Network visualisation of UK companion animal pharmacosurveillance, with focus on systemic antibacterials

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Abstract

The Small Animal Veterinary Surveillance Network (SAVSNET) is a UK-based collaborative project that collects large volumes of electronic health data from volunteer veterinary practices and diagnostic laboratories in real-time. Here for the first time we use this data to provide an overview of prescription (record of sale at consultation) in dogs and cats, and establish a novel community detection network method aimed at identifying drug groups preferentially co-prescribed.

Pharmaceutical prescription was surveyed between 01/04/2014 and 31/03/2016 in 216 veterinary practices across the UK, encompassing 918,333 canine (413,870 individual dogs) and 352,730 feline (200,541 cats) veterinary consultations. Prescription was found in 65.5% (64.6-66.3) of canine and 69.1% (67.9-70.2) of feline consultations. The top six most prescribed therapeutic categories encompassed 86.5% of canine and 89.1% feline total prescription, the majority being focused on prevention or treatment of infectious disease. Vaccines were the most common therapeutic category in both dogs (26.1%) and cats (22.4%). Three distinct prescription communities were found in both species: 'healthy', 'unwell' and 'terminal'. Finally, systemic antibacterial prescription revealed clear variation in prescription behaviour between dogs and cats.

This study represents the first known attempt to detect community behaviour in prescription practices, and the first time network modelling has been applied to veterinary prescription. It confirms widely expected behaviours revealing high preference for a small range of therapeutic categories and antibacterial classes, and provides a baseline against which to study future trends. Understanding the motivators of such patterns is of paramount importance considering the global pressure for responsible antibacterial prescription.

Keywords: *pharmacosurveillance, antimicrobial resistance; antibacterial; pharmacosphere; network science*

Introduction

Network modelling is traditionally associated with social science research; however, it's potential for health research is being increasingly realised (1). However, there have been few attempts to use it in pharmacosurveillance, leaving a significant gap in our understanding of not just prescription but also co-prescription.

The use of a network approach has been demonstrated in a 2013 paper which explored therapeutic category prescription (2) summarised by ATC codes (3). A further paper demonstrated co-prescription of drugs of similar intended action, e.g. cardiovascular (4). However, neither sought to directly establish existence of community behaviour. 'Community' is defined as drugs that might be preferentially co-prescribed. Establishing the existence of such behaviour is important for understanding the major themes of companion animal veterinary prescription and co-prescription, thus providing an evidence base for efficacy analysis and drug interaction dynamics.

A key challenge in establishing a globally applicable drug classification system is a lack of knowledge surrounding prescription in practice. Whilst a system is in use in veterinary medicine (3) it has largely been adapted from human medicine, it is unknown whether this is appropriate.

The Small Animal Veterinary Surveillance Network (SAVSNET) provides an invaluable opportunity to explore companion animal prescription on a scale never previously attempted. Whilst establishment of an effective pharmacosurveillance system is useful, it is imperative to be able to easily apply surveillance to areas of key current importance, such as antimicrobial resistance (AMR). Antimicrobial prescription (particularly systemic prescription) has been identified as a key driver of AMR; hence, finally we demonstrate the system capability to be able to identify antibacterial classes most commonly systemically prescribed in UK dogs and cats.

Materials and methods

Data collection

Electronic health records (EHRs) containing data from consultations were collected in real-time from volunteer veterinary practices; for more in-depth description please refer to Sánchez-Vizcaíno *et al.* 2015 (5). Of relevance to this study, each EHR included a unique patient identifier, the patient's species and any products prescribed (prescription = record of sale at consultation).

Pharmaceutical product identification

Prescription in this context referred to an item sold at consultation. Pharmaceutical products were identified by reference to the text-based 'product prescribed' category of the HER, e.g. 12x synulox 250mg tablets, which represents a set of product codes individually developed by each veterinary practice. A training set (n=52,267) of these were manually categorised by comparing them to the Veterinary Medicine Directorate's Product Information Database for veterinary authorised products, and for human the electronic Medicines Compendium (Datapharm Communications Ltd.). A third category, 'dual-generic' was utilised for a product authorised in both groups which was described in generic fashion e.g. amoxiclav.

A list (n=1,935) of Product Identifying Strings (PIDS), e.g. "synulox" was identified and applied to the full list of unique product codes (n=95,709). Pharmaceutical products were summarised by therapeutic category, e.g. antibacterial, informed in part by reference to ATCvet (3). Antibacterials were further characterised to enable identification of administration route, e.g. systemic or topical.

Statistical and network analyses

Where stated, proportions with 95% confidence intervals were calculated with adjustment for clustering (bootstrap method) within veterinary premises. Networks were constructed via the igraph package available in R (6). Prescription data were formed into a matrix of co-prescription by therapeutic category. A network was then visualised and examined for community structure via a propagating label algorithm (7), before being sparsified to reveal dominant prescription patterns. Therapeutic categories were excluded if they contributed <0.5% to total prescription, and co-prescription connections (edges) were excluded if they were less than the co-prescription mean (dog, 13.4%; cats, 10.8%).

Results

In total EHRs from 918,333 canine (413,870 dogs) and 352,730 feline (200,541 cats) veterinary consultations were analysed from 216 veterinary practices (457 sites) between 1 April 2014 and 31 March 2016. Prescription occurred in 65.5% (64.6-66.3) of canine and 69.1% (67.9-70.2) of feline consultations, yielding a total of 1,242,266 canine and 491,554 feline prescription events.

Product prescription and authorisation

When drugs were summarised into broad therapeutic categories (n=27), vaccines were the most common prescription in both dogs (26.1% of prescriptions) and cats (22.4%). A relatively small number of categories dominated prescription with the top six encompassing 86.5% of canine and 89.1% of feline prescriptions. With regards to authorisation, the majority of canine prescriptions in this population were veterinary authorised (93.1%, 92.6-93.6), comparing with 5.1% (4.7-5.5) human and 1.8% (1.6-2.0) dual-generic. In cats this was 95.9% (95.6-96.2) veterinary; 2.8% (2.6-3.0) human and 1.3% (1.1-1.5) dual-generic. When considering product authorisation, most frequently prescribed therapeutic categories trend towards prescribing a greater proportion of veterinary-authorised products. A summary of the top ten most frequently prescribed therapeutic categories can be observed for dogs in Table 1 and cats in Table 2.

Network visualisation

It was found that 18.4% (n=188,357) of canine prescriptions were co-prescribed with a drug belonging to a different therapeutic category, this compared with 12.0% (n=52,100) in cats. Co-prescription was fitted to a sparsified network model for detection of community structure (Figure 1). There is evidence to suggest that co-prescription does form into broad communities. For example, co-prescription of antibacterials; anti-inflammatories and anti-mycotics is common in both dogs and cats. This expands to form segregated communities where co-prescription outside of group is relatively uncommon. This appears to broadly consist of 'healthy' prescription, e.g. vaccination (Group 1); 'unwell' prescription, e.g. antibacterials (Group 2) and euthanasia (Group 3). Cats were found to have a fourth group, endocrine.

Table 1. Canine top 10 most common therapeutic categories, %P = percentage of total prescriptions, Authorisation = percentage of prescriptions veterinary, human and dual-generic authorised by category.

Category	%P	Authorisation		
		Vet	Human	Dual
Vaccine	26.1	100.0	NA	NA
Antibacterial	17.6	85.7	11.4	2.9
Anti-inflammatory	16.9	92.5	3.4	4.1
Endectocide	9.2	100.0	NA	NA
Endoparasiticide	8.8	100.0	NA	NA
Ectoparasiticide	8.0	100.0	NA	NA
Neurological	4.0	68.8	25.1	6.1
Antimycotic	3.0	99.4	0.3	0.3
Gastrointestinal	2.5	57.1	34.0	8.9
Cardiovascular	1.2	93.3	5.3	1.4

Table 2. Feline top 10 most common therapeutic categories.

Category	%P	Authorisation		
		Vet	Human	Dual
Vaccine	22.4	100.0	NA	NA
Anti-inflammatory	15.7	96.3	1.6	2.0
Antibacterial	14.5	91.8	5.7	2.5
Endectocide	12.9	100.0	NA	NA
Endoparasiticide	12.2	100.0	NA	NA
Ectoparasiticide	11.4	100.0	NA	NA
Neurological	2.5	86.9	9.6	3.5
Gastrointestinal	1.8	47.2	51.3	1.5
Euthanasia	1.7	100.0	NA	NA
Cardiovascular	1.4	63.0	26.7	10.3

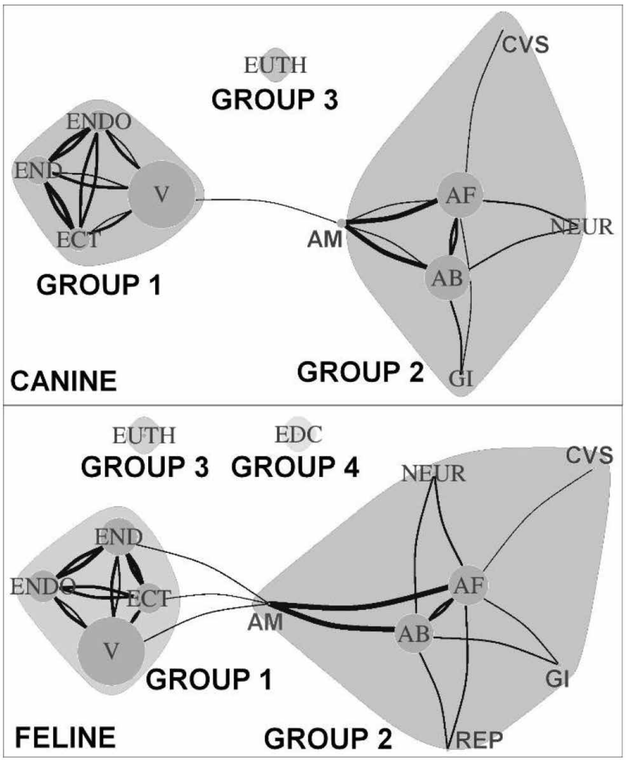
Systemic antibacterials

A number of key differences were found between dogs and cats (Table 3). The most apparent difference was in prescription of 3rd generation cephalosporins where dogs represented 1.5% (1.3-1.8) and cats represented 45.2% (42.1-48.4) of systemic antibacterial prescriptions, signifying 0.2% and 5.1% of all prescriptions (including non-antibacterials) respectively.

Discussion

The current paper demonstrates the potential of a big data resource such as SAVSNET to provide real insight into the prescription behaviour of a large cohort of UK practising small animal veterinary surgeons. Further, we have established a novel methodology to study a previously considered complex area of co-prescription.

Figure 1. Canine and feline sparsified network model for detection of community co-prescription structure. Node size = proportional frequency of therapeutic category prescription, edge width = co-prescription frequency.



AB=Antibacterial; AF=Anti-inflammatory; AM=Anti-mycotic; GI=Gastrointestinal; NEUR=Neurological; CVS=Cardiovascular; EUTH=Euthanasia; V=Vaccine; ENDO=Endo-parasiticide;END=Endectocide; ECT=Ecto-parasiticide; EDC=Endocrine; REP=Replacement agent.

The community detection and network sparsification method employed represents a relatively straightforward means to identify major prescription categories and show relative likelihood of co-prescription. It may be claimed that the sparsification method could be described as 'crude'; however, with little prior knowledge of expected outcome this might be viewed as an initial step towards development of more suitable models. Perhaps the indicator of model suitability for pharamacosurveillance is the formation of 'consult communities', or rather three dominant consult types, which would be familiar to most practising veterinary surgeons. Whilst model conclusions could therefore be viewed as not surprising, it does form a sound basis for more in-depth study, for example, within therapeutic category co-prescription.

There are some particularly strong co-prescription links, e.g. endoparasiticides, ectoparasiticides and endectocides; these are likely due to multi-active products. A further observation is that there is a generalised tendency towards greater proportional prescription of human-authorised drugs for less commonly prescribed therapeutic categories. This might provide a target for future efficacy evaluation and authorisation of new products, thereby decreasing clinical risk of prescribing non-veterinary authorised products.

Table 3. Percentage of systemic antibacterial prescriptions by class in cats and dogs.

Antibacterial class	Canine		Feline	
	%	95% CI	%	95% CI
Aminoglycoside	**0.1**	0.0-0.2	**0.2**	0.1-0.3
Beta-lactam	**73.8**	72.2-75.4	**87.8**	86.1-89.6
Amoxicillin	***9.0***	*7.1-10.8*	***15.2***	*12.1-18.3*
1st gen. ceph.	***14.3***	*13.2-15.3*	***0.5***	*0.3-0.6*
2nd gen. ceph.	***0.07***	*0.02-0.12*	***0.02***	*0.00-0.03*
3rd gen. ceph.	***1.5***	*1.3-1.8*	***45.2***	*42.1-48.4*
Clav. Pot. Amox.	***48.5***	*46.0-50.9*	***26.9***	*24.4-29.4*
Others	***0.5***	*0.0-1.3*	***0.02***	*0.00-0.05*
Fluoroquinolone	**4.1**	3.1-5.2	**3.2**	1.5-4.8
Lincosamide	**7.9**	7.0-8.8	**5.1**	4.4-5.9
Macrolide	**1.6**	1.1-2.1	**0.6**	0.4-0.8
Nitroimidazole	**9.3**	8.0-10.6	**2.2**	1.8-2.6
Sulphonamide	**2.5**	1.9-3.2	**0.06**	0.03-0.09
Tetracycline	**2.0**	1.7-2.2	**1.4**	1.2-1.6

It is interesting to note that the dominant prescription classes in both species seem to be concerned with prevention or treatment of infectious disease, indeed it could be argued that the primary prescription role of the companion animal veterinary surgeon is within this area. This suggests a clear need to establish surveillance priorities in the direction of infectious disease, particularly with regards to bacterial disease considering the global health threat presented by AMR. It is likely that the pressure to prescribe responsibly will increase, and thus the veterinary profession needs to not just describe antibacterial prescription but also justify its use and efficacy. This study demonstrates that small animal veterinary surgeons possess a strong preference for a small number of antibacterial classes. Veterinary surgeons also appear to commonly co-prescribe antibacterials with other therapeutic groups, a significant driver of this might well be availability of multi-active products. Exploring clinical benefit of such practises will be crucial to meeting rising demands for responsible prescription and evidence based veterinary medicine.

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