with fewer (30%) considering cytology useful (Hughes 359 et al., 2012).

360 Prescription of beta-lactams was common in our study, similar to previous publications from 361 the UK (Mateus et al., 2011; Radford et al., 2011). The most common prescribed beta-lactam 362 were penicillins, which were prescribed in 71.5% of dogs and 49.0% of cats. Nitroimidazoles 363 (i.e. metronidazole) was the second most commonly prescribed antibiotic class in dogs, higher 364 than in other reports (Mateus et al., 2011; Radford et al., 2011). This difference could be 365 attributed to a population bias of patients referred to Internal Medicine, where 366 gastrointestinal signs may be more common than within the general population and 367 metronidazole is commonly prescribed in cases with diarrhoea as previously mentioned 368 (Hughes et al., 2012). In cats, third generation cephalosporins were the second most used 369 antibiotic, more specifically cefovecin. This antibiotic choice was significantly different 370 between cats and dogs. This has previously been reported in the UK and Europe after 371 authorisation of cefovecin, and likely reflects ease-of-use of long-acting injections in a species 372 frequently non-compliant with oral therapeutics (Levy, 1998; Mateus et al., 2011; Burke et al., 373 2017). Cost associated with cefovecin administration may also negatively impacts use in dogs 374 (Mateus et al., 2011). 375 Fluoroquinolones or third generation cephalosporins were inappropriately prescribed in 89.0%

376 of the cases receiving these classes of antibiotics, as culture and sensitivity had not been 377 performed, and/or as other agents could have been used (Collignon *et al.*, 2016). The WHO 378 classifies these antibiotic classes as highest priority critically important antibiotics and it has 379 even been suggested that use of these antibiotics should be banned in animals to preserve 380 their effectiveness in human medicine (Hughes et al., 2012; Collignon et al., 2016). However, 381 there are concerns that a complete ban in veterinary medicine could be detrimental to animal 382 health and welfare (Hughes et al., 2012). UK antibiotic guidelines recommend use only when 383 an antibiotic better aligned with prescribing guidelines is inappropriate and/or ineffective, and 384 culture/sensitivity testing indicates that they will be effective.

385 Underdosing of antibiotics was documented in 26.9% of the cases included in our study, and 386 this practice could result in subinhibitory concentrations and resistance (Choe et al., 2000; 387 Gillespie et al., 2005; Ungemach, Müller-Bahrdt and Abraham, 2006). Reasons for underdosing 388 were not always apparent. Miscalculations or rounding dosages to the nearest tablet size are 389 considered possibilities. 390 Our study has several limitations that reflect its retrospective nature, a referral population 391 bias, and within that, limitation to Oncology and Internal Medicine disciplines. As is frequently 392 the case with retrospective studies, data was not always complete regarding clinical signs, 393 antibiotic prescription, and physical examination. We included cases where a bacterial 394 aetiology was "suspected" as one of the differential diagnosis based upon comment in the 395 referral communications, but it is possible that differentials associated with suspected 396 bacterial infection were not mentioned. 397 On its own, a referral population could be expected to bias data through increased case 398 complexity and perhaps a higher frequency of antibiotic use. Further restriction to only 399 Internal Medicine and Oncology cases could theoretically be expected to increase the overall 400 antibiotic prescription frequency in this cohort, compared to other disciplines if they were also 401 included. Discipline restriction could also have impacted choices around antibiotic classes 402 prescribed, for example exclusion of Dermatology might be expected to comparatively reduce 403 prescription of cephalosporins. 404 We decided to investigate a referral population as they underwent extensive referral 405 investigations so we considered that that appropriateness of the use of antibiotics could be 406 addressed better than in cases without it. However, our findings may under-represent 407 antibiotic prescriptions in a general practice setting, as cases that improved as a result of, or 408 spontaneously irrespective of antibiotic prescription, are unlikely to be referred. 409 Lastly, between the two referral hospitals included, different timeframes were assessed, 410 however this is considered unlikely to cause a significant shift in prescription patterns. This

411 timeframe did cover an update on the guidelines in November 2018, however we limited the 412 recommendations assessed and included to those present in both versions. 413 Specific UK guidelines were assessed, and it is possible that veterinarians were following a 414 different antibiotic guideline with conflicting recommendations. Apart from the discussed 415 previously regarding feline lower urinary tract disease and chronic diarrhoea already 416 mentioned, no other conflicting recommendations were found. 417 Given roles in managing domestic animals with close human bonds, as well as roles within the 418 human food chain, veterinarians have an integral role in promoting responsible use of 419 antibiotics. It has been estimated that without proactive solutions to slow rising antibiotic 420 resistance, or discovery of new antibiotics, that 10 million lives a year will be at risk by 2050 421 (Neill, 2014) We were not able, and did not set out, to evaluate veterinarians knowledge or 422 understanding of existing antibiotic stewardship guidelines, or to determine what barriers 423 might lead to non-compliance. However, our data identifies several aspects worthy of further 424 exploration and investment in improving education around appropriate diagnostics, antibiotic 425 class and dosage choices, thereby leading to improved compliance within antibiotic

426 stewardship guidelines and more responsible use of antibiotics.

427 In conclusion, over prescription of antibiotics, poor adherence to UK antibiotic guidelines and

428 infrequent use of diagnostics such as culture and cytology to guide antibiotic use was

429 observed.

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Review Cool

## 1 Antibiotic therapy in dogs and cats in general practice in the United

- 2 Kingdom prior to referral.
- 3

## 4 ABSTRACT

5 Objectives: To describe antibiotic prescription by veterinarians in general practices in the

6 United Kingdom (UK) prior to referral and analyse if UK antibiotic stewardship guidelines were

7 followed.

8 Materials and methods: The clinical records from dogs and cats referred to the Internal

9 Medicine and Oncology departments of two referral hospitals were retrospectively reviewed.

10 Results: There were 917 cases included, of which 486 (53.0%) had been prescribed antibiotics

11 for the presentation they were subsequently referred for. Bacterial culture or cytology to guide

12 antibiotic prescription had been performed in 43/486 (8.8%) and 9/486 cases (1.8%)

13 respectively. In four cases, both cytology and culture were performed. For those animals who

had received antibiotics, 344/486 (70.8%) prescriptions did not comply with local-UK antibiotic

15 stewardship guidelines. Following investigations at a referral centre, a bacterial aetiology was

16 found or suspected in <u>17.924.19.5</u>% of the cases that received antibiotics.

17 Clinical significance: Use of diagnostics, including culture and cytology, to prove or determine

18 the likelihood of a bacterial aetiology was infrequently performed prior to referral and may

19 have contributed to over prescription of antibiotics. Encouraging veterinarians to undertake

20 appropriate diagnostics, in combination with education around compliance with antibiotic

21 stewardship guidelines, might reduce antibiotic prescription.

22 Keywords: antibiotic, antimicrobial, prescription, resistance, responsible

23

Journal of Small Animal Practice

## 24 INTRODUCTION

25	Antibiotic resistance has been observed since antibiotics were first discovered. Antibiotic
26	therapy contributes to the development of antibiotic resistance (AR) in both humans and
27	animals (Jernberg et al., 2010; Schmidt et al., 2018). Any use of antibiotics exposes bacterial
28	pathogens and commensal microbiota to a selection pressure that can result in the emergence
29	of antibiotic resistance or, if a resistant subpopulation is present, an increase in the abundance
30	of resistant bacteria (Weese et al., 2015). This has increasingly become a problem in recent
31	decades where use of antibiotics has accelerated the rate at which resistance has developed
32	(Costelloe et al., 2010). Broad dissemination of AR amongst different bacterial populations has
33	resulted in treatment failures in both human and veterinary medicine (Huemer et al., 2020).
34	The concern regarding AR in veterinary medicine is further underpinned by studies
35	investigating the nature and frequency of the contacts that occur between pets and people,
36	which highlight the large number of opportunities that exist for the zoonotic transfer of
37	bacteria and that have provided evidence that bacteria can be transferred in both directions
38	(Westgarth et al., 2007; Wieler et al., 2011; Walther et al., 2012). This interspecies
39	transmission can further contribute to AR through a feedback loop of resistance reservoirs and
40	the evolution of generations of increasingly resistant bacteria (Manian, 2003; Guardabassi,
41	Loeber and Jacobson, 2004; Loeffler et al., 2005; Van Balen et al., 2017).
42	In the UK, many antibiotics are licensed for veterinary use and can only be prescribed by a
43	veterinary surgeon (UK Stationery Office, 2013). Responsible antibiotic use can be defined as
44	'an attitude to maximise therapeutic efficacy and minimise the selection of resistant
45	microorganisms' and should theoretically reduce the spread of antibiotic resistance (Duquette
46	and Nuttall, 2004). The Protect and ProtectMe guidelines (BSAVA/SAMSoc, 2013, 2018)
47	produced by the British Small Animal Veterinary Association (BSAVA) and Small Animal
48	Medicine Society (SAMSoc) were developed to promote responsible antibacterial prescribing

49 practises. However, it is unclear if these guidelines are widely followed in UK practice or if they

50 have had any widespread impact on antibiotic use (Hughes *et al.*, 2012).

51 The aim of this study was to assess prescription of antibiotics by veterinarians in general

- 52 practices in the UK prior to referral to Oncology and Internal Medicine departments for the
- 53 condition the patient was subsequently referred for. A secondary aim was to analyse whether
- 54 these prescriptions adhered to Protect and ProtectMe Guidelines.
- 55

#### 56 MATERIALS AND METHODS

57 Medical records of dogs and cats who were referred to the Internal Medicine department of 58 the hospital A between the 1<sup>st</sup> of March of 2018 and the 28<sup>th</sup> of February of 2019 and to the 59 Internal Medicine and Oncology departments of hospital B between the 1<sup>st</sup> November 2016 60 and the 1<sup>st</sup> November 2017 were reviewed in a retrospective manner.

61 The following information was collected from each patient's medical record: signalment, 62 clinical signs which resulted in patient referral and length of time the patient had been 63 experiencing these clinical signs, whether or not antibiotics had been prescribed for these 64 clinical findings, and the final or presumptive diagnosis made at the referral centres. Only information regarding antibiotics prescribed for the condition they were referred for were 65 66 recorded. If an antibiotic was prescribed for the condition the patient was referred for then 67 the following information was collected: antibiotic class, dose, route, duration and frequency 68 of administration, whether the animal was receiving the antibiotic(s) on the day they were 69 referred, and whether or not bacterial culture and sensitivity or cytology were performed to 70 guide antibiotic prescription. Where an animal received multiple antibiotics, but of the same 71 class, these were counted as different antibiotics. When the animal had received a long-acting 72 injection of cefovecin, 14 days was assumed for duration of the antibiotic (Stegemann et al., 73 2006; Stegemann, Sherington and Blanchflower, 2006). Where the clinical signs were reported

74	as chronic (lasting >4 weeks), clinical records were also analysed for antibiotic use up to three
75	months prior to referral. Animals receiving antibiotics to treat a condition independent of the
76	reason for their referral were excluded because the final diagnosis for these conditions could
77	not commonly be verified. Cats referred for radioiodine therapy for the treatment of
78	hyperthyroidism at one of the centres (hospital B) were also excluded.
79	If the patient had been prescribed an antibiotic / antibiotics for the condition they were
80	referred for then the patient heart rate, respiratory rate, body temperature and white blood
81	cell count at the time of antibiotic prescription were collected and used to determine if criteria
82	for systemic inflammatory response syndrome (SIRS) were met. When two or more (dogs) and
83	three or more (cats) of the following criteria were met, the patient was classified as following
84	SIRS criteria: hypothermia or fever, tachycardia or bradycardia (the latter only in cats),
85	tachypnoea, leukocytosis, leucopenia or increased band neutrophil count in animals with a
	normal white blood cell count (Hauptman, Walshaw and Olivier, 1997; Brady et al., 2000).
86	
86	Antibiotic use was analysed against using UK veterinary antibiotic guidelines (BSAVA/SAMSoc,
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87 88 90 91 92 93 94 95	Antibiotic use was analysed against using UK veterinary antibiotic guidelines (BSAVA/SAMSoc, 2013, 2018). In particular, we evaluated four ways the guidelines were not followed which recommendations which could be objectively analysed: 1, evidence of underdosing, which included inferior absolute dose and insufficient frequency of administration, and was assessed against the BSAVA Small Animal Formulary 8 <sup>th</sup> and 9 <sup>th</sup> editions (Ramsey, 2014, 2018); 2, or cycling through various antibiotics, defined as successive use of antibiotics of different classes without supportive culture and sensitivity results; 3, the inappropriate use of either fluoroquinolones or 3 <sup>rd</sup> and 4 <sup>th</sup> generation cephalosporins defined using the aforementioned guidelines without bacterial culture and sensitivity results, when an antibiotic better aligned

99 Animal Formulary 8th and 9th editions (Ramsey, 2014, 2018), whether antibiotics were 100 prescribed when defined as not indicated by aforementioned local-UK guidelines. Specifically 101 wWe assessed antibiotic prescription in the following settings: acute vomiting (regurgitation 102 was also included in this category), acute diarrhoea (including haemorrhagic), chronic 103 diarrhoea (cases that received a four week treatment were excluded as antibiotic trials have 104 been described for management of chronic diarrhoea and cases in which Giardia spp. infection 105 was diagnosed and metronidazole was prescribed were also excluded as it is a recognised 106 treatment) (Scorza V., 2012), canine sino-nasal disease, subclinical bacteriuria, feline lower 107 urinary tract disease, polyuria and polydipsia (unless pyogenic focus suspected), weight loss 108 and the use of prophylactic antibiotics except for a few specific medical conditions (e.g. 109 immunocompromised patients). If the patient met the SIRS/sepsis criteria at the time the 110 antibiotic was prescribed, they were not classified as inappropriate. 111 Cases were divided into subcategories depending on body system affected (i.e. respiratory, 112 gastrointestinal, multisystemic, hepatobiliary, endocrine, haematology/immunology, 113 urinary/reproductive and other). Oncological cases were categorised under the major body 114 system affected by the tumour, or where this was not possible then were classified as 115 multisystemic.

## 116 Statistics

117Descriptive statistics were used. Data were tested for normal distribution using histograms and118Shapiro Wilk tests. Non-normally distributed data are presented as median and range. Chi-119square tests were used to compare antibiotic prescription between species. All analyses were120performed using commercial software (IBM® SPSS® v.28.0.1.1). Statistical significance was set121as  $P \le 0.05$ .

180 168 RESULTS

## 169 Study Population

- 170 A total of 917 animals met the inclusion criteria for the study, 265 were referred to hospital A
- and 652 were referred to the hospital B. Of these, 666 cases were referred to internal
- 172 medicine and 251 cases to oncology.
- 173 There were 739 dogs, with 405 (54.8%) being male and 326 (44.1%) were female, of which 307
- 174 (75.8%) of males and 261 (80.0%) of females were neutered. There were 178 cats with 96
- 175 (53.9%) being male and 79 (44.4%) female, of which 89 (92.7%) of males and 74 (93.6%) of
- 176 females were neutered. The sex was unknown in eight dogs and three cats. Median age of
- dogs at the time of referral was 7.4 years (range 1 month to 16 years) and cats was 9.3 years
- 178 (range 2 months to 19 years) (Supporting information S1).

## 179 Antibiotic Prescription

180 There were 486 animals (53.0%), which compromised of 390/739 (52.8%) dogs and 96/178 181 (53.9%) cats, that had received antibiotics prior to referral for the clinical presentation they 182 were referred for. , which comprised of 390 dogs and 96 cats. Of the dogs who had received 183 antibiotics, there were 223 (57.2%) males and 166 (42.6%) females, of which 285-163 (73.1%) 184 of the males and 319-132 (79.5%) of the females were neutered. The gender was not reported 185 in one dog. Of the cats receiving antibiotics, 52 (54.23.6%) were male and 43 (44.83%) were 186 female; <u>43/52 (</u>82.7%) of males and <u>40/43 (</u>93.<u>0</u>1%) of females were neutered. The gender was 187 not reported in one cat. The median age of the dogs who received antibiotics was 8 years 188 (range 1 to 16 years) and for cats was 8 years (range 2 months to 19 years). 189 Three hundred and forty seven cases had been prescribed one antibiotic class. Two different 190 antibiotic classes had been prescribed for 133120/486 animals (27.424.7%), whilst 21-16 (3.3%) 191 had received three different antibiotic classes, three3 (0.6%) had received four antibiotic

192 classes and one animal received five different antibiotic classes. One hundred and sixty animals

193 (32.9%) were still receiving antibiotics at the time of referral.

194 Table 1 describes antibiotic classes prescribed. The antibiotic classes most commonly

195 prescribed in dogs were penicillins in 279/390 (71.5%) cases and nitroimidazoles (ie.

196 metronidazole) in 100/390 (25.6%) cases. For cats, the most common classes prescribed were

197 penicillins in 47/96 (49.0%) cases and third generation cephalosporins in 32/96 (33.3%). When

198 antibiotics were prescribed, cats were significantly less likely to receive a penicillin antibiotic

199  $(X^2 (1, N = 486) = 17.8, p < 0.001)$  and more likely to be prescribed a 3<sup>rd</sup> generation

200 cephalosporin compared with dogs ( $X^2$  (1, N = 486) = 79.5, p<0.001). The only third generation

201 cephalosporin that was prescribed for both dogs and cats was cefovecin.

202 The data for the combination of antibiotic classes prescribed is presented in Figure 1 and

203 2.-The most commonly prescribed combination of antibiotics was a nitroimidazole\_and a

penicillin in both dogs (40/390; 10.2%) and cats (6/96; 6.32%). In dogs, the second most

205 common combination of antibiotics included a penicillin and a fluoroquinolone (9/390; 2.3%)

and a penicillin and a lincosamide (9/390; 2.3%), whilst in cats a penicillin and a 3<sup>rd</sup> generation

207 cephalosporin was the second most common combination (5/96; 5.2%).

208 The data for the antibiotic classes prescribed for each body system is presented in Figure 3.

209 Penicillins were the most commonly prescribed antibiotic class for all body systems (endocrine

210 10/46; 21.7%, haematological/immunological 7/31; 22.6%, hepatobiliary 24/69; 34.8%,

211 multisystemic 108/320; 33.8%, respiratory 49/108; 45.4% and urinary/reproductive 43/86;

212 50%) apart from the gastrointestinal body system where it was nitroimidazoles (67/170;

213 39.4%). When lincosamides or second and third generation cephalosporines were prescribed,

they were most commonly prescribed for multisystemic disease (lincosamides 17/320; 5.3%,

second generation cephalosporines 15/320; 4.7% and third generation cephalosporines

216 19/320; 5.9%) (Supporting information S2).

2	_
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### 218 Use of culture and sensitivity and/or cytology to guide antibiotic prescription

- A bacterial culture and sensitivity had been performed in 43/486 (8.8%) animals that had been
- 220 prescribed antibiotics prior to referral. In 10/43 (23.3%), the antibiotic prescription was
- 221 considered inappropriate on the basis that results were obtained from nasal swabs, which
- typically isolates microorganisms representative of colonisation rather than true infection
- 223 (Meler, Dunn and Lecuyer, 2008).

Nine (1.9%) patients underwent cytology testing to guide antibiotic prescription. The antibiotic prescription was considered questionable in one dog where extracellular bacteria were seen in an otherwise inactive urine sediment and in one cat where bacteria likely representing normal flora were seen in an upper respiratory secretion. In four cases, both cytology and culture were performed.

## 229 SIRS/sepsis criteria

Out of 390 dogs that had received antibiotics, 85 dogs (21.8%) had data in the clinical records 230 231 available to assess for SIRS criteria at the time of antibiotics prescription. Of these, 10 (11.8) 232 dogs had all 4-four criteria available (i.e., heart rate, respiratory rate, temperature and 233 haematology), 38 (44.7%) dogs had <u>3-three</u>criteria available and 37 (43.5%) had <u>2-two</u>criteria 234 available. Of the 10 dogs with 4-four criteria available, 8-eight were classified as following SIRS 235 criteria. Fourteen-Ten of 38 dogs with 3-three criteria available were classified as following SIRS 236 criteria and 10-six of 37 dogs with 2-two criteria available were classified as following SIRS 237 criteria.

Out of 96 cats that received antibiotics, 9 (9.4%) cats had data in the clinical records available to assess for SIRS at the time of antibiotic prescription. One cat had all 4-<u>four</u> criteria available and 8 cats had <u>3-three</u> criteria available. The cat with the four criteria available was classified

- as following SIRS criteria and one <u>six out</u> of <u>9-nine</u> cats with 3 criteria available was were
- 242 classified as following SIRS criteria.
- Therefore, only 3427/94 (36.214.3%) animals with enough data available to assess SIRS met
- the criteria for SIRS at the time they had been prescribed an antibiotic.
- 245 Local a<u>A</u>ntibiotic guidelines
- 246 When considering Protect/ProtectME guidelines, 344/486 (70.8%) cases did not have antibiotic
- prescription in line with these guidelines in one way only (i.e. underdosing, cycling antibiotics,
- 248 inappropriate prescription of fluoroquinolones or third generation cephalosporins and use of
- 249 antibiotics for clinical signs that were recommended against antibiotic use by the guidelines.)-
- 250 One hundred and eleven (47.8%) cases did not adhere with the guidelines in two different
- 251 ways, 31 (17.7%) cases in three different ways and 8 (3.4%) cases in the four ways assessed.
- 252 <u>(i.e. underdosing, cycling antibiotics, inappropriate prescription of fluoroquinolones or 3<sup>rd</sup></u>
- 253 generation cephalosporins and use of antibiotics for clinical signs that were recommended
- 254 <u>against antibiotic use by the guidelines.</u>}
- 255 Underdosing was recorded in 131/486 (26.9%) cases. Cycling antibiotics occurred in 97/467
- 256 (i.e. 20.8%, 19 patients were prescribed two antibiotics from the start of their treatment),
- 257 <u>following apparent failure of a first antibiotic, cases were prescribed a second antibiotic</u>
- 258 <u>without supportive culture and sensitivity results.</u>). There were 91/486 (18.7%) cases that were
- 259 prescribed a fluoroquinolone or third generation cephalosporin, and Inappropriate
- 260 prescription of these two classes of antibiotics occurred There were 91/486 (18.7%) cases that
- 261 were prescribed a fluoroquinolone or third generation cephalosporin, inof which 81/91
- 262 (89.0%) <u>cases</u>. were prescribed when another more appropriate class could have been
- 263 prescribed. A culture and sensitivity test had been performed in 1/91 cases that were
- 264 prescribed these class of antibiotics.-

265	Following apparent failure of a first-line antibiotic, 97/486 (19.9%) cases were prescribed a
266	second line antibiotic without supportive culture and sensitivity results. Underdosing was
267	recorded in 131/486 (26.9%) cases.
268	There were 232/486 (47.7%) cases that had been prescribed antibiotics for clinical signs where
269	antibiotics are not recommended by the Protect/ProtectME guidelines.
270	Of the patients who received a prior antibiotics as indicated by UK guidelines, only clinical
271	variables met SIRS/sepsis criteria, 13/20 dogs and 3/7 cats who met these criteria
272	subsequently received antibiotics which did not adhere to UK guidelines (Supporting
273	information S3, S4 and S5).
274	One hundred and eleven (47.8%) cases did not adhere with the guidelines in two different
275	ways, 31 (17.7%) cases in three different ways and 8 (3.4%) cases in the four ways (i.e.
276	underdosing, cycling antibiotics, inappropriate prescription of fluoroquinolones or 3 <sup>rd</sup>
277	generation cephalosporins and use of antibiotics for clinical signs that were recommended
278	against antibiotic use by the guidelines.)
279	Bacterial infection documented
280	After investigations within a referral centre setting, a bacterial aetiology was found in
281	5566/486 (1 $13.36%$ ) cases that received antibiotics, and was suspected in a further $3251$
282	( $6.610.5\%$ ) cases. Therefore, a bacterial aetiology was found or suspected in $17.924.1\%$ of the
283	cases that received antibiotics. For one cat included here, Helicobacter spp was diagnosed
284	within gastric biopsy samples.
285	
286	DISCUSSION
287	Our data demonstrates that substantial improvement on adherence to antibiotic guidelines in

289 <u>medicine or oncology</u> the guidelines were not followed. It also demonstrates over-prescription
 290 of antibiotics and <u>infrequent use of appropriate tools uncommon use of tools</u> to diagnose
 291 bacterial infection such as culture or cytology.

Three general approaches have been recommended to help limit antibiotic resistance: a)
preventing disease occurrence, b) reducing overall antibiotic use and c) improved antibiotic
use (Weese *et al.*, 2015).

295 Setting aside prevention of disease, which was not a focus of our study, and focusing on the 296 approach of reducing overall antibiotic use, our data demonstrated an over-prescription of 297 antibiotics in general practice in the UK relative to indication. This study reports that in 298 17.924.1% of the cases who had received antibiotics and were referred to internal medicine 299 and oncology services ultimately had a bacterial aetiology confirmed or suspected at the 300 referral centre. In an attempt to limit an underestimation of cases with a bacterial aetiology, 301 we included both confirmed and suspected bacterial aetiology as categories for analysis. 302 Various drivers have been attributed to the over-prescription of antibiotics in veterinary 303 practice. This includes client factors such as perceived client satisfaction, commercial pressures 304 to retain clients and the symbolic value of giving treatment (Smith *et al.*, 2018). Interestingly 305 however, this was not borne out in pet owner surveys, where pet owners reported a 306 perception of over-prescription by veterinarians (Smith et al., 2018). Additional contributing 307 factors to consider may include time pressures and clinical and financial resources available to 308 allow a definitive diagnosis.

309 Focusing on the approach to limit AR of improved antibiotic use, the Protect / ProtectMe

310 Guidelines attempt to guide veterinarians when antibiotics might be appropriate, and thereby

311 reduce unnecessary prescription. Our data demonstrates poor adherence to antibiotic

- 312 guidelines.. The most common way in which the Protect/ProtectMe guidelines were not
- followed was the prescription of antibiotics for clinical signs for which the guidelines were

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314	specifically advising veterinarians against, which happened in 47.7% of the cases that received
315	antibiotics. Of those, the most common were uncomplicated vomiting and/or diarrhoea. In
316	addition to breaking from the Protect / ProtectMe guidelines, this also goes against additional
317	antibiotic use guidelines, where recommendations around managing enteropathogenic
318	bacterial infections recommend reserving antibiotics for patients demonstrating signs of sepsis
319	(Marks et al., 2011). Furthermore, although a recent study suggests that metronidazole can
320	shorten duration of acute non-specific diarrhoea in some dogs (Langlois, Koenigshof and Mani,
321	2020), multiple other veterinary studies indicate a limited benefit (Jergens et al., 2010;
322	Shmalberg <i>et al.</i> , 2019; Werner <i>et al.</i> , 2020, Busch <i>et al.</i> , 2015)). For chronic enteropathies,
323	current local-UK antibiotic guidelines consider appropriate a four-week trial of antibiotics for
324	determining if the clinical presentation is antibiotic-responsive. However, a recent publication
325	proposes antibiotic use is reserved until other therapeutic trials are proven unsuccessful,
326	including diet/pre-probiotics or immunosuppressive drugs (Cerquetella et al., 2020).
327	In our cohort, metronidazole was commonly prescribed to manage both acute and chronic
328	gastrointestinal disorders, similar to data collected across Europe (Hughes et al., 2012). Whilst
329	metronidazole is a popular choice to manage <i>Clostridial sp.</i> in people, the role of <i>Clostridial sp</i> .
330	in canine diarrhoea syndromes remains uncertain (Busch et al., 2015). Metronidazole also
331	disrupts the normal canine microbial flora, and is associated with an increased risk of
332	becoming a carrier for multi-drug-resistant <i>Escherichia coli</i> (Gibson et al., 2011; Igarashi et al.,
333	2014). Further, it may increase the risk of bacterial translocation, which has been shown in
334	laboratory mice. (Wells <i>et al.,</i> 1987).
335	Another clinical sign in which antibiotics were frequently prescribed but which contradicted
336	Protect/ProtectMe guidance against their use was feline lower urinary tract signs. Similar to
337	recommendations within the ICCAID suidelines (Masses at s. 2011, 2010) Dratest (Dratest)
	recommendations within the ISCAID guidelines (Weese et al., 2011, 2019), Protect/ProtectMe
339	cases of suspected bacterial cystitis. However, an update to those guidelines (Weese et al.,
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340	2019), was not available for use at the time of the study, with older guidelines (Weese et al.,
341	2011) conflicting with Protect / ProtectMe guidance in that they supported empiric antibiotic
342	therapy while awaiting culture and susceptibility results to relieve patient discomfort. This
343	could have been one reason why antibiotics were prescribed in this setting. Current
344	recommendations are to confirm a diagnosis of bacterial cystitis, by culture, in all feline
345	patients due to the low likelihood of bacterial cystitis in cats. Further to this, clinical signs of
346	bacterial cystitis are frequently a result of inflammation and there is some evidence from
347	humans that analgesics alone may be as effective as antibiotics in uncomplicated cases
348	(Bleidorn <i>et al.,</i> 2016).
349	Both polyuria/polydipsia and canine sino-nasal disease were also associated with poor
350	adherence to Protect / ProtectMe guidelines. Multiple aetiologies can result in polyuria and
351	polydipsia in dogs and cats, with antibiotics only necessary where a septic focus is identified or
352	strongly suspected. Primary bacterial rhinitis is an uncommon entity in dogs, with bacterial
353	rhinitis more likely to occur as a sequela to inhaled foreign bodies or as a consequence of loss
354	of turbinates resulting from mycotic disease, or trauma. In these cases, antibiotics might
355	improve clinical signs but rarely permanently_(Windsor <i>et al.</i> , 2006) (Windsor and Johnson,
356	<del>2006)</del> .
357	In human medicine sepsis guidelines, antibiotics are recommended within one hour of
358	recognition in patients with septic shock or high likelihood/confirmed of sepsis, given the
359	strong association of antibiotic timing and mortality (Evans <i>et al.</i> , 2021). SIRS/sepsis criteria
360	were assessed as a possible reason why antibiotics may have been prescribed in these patients
361	in which assessing clinical signs alone, the prescription was considered inappropriate. Only
362	6.9% of the population met the criteria for SIRS/sepsis at the time they were prescribed with

antibiotics. However, only 85 (21.8%) dogs and 9 (9.4%) cats had criteria available at the time

364 of antibiotic prescription to make some assessment for SIRS, with the vast majority not having 365 complete criteria available. Of those, 36.2% of the animals met the SIRS criteria, although a 366 significant proportion of these were classified based upon 2 or 3 criteria alone. It is difficult to 367 make robust conclusions around the incidence of SIRS in this cohort given the vast majority of 368 cases prescribed antibiotics had insufficient information available to make an assessment at 369 all. This could reflect those parameters were normal but were not documented, were not 370 assessed due to short consultation durations in general practise in the UK, or a lack of 371 emphasis regarding the importance of those factors in decision making around antibiotic use. 372 Failure to confirm a bacterial aetiology and evaluate antibiotic susceptibilities leads to the 373 misuse of antibiotics, and does not allow veterinarians to make adequate choices around 374 appropriate prescription (EMA, 2015; The Veterinary Medicines, 2015; Weese et al., 2015). The 375 data from our study demonstrates that antibiotic prescription was based on results of culture 376 and sensitivity in only 8.8% of cases, whilst cytology was used in only 1.8% of cases, with only a 377 very small number of cases having both. This is similar to data reported elsewhere, where only 378 approximately half of veterinarians surveyed considered bacterial culture and sensitivity as 379 important prior to prescribing antibiotics with fewer (30%) considering cytology useful (Hughes 380 et al., 2012).

381 Prescription of beta-lactams was common in our study, similar to previous publications from 382 the UK (Mateus et al., 2011; Radford et al., 2011). The most common prescribed beta-lactam 383 were penicillins, which were prescribed in 71.5% of dogs and 49.0% of cats. Nitroimidazoles 384 (i.e. metronidazole) was the second most commonly prescribed antibiotic class in dogs, higher 385 than in other reports (Mateus et al., 2011; Radford et al., 2011). This difference could be 386 attributed to a population bias of patients referred to Internal Medicine, where 387 gastrointestinal signs may be more common than within the general population and 388 metronidazole is commonly prescribed in cases with diarrhoea as previously mentioned

389 (Hughes et al., 2012). In cats, third generation cephalosporins were the second most used 390 antibiotic, more specifically cefovecin. This antibiotic choice was significantly different 391 between cats and dogs. This has previously been reported in the UK and Europe after 392 authorisation of cefovecin, and likely reflects ease-of-use of long-acting injections in a species 393 frequently non-compliant with oral therapeutics (Curt , Simon and HuckabeeLevy, 1998; 394 Mateus et al., 2011; Burke et al., 2017). Cost associated with cefovecin administration may 395 also negatively impacts use in dogs (Mateus et al., 2011). 396 Fluoroquinolones or third generation cephalosporins were inappropriately prescribed in 89.0% 397 of the cases receiving these classes of antibiotics, as culture and sensitivity had not been 398 performed, and/or as other agents could have been used (Collignon et al., 2016). The WHO 399 classifies these antibiotic classes as highest priority critically important antibiotics and it has 400 even been suggested that use of these antibiotics should be banned in animals to preserve 401 their effectiveness in human medicine (Hughes et al., 2012; Collignon et al., 2016). However, 402 there are concerns that a complete ban in veterinary medicine could be detrimental to animal 403 health and welfare (Hughes et al., 2012). Local UK antibiotic guidelines recommend use only 404 when an antibiotic better aligned with prescribing guidelines is inappropriate and/or 405 ineffective, and culture/sensitivity testing indicates that they will be effective. 406 Underdosing of antibiotics was documented in 26.9% of the cases included in our study, and 407 this practice could result in subinhibitory concentrations and resistance (Choe et al., 2000; 408 Gillespie et al., 2005; Ungemach, Müller-Bahrdt and Abraham, 2006). Reasons for underdosing

- 409 were not always apparent. Miscalculations or rounding dosages to the nearest tablet size are
- 410 considered possibilities.
- 411 Our study has several limitations that reflect its retrospective nature, a referral population
- 412 bias, and within that, limitation to Oncology and Internal Medicine disciplines. As is frequently
- 413 the case with retrospective studies, data was not always complete regarding clinical signs,

414 antibiotic prescription, and physical examination. We included cases where a bacterial 415 aetiology was "suspected" as one of the differential diagnosis based upon comment in the 416 referral communications, but it is possible that differentials associated with suspected 417 bacterial infection were not mentioned. 418 On its own, a referral population could be expected to bias data through increased case 419 complexity and perhaps a higher frequency of antibiotic use. Further restriction to only 420 Internal Medicine and Oncology cases could theoretically be expected to increase the overall 421 antibiotic prescription frequency in this cohort, compared to where other disciplines if they 422 were are also included. Discipline restriction could also have impacted choices around 423 antibiotic classes prescribed, for example exclusion of Dermatology might be expected to 424 comparatively reduce prescription of cephalosporins. 425 We decided to investigate this a referral population as they underwent extensive referral 426 investigations so we considered that that appropriateness of the use of antibiotics could be 427 addressed better than in cases without it. However, our findings may under-represent 428 antibiotic prescriptions in a general practice setting, as cases that improved as a result of, or 429 spontaneously irrespective of antibiotic prescription, are unlikely to be referred. 430 Lastly, between the two referral hospitals included, different timeframes were assessed, 431 however this is considered unlikely to cause a significant shift in prescription patterns. This 432 timeframe did cover an update on the guidelines in November 2018, however we limited the 433 recommendations assessed and included to those present in both versions. 434 Specific localUK- guidelines were assessed, and it is possible that veterinarians were following a 435 different antibiotic guideline with conflicting recommendations. Apart from the discussed 436 previously regarding feline lower urinary tract disease and chronic diarrhoea already 437 mentioned, no other conflicting recommendations were found. 438 Given roles in managing domestic animals with close human bonds, as well as roles within the 439 human food chain, veterinarians have an integral role in promoting responsible use of

440 antibiotics. It has been estimated that without proactive solutions to slow rising antibiotic

- resistance, or discovery of new antibiotics, that 10 million lives a year will be at risk by 2050
- 442 (Neill, 2014) We were not able, and did not set out, to evaluate veterinarians knowledge or
- 443 understanding of existing antibiotic stewardship guidelines, or to determine what barriers
- 444 might lead to non-compliance. However, our data identifies several aspects worthy of further
- 445 exploration and investment in improving education around appropriate diagnostics, antibiotic
- 446 class and dosage choices, thereby leading to improved compliance within antibiotic
- 447 stewardship guidelines and more responsible use of antibiotics.
- In conclusion, over prescription of antibiotics, poor adherence to local <u>UK</u> antibiotic guidelines
   and infrequent use of diagnostics such as culture and cytology to guide antibiotic use was
- 450 observed.
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Figure 1. Most common combinations of antibiotic classes in dogs



Figure 2. Most common combinations of antibiotic classes in cats



Figure 3. Antibiotic classes prescribed for each body system.

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280 (71.8%)	49 (50.5%)
102 (26.2%)	14 (14.4%)
31 (7.9%)	11 (11.3%)
22 (5.6%)	6 (6.2%)
25 (6.4%)	4 (4.1%)
•	
31 (7.9%)	6 (6.2%)
2	
15 (3.8%)	34 (35.1%)
°O,	
9 (2.3%)	0 (0%)
0(0%)	1 (1%)
1 (0.25%)	0 (0%)
	1 (7.9%) 22 (5.6%) 55 (6.4%) 55 (3.8%) 9 (2.3%)

Table 1. Types of antibiotics prescribed prior to referral in dogs and cats.

Institute	Discpline	Species		Gender and neutered status	Frequency (n)	Percent
				male neutered	89	42,2
				male entire	28	13,3
				female neutered	74	35,1
		dog		female entire	19	9
				Total	210	99,5
А	medicine		Missing		1	0,5
			Total		211	100
				male neutered	32	59,3
		aat		female neutered	20	37
		cat		female entire	2	3,7
			Total		54	100
		dog		male neutered	129	41,5
	modicina			male entire	46	14,8
				female neutered	104	33,4
				female entire	32	10,3
			Total		311	100
	medicine	cat		male neutered	40	44,4
				male entire	7	7,8
				female neutered	40	44,4
				female entire	3	3,3
			Total		90	100
n				male neutered	89	41
В				male entire	24	11,1
				female neutered	83	38,2
		dog		female entire	14	6,5
				Total	210	96,8
			Missing		7	3,2
	oncology		Total		217	100
				male neutered	17	50
				female neutered	14	41,2
		cat		Total	31	91,2
			Missing		3	8,8
			Total		34	100

Supporting information S1 (patients characteristics)

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Supporting information S2	(treatment with antibiot	ics prior to referral)
Supporting information 32		ics prior to referrally

Institute	Discpline	Treated with antibiotics prior to referral	Body system	Frequency (n)	Percent
			endocrine	4	3
			gastrointestinal	41	30,4
			haematological/immunological	11	8,1
			hepatobiliary	16	11,9
		yes	multi-systemic	5	3,7
		,	other	11	8,1
			respiratory	22	16,3
			urinary / reproduction	25	18,5
			Total	135	100
A	medicine		endocrine	7	5,4
			gastrointestinal	23	17,7
			haematological/immunological	12	9,2
			hepatobiliary	6	4,6
		no	multi-systemic	29	22,3
			other	26	20
			respiratory	12	9,2
			urinary / reproduction	15	11,5
			Total	130	100
			endocrine	9	4,2
			gastrointestinal	61	28,2
			haematological/immunological	2	0,9
			hepatobiliary	19	8,8
		yes	multi-systemic	23	10,6
			other	18	8,3
			respiratory	54	25
			urinary / reproduction	30	13,9
			Total	216	100
	medicine		endocrine	26	14,1
			gastrointestinal	44	23,8
			haematological/immunological	5	2,7
			hepatobiliary	27	14,6
В		no	multi-systemic	19	10,3
			other	29	15,7
			respiratory	20	10,8
			urinary / reproduction	15	8,1
			Total	185	100
			gastrointestinal	1	0,7
			haematological/immunological	1	0,7
			hepatobiliary	1	0,7
		yes	multi-systemic	128	94,8
	oncology	-	other	3	2,2
			urinary / reproduction	1	0,7
			Total	135	100
		xf	oncology	116	100

A medicine gast imm mu ref gast mu her ref gast haer imm	endocrine strointestinal ematological / ematological / epatobiliary ulti-systemic other respiratory urinary / eproduction endocrine strointestinal	yes           no           yes           no	1 3 2 39 3 8 2 13 1 3 7 2 6 16 13 11 2	1 3 2 39 3 8 2 13 1 3 7 2 6 16	1 3 39 39 13 1 1 3 7 7 2	1 3 39 3 2 13 1 3 7 2	1 3 2 39 3 8 2 13 1 3 7	1 3 39 3 8 2 13 1 3	1 3 39 3 8 2 13 1	1 3 39 3 8 2 13 1
A medicine gast imm mu ref gast mu her ref gast haer imm	strointestinal ematological / ematological epatobiliary ulti-systemic other respiratory urinary / eproduction endocrine strointestinal	yes no yes no yes no yes no yes no yes no yes no yes no yes no	2 39 3 8 2 13 1 3 7 2 6 16 13 11	2 39 3 8 2 13 1 3 7 2 6 16	2 39 3 2 13 1 3 7 2	2 39 3 2 13 1 3 7	2 39 3 2 13 1 3	2 39 3 8 2 13 1 3	2 39 3 8 2 13 1	2 39 3 8 2 13
A medicine haer imm A medicine function mu rec rec gast haer imm	ematological / imunological epatobiliary ulti-systemic other respiratory urinary / eproduction endocrine strointestinal	no yes no yes no yes no yes no yes no yes no yes no yes no	39 3 8 2 13 1 3 7 2 6 16 16 13 11	39 3 8 2 13 1 3 7 2 6 16	39 3 8 2 13 1 3 7 2	39 3 8 2 13 1 3 7	39 3 2 13 1 3	39 3 2 13 1 3	39 3 8 2 13 1	39 3 8 2 13
A medicine mu mu re gast haer imm	munological epatobiliary ulti-systemic other respiratory urinary / eproduction endocrine strointestinal	yes no yes no yes no yes no yes no yes no yes no	3 8 2 13 1 3 7 2 6 16 13 11	3 8 2 13 7 2 6 16	3 8 2 13 1 3 7 2	3 8 2 13 1 3 7	3 8 2 13 1 3	3 8 2 13 1 3	3 8 2 13 1	3 8 2 13
A medicine mu mu re gast haer imm	munological epatobiliary ulti-systemic other respiratory urinary / eproduction endocrine strointestinal	no yes no yes no yes no yes no yes no yes no	8 2 13 3 7 2 6 16 13 11	8 2 13 1 3 7 2 6 16	8 2 13 1 3 7 2	8 2 13 1 3 7	8 2 13 1 3	8 2 13 1 3	8 2 13 1	8 2 13
A medicine mu mu ref gast haer imm	epatobiliary ulti-systemic other respiratory urinary / eproduction endocrine strointestinal	yes no yes no yes no yes no yes no yes no	2 13 1 7 2 6 16 13 11	2 13 1 3 7 2 6 16	2 13 1 3 7 2	2 13 1 3 7	2 13 1 3	2 13 1 3	2 13 1	2 13
A medicine mu ref gast haer imm	ulti-systemic other respiratory urinary / eproduction endocrine strointestinal	no yes no yes no yes no yes no yes no	1 3 7 2 6 16 13 11	1 3 7 2 6 16	1 3 7 2	1 3 7	1 3	1	1	
re reg gast haer imm	other respiratory urinary / eproduction endocrine strointestinal	no yes no yes no yes no yes no	3 7 2 6 16 13 11	3 7 2 6 16	3 7 2	3 7	3	3		1
reg gast haer imm	other respiratory urinary / eproduction endocrine strointestinal	no yes no yes no yes no yes no	7 2 6 16 13 11	7 2 6 16	7 2	7			-	
e gast haer imm	respiratory urinary / eproduction endocrine strointestinal	yes no yes no yes no yes no	7 2 6 16 13 11	7 2 6 16	7 2	7	7		3	3
e gast haer imm	respiratory urinary / eproduction endocrine strointestinal	no yes no yes no yes no	6 16 13 11	6 16		2		7	7	7
e gast haer imm	urinary / eproduction endocrine strointestinal	yes no yes no yes no	6 16 13 11	6 16			2	2	2	2
e gast haer imm	urinary / eproduction endocrine strointestinal	no yes no yes no	13 11		6	6	6	6	6	6
gast imm	eproduction endocrine strointestinal	yes no yes no	13 11		16	16	16	16	16	16
gast imm	eproduction endocrine strointestinal	no yes no	11	13	13	13	13	13	13	13
e gast haer imm	endocrine strointestinal	yes no		11	11	11	11	11	11	11
gast haer imn	strointestinal	no		2	2	2	2	2	2	2
haer imn			7	7	7	7	7	7	7	7
haer imn		yes	8	8	8	8	8	8	8	8
imn		no	53	53	53	53	53	53		53
imn	ematological /	yes	1	1	1	1	1	53         53           1         1           1         1           6         6	1	
	munological	no	1	1	1	1	1			1
he		yes	6	6	6	6	6			6
	hepatobiliary	no	13	13	13	13	13	13	13	13
medicine	and the sector set of	yes	7	7	7	7	7	7	7	7
mu	ulti-systemic	no	17	17	17	17	17	17	17	17
		yes	5	5	5	5	5	5	5	5
	other	no	13	13	13	13	13	13	13	13
		yes	13	13	13	13	13	13	13	13
B	respiratory	no	41	41	41	41	41	41	41	41
	urinary /	yes	16	16	16	16	16	16	16	16
	production	no	14	14	14	14	14	14	14	14
		yes	1	1	1	1	1	1	1	1
gast	strointestinal	no	1	1	1	1	1	1	1	1
	ematological / munological	no	1	1	1	1	1	1	1	1
		yes	43	43	43	43	43	43	43	43
oncology mu	ulti-systemic	no	85	85	85	85	85	85	85	85
		yes	1	1	1	1	1	1	1	1
	other	no	2	2	2	2	2	2	2	2
	urinary /	110								
	eproduction	no	1	1	1	1	1	1	1	1

## Supporting information S3 (antibiotic compliance)

## Supporting information S4 (reason for no compliance)

Chi-squared significance value								
	Antibiotic							
	1st and 2nd generation cephalosporin	3rd generation cephalosporin	fluoroquinolone	lincosamide	nitrimadazole	penicillin	tetracycline	sulphonamide
underdosed	0,565	0,061	0.029*	0,638	0.009*	0,435	0,137	0,142
used as second line with no bacterial culture	0.019*	0,568	<0.001*	0,116	<0.001*	0.001*	<0.001*	0,272
used as inappropriate prophylaxis	0,257	<0.001*	<0.001*	0,48	0.003*	<0.001*	0,977	0,373
used for condition where the antibiotic is not indicated	0,171	<0.001*	0.016*	0,256	0.006*	0.031*	0.012*	0,428

## Supporting information S5 (Adherence to local guidelines)

			Adherence to local guidelin		
			yes	no	
Body system	endocrine	Count	3	10	
		Expected Count	3,7	9,2	
		% within Body_system	23,10%	76,90%	
		Adjusted Residual	-0,4	0,5	
	gastrointestinal	Count	11	92	
		Expected Count	29,3	73,1	
		% within Body_system	10,70%	89,30%	
		Adjusted Residual	-4,5	4,6	
	haematological / immunological	Count	4	10	
		Expected Count	4	9,9	
		% within Body_system	28,60%	71,40%	
		Adjusted Residual	0	0	
	hepatobiliary	Count	8	27	
		Expected Count	10,2	25,5	
		% within Body_system	22,20%	75,00%	
		Adjusted Residual	-0,9	0,6	
	oncology	Count	51	105	
		Expected Count	44,7	111,4	
		% within Body_system	32,50%	66,90%	
		Adjusted Residual	1,4	-1,4	
	other	Count	13	17	
		Expected Count	8,5	21,3	
		% within Body_system	43,30%	56,70%	
		Adjusted Residual	1,9	-1,8	
	respiratory	Count	19	57	
	-	Expected Count	21,6	53,9	
		% within Body_system	25,00%	75,00%	
		Adjusted Residual	-0,7	0,9	
	urinary / reproductive	Count	29	26	
		Expected Count	15,9	39,7	
		% within Body_system	51,80%	46,40%	
		Adjusted Residual	4,1	-4,3	