Characterisation of antimicrobial usage in cats and dogs attending UK primary-care companion animal veterinary practices

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Abstract (200 words)

There is scant evidence describing antimicrobial usage in companion animal primary-care veterinary practices in the UK. The use of antimicrobials in dogs and cats was quantified using data extracted from 374 veterinary practices participating in VetCompass. The frequency and quantity of systemic antimicrobial usage was described.

Overall, 25% of 963,463 dogs and 21% of 594,812 cats seen at veterinary practices received at least one antimicrobial over the two-year period (2012-14), and 42% of these animals were given repeated antimicrobials. The main agents used were amino-penicillin-types and cephalosporins. Of the AM events, 60% in dogs and 81% in cats were antimicrobials classified as critically important (CIAs) to human health by the World Health Organisation. CIAs of highest importance (fluoroquinolones, macrolides, third-generation cephalosporins) accounted for just over 6% and 34% of antimicrobials in dogs and cats, respectively. The total quantity of antimicrobials used within the study population was estimated to be 1473Kg for dogs and 58Kg for cats.

This study has identified a high frequency of usage of antimicrobials in companion animal practice and for certain agents classified as of critical importance in human medicine. The study highlights the usefulness of veterinary practice electronic health records for studying AM usage.

Introduction

There is scant evidence describing the extent of antimicrobial (AM) usage in companion animal species attending veterinary practices in the United Kingdom and these species have received limited attention as a reservoir of antimicrobial resistance (AMR). AM usage in companion animals is potentially of considerable importance to the efforts to control AMR, a growing problem in human and animal medicine (Prescott 2008), since companion animals are often in close contact with the human population (Guardabassi and others 2004; Cain 2013). Central to addressing AMR in companion animal veterinary practice is the need for a clear understanding of current levels and patterns of AM usage in veterinary practice. The frequency of AM use in companion animals may be growing as a result of increased population, better availability of veterinary services and use of antimicrobials for a range of health conditions (Guardabassi and others 2004). In Norway, there were 338 prescriptions per 1000 dogs per year in 2004, increasing by 13.3% by 2008 (Kvaale and others 2013). Previous studies have described the use of AMs in UK companion animal practices (Radford and others 2011; Mateus and others 2011) and agents most frequently used were amoxicillin-clavulanate, cephalexin, clindamycin and cefovecin (Radford and others 2011; Mateus and others 2011; Summers and others 2012). However these studies were limited by small sample sizes, and were therefore not able to fully quantify AM usage across the UK. Annual antibiotic sales data have been used as a proxy for the assessment of antibiotic use (VMD 2014), with the recognition that sales data are likely to overestimate actual usage and provide little information on the species and dosages used. There is a need to develop ongoing systematic capture of AM usage data by either utilising existing technologies or creating new systems to improve data capture in order to more fully estimate the scale of usage and potential role of companion animals in AMR and zoonotic transmission. There may be geographic differences in patterns of usage, for example in urban versus rural areas, with potentially important implications for tackling AMR (Kvaale and others 2013). A greater understanding of the absolute quantities dispensed and administered in companion animal practice would aid policy makers in their assessment of the relative contribution of this veterinary subgroup to overall AM levels of usage and AMR.

In order to establish a current baseline for AM usage in the UK, this study aimed to characterise the frequency and quantity of AM usage in cats and dogs over a two-year study period in a large sample of practices participating with the VetCompass Programme (www.rvc.ac.uk/VetCompass), which collects de-identified clinical data from veterinary practices across the UK. The objectives of the study were to identify the frequency of AM events and the respective quantities of AM product as indicators of the magnitude of usage, especially those classified as critically important in human medicine, and to evaluate variation in spatial distribution in AM usage across the UK. These data can be used to support policy on AM usage in companion animal species.

Methods

The study was approved by the Ethics and Welfare Committee of the Royal Veterinary College (RVC) (reference number: 2010 1076k). VetCompass is a collaborative research programme that shares veterinary clinical information to support the improvement of clinical services and animal health and welfare (O'Neill et al 2014a). Data were extracted centrally from veterinary practice management software (PMS) systems via a bespoke clinical reporting query (Microsoft Access, 2011). Data from primary-care practices only were included in the study (i.e. practices engaged mainly in referral and emergency care were excluded). VetCompass data management is underpinned by the Venom Coding platform (http://www.venomcoding.org), which provides open-access terminology enabled in the PMSs of participating VetCompass practices.

For the current study, AMs were defined as those medicines that destroy or inhibit the growth of bacterial microorganisms (i.e. antibacterials; Giguère 2013) authorised for systemic use (i.e. injectable, tablets/capsules ['tablet'] and oral suspensions ['other oral']). Other AM agents (e.g. antiviral, antifungal, biocides) were not included in this study. AM agents were categorised into AM groups (e.g. macrolides, penicillins) based on their mechanism of action, chemical structure, or spectrum of activity. Data were presented for AM groups and AM agents; specific AM products were not reported. AM agents were categorised as critically important AM agents (CIAs) according to the most recent World Health Organisation publication (WHO 2012). A master table of AM agents was created based on data from recent BSAVA formularies (BSAVA 2014, 2011), NOAH and VMD authorised veterinary product databases[1] and previous published work on antimicrobial usage in small animals (Mateus and others 2011). For each specific AM agent listed in the master table, information was collated on agent group (e.g. cephalosporin), recommended International Non-proprietary Name (Cefalexin), authorised UK trade names (Cephacare™) and specific item names (Cephacare Flavour 250 mg Tablets for Dogs). Product formulation, method of administration and base active ingredient strength (i.e. removing the molecular weight of associated water and/or salt) were also recorded for each unique AM product. The master table included veterinary products licensed for use in companion animals, other species and humans, where identifiable under the search terms generated by the master table. Products licensed for other animal species and humans may be used in companion animals under the Cascade principle, a regulatory framework that allows such use when there are no available alternative licensed veterinary products to appropriately treat an animal patient (EU Commission Regulation No 37/2010).

The study population included all dogs and cats that had at least one electronic patient record (EPR) entry (clinical note, VeNom term, bodyweight or treatment record) within the VetCompass Programme database within the 2-year study period from June 1st, 2012 to May 31st, 2014. EPRs were analysed for recorded dispensing and administration of AM events. Written prescriptions accounted for a minority (0.10%) of all AM events, and were excluded because it could not be ascertained whether these scripts were subsequently fulfilled. AM agent usage was reported by episode of care, i.e. each independent record in the PMS was defined as a single event. The number of single and repeated AM therapies given to animals within the study period, identified via unique patient identification numbers, were reported separately but without reference to whether these repeated events were for distinct conditions, recurring conditions or repeated prescriptions. AM products that combined multiple agents within the same preparation (e.g. amoxicillin plus clavulanic acid) were classified as a single antimicrobial substance (potentiated amoxicillin). If potentiated AM products contained multiple AM agents (e.g. Stomorgyl™, Merial Animal Health Ltd, containing spiramycin and metronidazole), the quantity of active ingredients were for each AM substances.

The usage of antimicrobial agents were identified from the VetCompass database by querying the AM terms from the master AM table against the clinical records (Microsoft Access, 2015) in order to extract relevant treatment records. Additional data from relevant records were extracted from the following data fields: clinic (identification code and postal code location), unique patient identification code, species (dog or cat), the date of AM event, product item name, units purchased by client, and dosage (free-text). Details, where available, identified from the product item name and dosage fields included the product name and size of product (i.e. strength), label information referencing method of administration (systemic: injection, oral [tablet] or other oral [e.g. liquid/powder]). The total quantity of AM product per event was calculated using the number of units purchased by clients

[1] databases: http://www.noahcompendium.co.uk/Compendium/Overview/-21789.html and http://www.vmd.defra.gov.uk/ProductInformationDatabase/

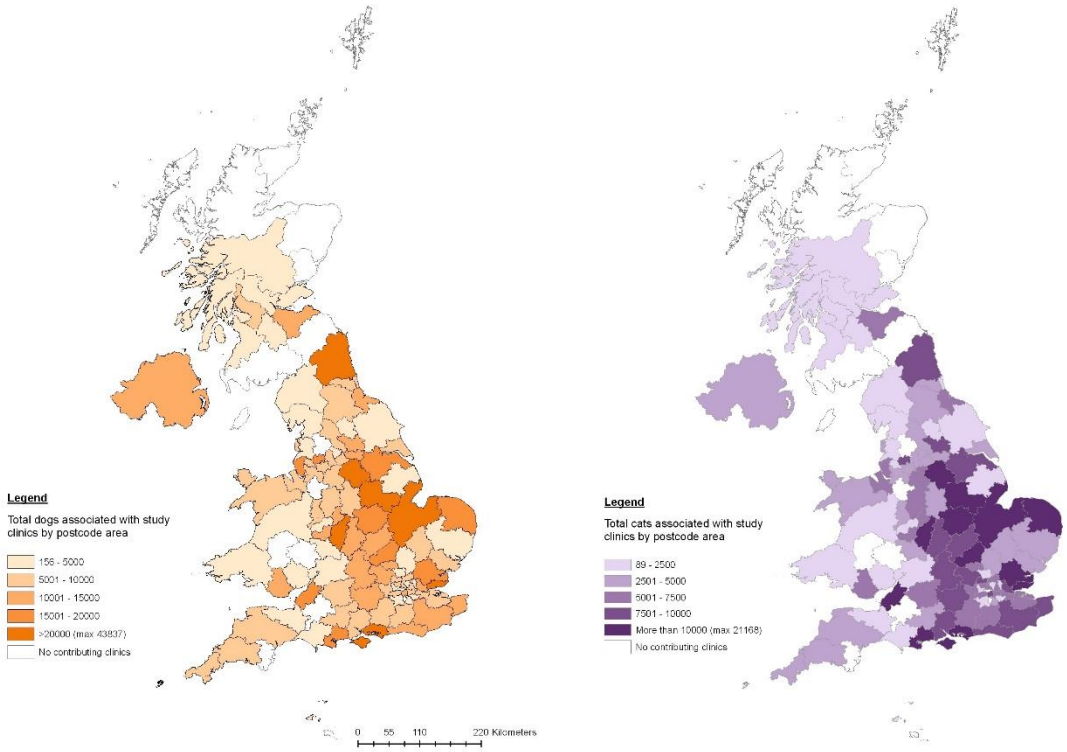
associated with each event, as recorded in the PMS. The quantity of each AM product per event was calculated using the base strength per mg/ml of active ingredient of the product multiplied by the mg or ml of product dispensed or administered, where this information was available. Quantities were reported separately for AM groups and individual AM agents for dogs and cats.

The geographical distributions of the study population and frequency of AM events were plotted for dogs and cats, respectively. Clinic postcode data were used to generate coordinates for mapping geographical locations of all UK veterinary clinics registered with the Royal College of Veterinary Surgeons (RCVS) including those VetCompass clinics from which AM data were derived. Clinic sites and UK postcode area boundaries were projected onto shapefiles representing the UK (with polygons for each UK postcode area) according to the British National Grid system. Figures for geographical data description were produced using ArcMap version 10.2 geographic information system (GIS) software (ESRI 2015. ArcGIS Desktop: Release 10.2. Redlands, CA: Environmental Systems Research Institute). The frequency maps were based on mean number of AM events divided by total number of practice-attending dogs or cats in the study population for participating VetCompass clinics in that area. Density categories were defined using a system of equal intervals: darker coloured regions represented greater density (i.e. more animals or higher AM use). Moran's *I* test of spatial autocorrelation (GeoDA software, School of Geographical Sciences and Urban Planning, Tempe AZ, USA) was used to determine whether there was significant clustering of postcode areas with similar mean AV events. The spatial weights matrix was based on queen contiguity (common border and/or corner) and significance was based on 499 permutations ($P<0.05$).

Results

De-identified clinical data from 374 UK companion animal practices were accessed via the VetCompass Programme. Participating practices comprised principally of two large practice groups as well as several independent practices and reflected a geographically widely dispersed cohort of practices. Three clinics (0.8%) did not have a usable postcode and were therefore not included in any map figures throughout the report, but were included for all other AM event and quantity analyses. The majority of practices were located in England, particularly the Midlands and East England and few practices were located in Northern Scotland. In total across the practices, 963,463 dogs and 594,812 cats had at least one EPR recorded within the two-year period and these animals comprised the study population, shown in Figure 1.

Figure 1. Geographical distribution of study population of 963,463 dogs (orange shaded map) and 594,812 cats (purple shaded map) with at least one electronic patient record entry within the two-year period across participating VetCompass practices (N=374), showing the number of practice-attending dogs and cats per postcode area.



Frequency of AM usage events

Over the two-year period, 242,736 of the 963,463 study dogs (25.19%; 95% confidence interval [CI]: 25.11-25.28) and 122,594 of the 594,812 study cats (20.61%; 95% CI: 20.51-20.71) were given at least one AM event. A total of 676,712 dispensing and administering events related to 211 AM products with a unique Marketing Authorisation number. Of these, 472,159 (70.48%) and 196,923 (29.52%) AM events were for dogs and cats, respectively (Table 1). The method of administration of AM events was principally oral tablets for dogs (381,532 events, 80.81% of total dog events) and injections for cats (109,187 events, 55.45%, Table 1). For both species, the main agents dispensed or administered were penicillin-types (dogs: 254,394 events, 53.88% of total; cats: 91,318 events, 46.37%) and cephalosporins (dogs: 80,982 events, 17.15%; cats: 63,505 events, 32.25%; Figure 2). WHO CIAs were used in 284,721 events in dogs (60.30% of total) and 159,433 events in cats (80.96% of total). Of CIAs, agents of highest importance were used in 30,241 of events in dogs (6.40% of total) and 68,084 events in cats (34.57%; Table 1). Fluoroquinolones and third-generation cephalosporins were the most commonly used CIAs of highest importance in dogs and cats, respectively. Potentiated agents were used for 229,919 (49%) and 59,496 (30%) events in dogs and cats, respectively and potentiated amoxicillin (amoxicillin-clavulanate) was the most commonly used potentiated agent for both species. For both dogs and cats, pleuromutilin (e.g. tiamulin), dihydrofolate reductase inhibitor (e.g. trimethoprim) and aminoglycosides (e.g. amikacin) events were low in frequency (<0.01% of total AM quantity) and these groups were therefore not reported further (including for quantity), but are included in total frequency and quantities for AM usage.

Of dogs that received at least one AM event, 139,920 dogs (57.64%) received a single AM event over the two-year period, whilst 102,816 dogs (42.36%) received multiple AM events. For cats, 84,175 cats

(68.66%) received a single AM event, whilst 38,419 cats (31.34%) received multiple AM events. The median number of events per animal was 1 (IQR: 1-2; range 1-60) for dogs and 1 (IQR: 1-2, range 1-216) for cats. The maximum of 216 events for one cat was an outlier (though appeared biologically possible), and after removal, the next highest maximum was 75 events for a single cat over the two year period.

Figure 2. The proportion of AM events comprising AM agent groups in dogs and cats, respectively. AM groups with less than 0.01% of AM events were not shown.

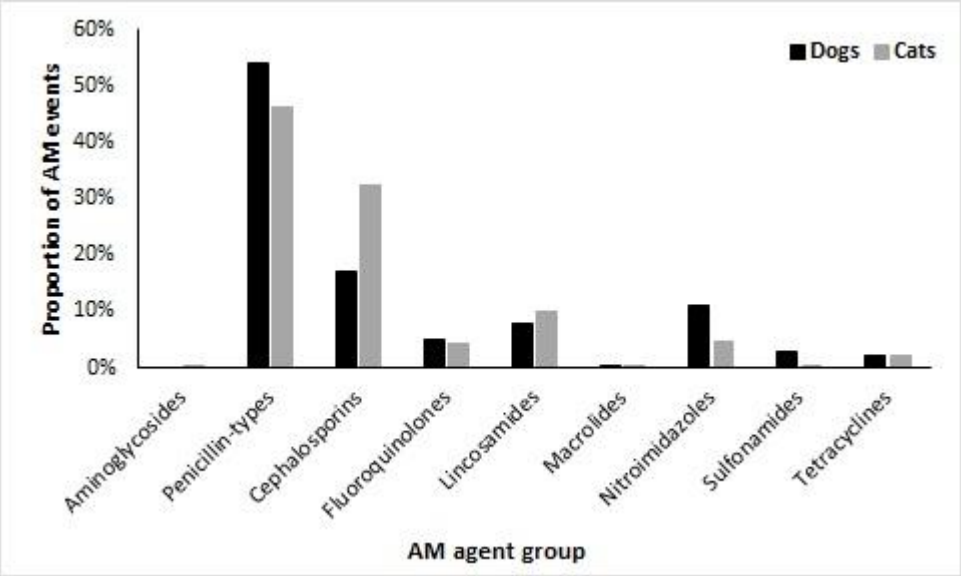


Table 1. Frequency of events for AM groups and individual agents, per species (dog and cat) and method of administration (injection, tablet, other oral). AM groups with less than 0.02% of AM events were not provided in the table but were included in the grand total frequency of events. AM agents are classified by WHO as critically important (*) for human medicine (WHO 2012), and of these some are considered of highest importance (**).

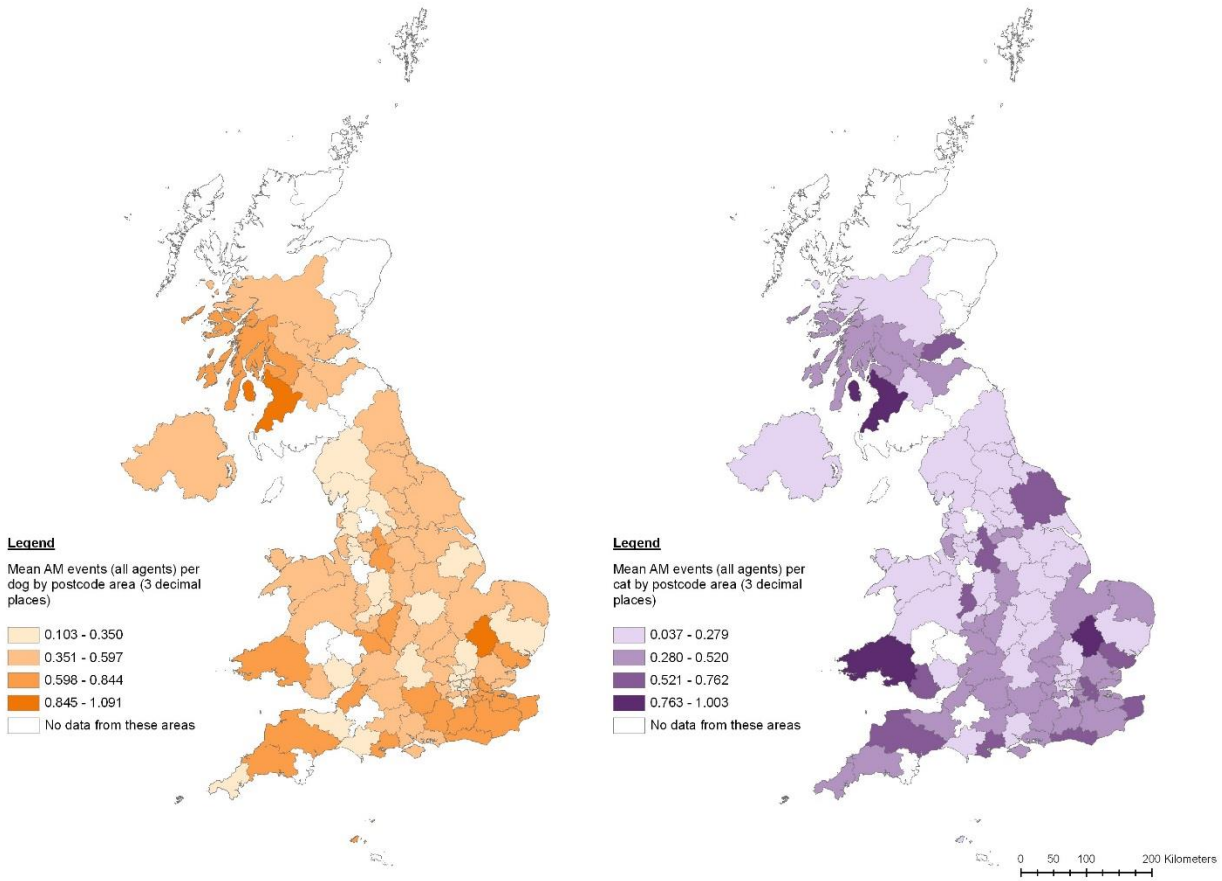
Species and administration[a] / AM group and substance name	Dogs					Cats				
	Injection	Tablet	Oral Other	Total/% usage per AM group		Injection	Tablet	Oral Other	Total/% usage per AM group	
Aminoglycosides	**84**	**0**	**0**	**85**	**0.02%**	**25**			**25**	**0.01%**
Amikacin*	25	0	0	**25**	**0.01%**	14	0	0	**14**	**0.01%**
Gentamicin*	42		0	**43**	**0.01%**	11	0	0	**11**	**0.01%**
Tobramycin*	17	0	0	**17**	**<0.01%**	0	0	0	**0**	**0**
Penicillin-types	**61182**	**192970**	**236**	**254394**	**53.88%**	**42287**	**48313**	**712**	**91318**	**46.37%**
Amoxicillin*	39272	2928	215	**42415**	**8.98%**	32879	97	697	**33675**	**17.10%**
Ampicillin*	342	279	21	**642**	**0.14%**	300	2	14	**316**	**0.16%**
Penicillin*	236	0	0	**236**	**0.05%**	66	0	0	**66**	**0.03%**
Potentiated amoxicillin*	21202	189763	0	**210971**	**44.68%**	8836	48214	1	**57055**	**28.97%**
Potentiated penicillin*	117	0	0	**117**	**0.02%**	203	0	0	**203**	**0.10%**
Ticarcillin*	13	0	0	**13**	**<0.01%**	3	0	0	**3**	**<0.01%**
Cephalosporins	**10791**	**70171**	**18**	**80982**	**17.15%**	**60534**	**2957**	**14**	**63505**	**32.25%**
Cefalexin (1st generation)	2102	70171	18	**72293**	**15.31%**	328	2957	14	**3299**	**1.68%**
Cefovecin (3rd) **	6162	0	0	**6162**	**1.31%**	59442	0	0	**59442**	**30.19%**
Ceftazidime (3rd) **	73	0	0	**73**	**0.02%**	14	0	0	**14**	**0.01%**
Cefuroxime (2nd)	2454	0	0	**2454**	**0.52%**	750	0	0	**750**	**0.38%**
Fluoroquinolones	**4022**	**18339**	**501**	**22866**	**4.84%**	**2556**	**3677**	**2035**	**8269**	**4.20%**
Ciprofloxacin**	0	27	0	**27**	**0.01%**	0	1	0	**1**	**<0.01%**
Enrofloxacin**	3219	9521	434	**13176**	**2.79%**	1887	2063	353	**4303**	**2.19%**
Ibafloxacin**				**0**	**<0.01%**	0	0	7	**7**	**<0.01%**
Marbofloxacin**	803	3959	0	**4762**	**1.01%**	669	1043	1	**1713**	**0.87%**
Pradofloxacin**	0	4832	67	**4901**	**1.04%**	0	570	1674	**2245**	**1.14%**
Lincosamides	**2652**	**34,713**	**0**	**37,366**	**7.91%**	**2419**	**17,064**	**5**	**19,491**	**9.90%**
Clindamycin	1	34,713	0	**34714**	**7.35%**	0	17064	5	**17,070**	**8.67%**

Lincomycin	2651	0	0	**2652**	**0.56%**	2419	0	0	**2421**	**1.23%**
Macrolides	**4**	**564**	**572**	**1141**	**0.24%**	**0**	**22**	**335**	**359**	**0.18%**
Azithromycin**	0	11	50	**61**	**0.01%**	0	2	166	**170**	**0.09%**
Clarithromycin**	0	0	2	**2**	**<0.01%**	0	1	0	**1**	**<0.01%**
Erythromycin**	0	553	474	**1027**	**0.22%**	0	19	147	**166**	**0.08%**
Tylosin**	4	0	46	**51**	**0.01%**	0	0	22	**22**	**0.01%**
Nitroimidazoles	**7202**	**42,884**	**2532**	**52,638**	**11.15%**	**1305**	**5417**	**2374**	**9117**	**4.63%**
Metronidazole	7202	37,352	2532	**47,106**	**9.98%**	1305	3703	2374	**7403**	**3.76%**
Potentiated Metronidazole	0	5532	0	**5532**	**1.17%**	0	1714	0	**1714**	**0.87%**
Sulfonamides	**193**	**12,532**	**574**	**13,299**	**2.82%**	**57**	**227**	**239**	**524**	**0.27%**
Potentiated sulfadiazine	193	12,532	4	**12,729**	**2.70%**	57	227	0	**285**	**0.14%**
Potentiated sulphonamide	0	0	570	**570**	**0.12%**	0	0	239	**239**	**0.12%**
Tetracyclines	**24**	**9347**	**2**	**9374**	**1.99%**	**4**	**4297**	**4**	**4305**	**2.19%**
Doxycycline	0	7234	2	**7236**	**1.53%**	0	4182	4	**4186**	**2.13%**
Oxytetracycline	24	2089	0	**2114**	**0.45%**	4	115	0	**119**	**0.06%**
Tetracycline	0	24	0	**24**	**0.01%**	0	0	0	**0**	**0**
Grand Total	**86,154**	**381,532**	**4436**	**472,159**		**109,187**	**81,978**	**5723**	**196,923**	
Total WHO CIAs *	**71,527**	**211,873**	**1309**	**284,721**	**60.30%**	**104,324**	**52,013**	**3087**	**159,433**	**80.96%**
Total CIAs of highest importance **	**10,260**	**1073**	**18,903**	**30,241**	**6.40%**	**62,012**	**2370**	**3699**	**68,084**	**34.57%**
a. there were 37 and 35 events in dogs and cats, respectively, for which method of administration was unknown (included in totals)										

Spatial distribution of AM events

Figure 3 displays the geographical distribution of the total number of AM events dispensed or administered for dogs (a) and cats (b). Statistical comparisons were not made but dogs appeared to receive a higher frequency of AM events per animal than cats in many regions, with a density range of 0.10-1.09 AM events per dog per postcode area versus 0.04-1.00 AM events per cat per postcode area, though. Both dogs and cats appeared to have a similar disparate pattern of regional AM events, with greater proportional use in the South of England and South West Scotland regions. There was statistically significant positive spatial autocorrelation of mean AM events in dogs (Moran's *I*: 0.221; p-value = 0.002) but not in cats (Moran's *I*: 0.062; p-value = 0.100).

Figure 3. The geographical distribution of the frequency of AM events in dogs (a, orange) and cats (a, purple), expressed as the mean number of antimicrobial usage events per individual within the study population of* practice-attending *animals within each postcode region.



Quantity of AM used

The quantity of AM administered/dispensed was calculated for 470,159 events for dogs (99.57% of the total dog events) and 195,128 events for cats (99.09% of the total cat events), after removing events where strength of the active ingredient could not be determined from the data available (2,000 for dogs; 1,795 for cats).

The overall quantity of AMs used in dogs was 1472.910 Kg and 58.383 Kg for cats over the two-year study period (Table 2).The agent groupings with the highest quantities administered/dispensed were penicillin-types (dogs: 568.197Kg; cats: 33.810Kg) and cephalosporins (dogs: 505.004Kg; cats: 5.746Kg; Figure 4; Table 2), though there was also relatively high quantities of nitromidazoles for dogs (170.237Kg) and of lincosamides for cats (8.565Kg). For individual AM agents in dogs, the highest quantities were given for potentiated amoxicillin (538.473Kg), cefalexin (503.672Kg), metronidazole (152.004Kg) and potentiated sulfadiazine (114.004Kg; Table 2). For individual agents in cats, the highest quantities were given for potentiated amoxicillin (31.206Kg), clindamycin (8.331Kg), metronidazole (3.763Kg) and cephalexin (3.556Kg; Table 2).

Figure 4. Proportional quantities by weight (Kg) of antimicrobials administered or dispensed over the two-year period, per AM group for dogs and cats attending veterinary practices in the UK, respectively.

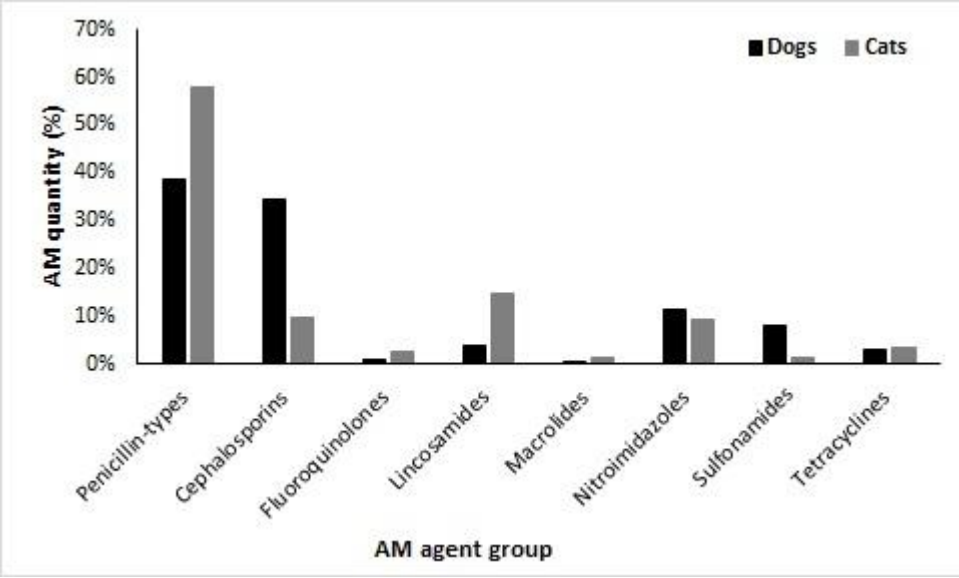


Table 1. Total quantities (in Kg) of antimicrobial medicines for dogs and cats, respectively, per AM grouping and substance name, based on the 'units purchased by client' data. AM medicines are marked * according to their critically important status (CIAs: WHO 2012) and ** for CIAs of highest

importance. AM groups with <0.01% of total AM frequency are not reported here but are included in the total AM quantities.

AM grouping	Generic agent name	Dogs		Cats	
		Kg	Total (Kg) / % of total AM usage in dogs	Kg	Total (Kg) / % of total AM usage in cats
Penicillin-types	Amoxicillin*	26.154		2.478	
	Ampicillin*	3.073		0.082	
	Penicillin*	0.259		0.011	
	Potentiated amoxicillin*	538.473		31.206	
	Potentiated penicillin*	0.181	**568.197**	0.023	**33.81**
	Ticarcillin*	0.057	**(38.54%)**	0.009	**(57.91%)**
Cephalosporins	Cefalexin (1st)	503.672		3.556	
	Cefovecin (3rd) **	0.481		2.05	
	Ceftazidime (3rd) **	0.157	**505.004**	0.007	**5.746**
	Cefuroxime (2nd)	0.693	**(34.25%)**	0.133	**(9.84%)**
Fluoroquinolones	Ciprofloxacin**	0.52		0.002	
	Enrofloxacin**	9.026		0.564	
	Marbofloxacin**	1.715	**14.535**	0.106	**1.387**
	Pradofloxacin**	3.274	**(0.99%)**	0.715	**(2.38%)**
Lincosamides	Clindamycin	54.149	**54.902**	8.331	**8.565**
	Lincomycin	0.753	**(3.72%)**	0.234	**(14.67%)**
Macrolides	Azithromycin**	0.071		0.1	
	Clarithromycin**	0.007		0.004	
	Erythromycin**	4.78	**4.861**	0.533	**0.638**
	Tylosin**	0.003	**(0.33%)**	0.001	**(1.09%)**
Nitroimidazoles	Metronidazole	152.004	**170.237**	3.763	**5.405**
	Potentiated Metronidazole	18.233	**(11.55%)**	1.641	**(9.26%)**
Sulfonamides	Potentiated sulfadiazine	114.004		0.479	
	Potentiated sulphonamides	0.823	**114.827 (7.79%)**	0.34	**0.819 (1.40%)**
Tetracyclines	Doxycycline	8.09		1.722	
	Oxytetracycline	33.351	**41.731**	0.275	**1.997**
	Tetracycline	0.29	**(2.83%)**	0	**(3.42%)**
Grand Total			**1474.357 Kg**		**58.383 Kg**
Total WHO CIAs *			**588.252 Kg (39.90%)**		**37.905 Kg (64.92%)**
Total WHO CIAs of highest importance **			**20.035 (1.36%)**		**4.082 (6.99%)**

Discussion

A broad evaluation of AM usage within veterinary practices is now possible with the development of practice-based research programmes such as VetCompass. This study reports on the usage of AM products for dogs and cats across a large sample of UK veterinary practices. The results highlight the relatively high frequency of usage of AMs per animal in veterinary practice and of those considered of

critical importance to human health (CIA) and provide a valuable evaluation of current veterinary prescribing activity and a baseline from which to evaluate future usage.

Of those animals which attended a veterinary practice during the two-year study period, 25% and 21% of dogs and cats, respectively, were dispensed or administered at least one AM. Mateus and colleagues (2011) reported administration or prescription of AMs in 45% and 33% of dogs and cats that presented for consultations, respectively over a one year period in 2007. Radford and others (2011) reported a higher proportion of AM use per consultation, 35% of consultations for dogs and 49% consultations for cats. These earlier AM usage figures reflect different methods of reporting AM events per consultation or AM usage within dogs presenting for consultations and represented much smaller sample sizes of 16 and 11 practices respectively. The current study reported usage per animal under practices' veterinary care and included animals deemed to be actively registered at participating practices as indicated by EPR evidence of presenting for a consultation as well as for other services or recorded communication with the practice during the study period. The current study utilised data from 374 small animal veterinary practices, which is the largest sample used to investigate AM usage in the UK to date, approximately 7% of all UK RCVS registered veterinary premises (RCVS, 2014). The participating practices came from all regions of the UK, and although the data derived principally from two large practice groups, a number of independent practices were also involved and therefore the data were likely to give a reliable example of the level of usage across UK companion animal general practice. Emergency and referral hospitals or charity-based practices were not included in this study, and thus the level of AM usage reported here may be less generalisable to those practice types. The representativeness of data in the current study according to the total UK dog and cat population is difficult to determine, and although the values are accurate in terms of AM events per animals attending study practices, the data may over-estimate usage per animal in the population, due to the absence of animals that are not registered at a veterinary practice or that did not attend a veterinary practice within the two-year study period. For example, it is known that not all dogs and cats are registered with veterinary practices; Asher and others (2011) reported that approximately 17% of owners in the public survey had not registered their dog with a veterinary practice.

In the current study, there was widespread use of broad-spectrum agents such as aminopenicillins plus clavulanic acid, cephalosporins and fluoroquinolones across the participating VetCompass practices for both dogs and cats, in agreement with previous UK data (Radford and others 2011; Mateus and others 2011) and data from other European countries e.g. France (Anses, 2014) . Many of these agents, and up to 81% of the AM events together across both species, were considered to be critically important for human health (WHO 2012), including those deemed of highest importance (approximately 40% of AMs used). This raises concerns about potential horizontal transmission of resistance determinants and resistant bacteria to CIAs through companion animals. Mateus and others (2011) reported a similar proportion of CIA usage – 61% in dogs and 83% in cats from 2007, which suggests usage of CIAs has not decreased in the UK from 2007 to 2014. A recent survey study reported 30% and 15% of antibiotics used for dogs and cats, respectively, in Europe were highest importance CIAs, with more AMs prescribed being considered of lower importance (e.g. tetracylines, De Briyne and others 2014), suggesting that there may be differences in prescribing behaviour between EU member states. Only a small proportion of veterinarians were surveyed and the methodological differences in how these data were collected may also contribute to these differing results.

Antimicrobial usage patterns differed substantially between dogs and cats in the current study. Administration of AM agents used for dogs was principally by oral tablet (81%) whereas the majority of AM agents for cats were administered via the injectable method (55%). This likely reflects general

differences in methods of administering medicines between the species, with oral tablets being perceived as more difficult to effectively administer in cats (Traas and others 2010). Dogs received proportionally more aminopenicillin-types (54% versus 46%) and nitromidazoles (11% versus 5%) than cats. Cats received proportionally higher usage of 3rd generation cephalosporins, critically important agents of highest importance, and this was largely explained by the more frequent use of cefovecin injectable products in cats (54% of total cat events versus 1.31% of dogs). This is in agreement with other studies, e.g. Murphy and others (2012) found higher use of cefovecin in cats and amoxicillin-clavulanic acid in dogs. A higher frequency of cats received a single AM event over the two year period, 69% of cats versus 58% of dogs. However, the range of counts for repeat AM events was more diverse for cats. These differences may reflect differences in the deliverance of AMs for the two species, e.g. preference for a single long-lasting injectable in cats. No attempt was made to evaluate the underlying disorders requiring AMs in these animals, or the clinical appropriateness of dosages, though this is possible with further analysis of the data contained with VetCompass. Murphy and others (2012) showed overuse of cefovecin and fluoroquinolones for the treatment of common diseases in dogs and cats (feline upper respiratory tract disease, feline lower urinary tract disease and canine infectious tracheobronchitis) in Ontario, where 67-74% of disease events were treated with antimicrobials, and 65% of antimicrobials prescribed were beta-lactams.

For both dogs and cats, spatial analysis suggested that there was a trend towards higher AM event frequency in South East England, South Wales, and South West Scotland, with significant spatial clustering observed in dog but not cat AM usage overall, though the latter lack of statistical significance may have reflected the smaller sample size for cats. Spatial distribution accounted for variation in animal density distributions and so any differences identified were unlikely to be explained by regional differences in the numbers of animals attending practices. Possible explanations for the geographical variation seen could be differences in animal demographics, associated diseases and/or regional variations in prescribing and administering behaviours of the veterinary practices. The spatial clustering undertaken was exploratory only in nature and any underlying reasons for differences in regional distribution of AM events would need to be investigated further. Similar regional differences in AM prescriptions were described in Norway (Kvaale and others 2013), although here, the differences were likely to correspond to the density of dogs and veterinary clinics. Geographical differences in AMR have also been reported; dogs in an urban habitat had a higher risk of carrying isolates resistant to methicillin and other antimicrobials compared with dogs in a rural environment (Huerta and others 2011). Such differences may in part be related to differences in AM usage, exposure to other sources of AMR and/or awareness of regional resistance patterns. Nonetheless, maps of the geographical distribution of AM usage have been used in risk-based sampling approaches to monitor AM usage and AMR (Stärk and others 2006) and future work is merited to explore these geographical differences further.

For both species, the quantities of AM used corresponded approximately with the number of events recorded, e.g. proportionally greater number and quantity of penicillin-types were dispensed and administered in both cats and dogs. The quantity data also reflected the method of administration, since tablets had a greater strength and/or longer recommended course of therapy than injection or other oral medicines. Substantially greater quantities (1472.910Kg) of AMs were administered or dispensed for use in dogs compared to cats (58.383Kg) which would be explained at least in part by the smaller average body weight of cats (O'Neill and others 2014a,b). The data for units purchased by clients were likely to correspond closely to the actual levels of dispensed and administered AMs as these data are derived from financial transactions. It is important to note, however, that data on AMs purchased by clients may, overestimate actual use, since there may be wastage due to pack sizes which exceed dosage needs and due to medicine expiry. The approximate dose rate could be

calculated to validate the data, based on the total quantity sold and number of events. For example, 2Kg of AM related to 59,000 cefovecin injectable events, which equated to approximately 34mg per injection or around 8mg/Kg for approximate average 4Kg cat, which is the recommended dose (Convenia, Noah Compendium).

Data analysis in this study was limited by the lack of standardisation of some EPR fields. For example, over 15,000 unique AM treatment items were recorded across the practice data, and this related to only 211 unique products. Data entry varied with different practitioners, practices and PMS systems, including variations in spelling, order of wording, limited/incomplete options available and/or a lack of specificity in free-text descriptions. It is possible that the master list of AM agents included in this study was not exhaustive and did not allow complete identification of all antimicrobial medicinal products available and used in companion cats and dogs. In particular the use of AM products not licensed for animals (e.g. human medicines) would not be listed in the veterinary authorised databases. It is not known to what extent AM products are dispensed or administered to veterinary patients under the Cascade system. Neither the commercial Marketing Authorisation (MA) number nor the Global Trade Item Number (GTIN) for veterinary medicinal product sales are currently routinely recorded in PMS databases, but could provide complete and automated identification of UK authorised AM products for all species.

With the frequent use of AMs for cat and dog species, and in particular of agents considered critically important to human health, combined with evidence of the risk for AMR for antimicrobial therapy in pet species and the potential for zoonotic transmission (Guardabassi and others 2004), there is a need to reflect on current usage patterns for small-animal veterinary species and to further develop protocols for responsible antimicrobial usage. Further work should focus on the assessment of appropriateness of AM therapy using more detailed analysis of the clinical condition, the relatedness of treatments and the dosage applied, and this may further identify important patterns of AM usage in both species. Baseline data on the types and quantities of AMs used in dog and cat species are essential to enable associations and trends to be identified, followed and analysed and appropriate adjustments to best practice guidelines to be made. Such data may be used for benchmarking practises, in order to help veterinarians reduce use of antimicrobials. In the Netherlands, discovery of extensive overuse of antimicrobial and significant reservoirs of antimicrobial resistant pathogens led to a successful collaboration between government and stakeholders to reduce antimicrobial use in farm animals, by as much as 56% (Speksnijder and others 2015). Antimicrobial use in Danish pig production significantly reduced with the introduction of the “Yellow card” intervention, as monitored with the national database of veterinary prescribed medicines (Jensen and others 2014). Databases such as the VetCompass programme could be used to monitor temporal and geographical trends for antimicrobial use in the UK, following compulsory or voluntary actions. Practice-based guidelines on appropriate use of antimicrobials have been developed in the UK by expert panels (e.g. BSAVA, 2016; FECAVA, 2014) though relevant policies were reported to be applied in as few as 3.5% of small animal veterinary practices (Hughes and others 2012). Complex intrinsic and extrinsic factors affect veterinarians’ decision-making for prescribing antimicrobial therapy, such as a veterinarian's preference for certain products, perceived efficacy, ease of administration and perceived owner compliance (Mateus and others 2014). Better understanding of these factors, and of the importance of AMR transmission between pets and humans, could promote more conscientious AM prescribing behaviour in veterinary clinics (Beco and others 2013).

Conclusions

Overall, approximately a quarter of dogs and cats attending veterinary practices in the UK received at least one AM event over the two-year period 2012-2014. Dogs mainly received oral tablets whilst cats

had AMs administered mainly as injectable preparations. The total AM quantity, by weight of active ingredient, was estimated to be 1473Kg for dogs and 58Kg for cats. In particular, the most common agents used for cats and dogs were amino-penicillin-types and cephalosporins. Of the AM events, 60% in dogs and 81% in cats were of AMs classified as critically important (CIAs) to human health by the WHO, and this may be important to consider when addressing companion animals as a potential source or reservoir for AMR in humans. These findings can provide a baseline for AM usage in companion animals in the UK, and can support continued surveillance of AM usage and investigation of the role of companion animal veterinary practices in AMR.

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