What drives antimicrobial prescribing for companion animals? A mixed-methods study of UK veterinary clinics

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Abstract

Antimicrobial use in companion animals is a largely overlooked contributor to the complex problem of antimicrobial resistance. Humans and companion animals share living spaces and some classes of antimicrobials, including those categorised as Highest Priority Critically Important Antimicrobials (HPCIAs). Veterinary guidelines recommend that these agents are not used as routine first line treatment and their frequent deployment could offer a surrogate measure of 'inappropriate' antimicrobial use. Anthropological methods provide a complementary means to understand how medicines use makes sense 'on-the-ground' and situated in the broader social context.

This mixed-methods study sought to investigate antimicrobial use in companion animals whilst considering the organisational context in which increasing numbers of veterinarians work. Its aims were to i) to epidemiologically analyse the variation in the percentage of antimicrobial events comprising of HPCIAs in companion animal dogs attending UK clinics belonging to large veterinary groups and, ii) to analyse how the organisational structure of companion animal practice influences antimicrobial use, based on insight gained from anthropological fieldwork.

A VetCompass™ dataset composed of 468,665 antimicrobial dispensing events in 240,998 dogs from June 2012 to June 2014 was analysed. A hierarchical model for HPCIA usage was built using a backwards elimination approach with clinic and dog identity numbers included as random effects, whilst veterinary group, age quartile, breed and clinic region were included as fixed effects. The largest odds ratio of an antimicrobial event comprising of a HPCIA by veterinary group was 7.34 (95% confidence interval 5.14 – 10.49), compared to the lowest group (p<0.001). Intraclass correlation was more strongly clustered at dog (0.710, 95% confidence interval 0.701 - 0.719) than clinic level (0.089, 95% confidence interval 0.076 -0.104). This suggests that veterinarians working in the same clinic do not automatically share ways of working with antimicrobials. Fieldwork revealed how the structure of the companion animal veterinary sector was more fluid than that depicted in the statistical model, and identified opportunities and challenges regarding altering antimicrobial use. These findings were organised into the following themes: *“Highest priority what?”; “He’s just not himself”; “Oh no – here comes the antibiotics police”; “We’re like ships that pass in the night”;* and *“There’s not enough hours in the day”.*

This rigorous mixed-methods study demonstrates the importance of working across disciplinary silos when tackling the complex problem of antimicrobial resistance. The findings

can help inform the design of sustainable stewardship schemes for the companion animal veterinary sector.

Keywords

Antibiotic, Antimicrobial consumption, Treatment incidence, Companion animal, Social sciences, Epidemiology

Introduction

Antimicrobial resistance is recognised as a key threat to global health and the global economy (O'Neill, 2016). However, major initiatives seeking to tackle this complex problem have largely overlooked antimicrobial use in companion animals (UK Government, 2013; O'Neill, 2016). This is despite humans and companion animals sharing classes of antimicrobials and living spaces, circumstances that could drive the development and spread of antimicrobial resistance relevant to human health (Pomba et al., 2017). Therefore, it is important to include companion animal veterinary care within antimicrobial stewardship activities.

The term antimicrobial stewardship is used to describe a range of approaches and interventions seeking to 'optimize' antimicrobial use (Dyar et al., 2017). It originated in human healthcare but is now applied in broader One Health contexts. In companion animal veterinary medicine, it has been interpreted as schemes to encourage the responsible use of antimicrobials by decreasing prescription rates without increasing negative patient outcomes (Allerton, 2018). The World Health Organisation (WHO) focuses stewardship efforts on antimicrobials with the strongest evidence of transmission of resistant microbes or resistance genes from animal sources to humans (World Health Organisation, 2019). These medicines, designated by the WHO as Highest Priority Critically Important Antimicrobials (HPCIAs), include third and fourth generation cephalosporins, fluoroquinolones and macrolides, which are all also available for use by companion animal veterinarians (National Office of Animal Health, 2019).

Epidemiological programmes such as VetCompass™ (O'Neill, 2013) and Small Animal Veterinary Surveillance Network (SAVSNET) (Radford et al., 2010) collate anonymised electronic patient records (EPRs) from primary-care veterinary clinics and enable the quantification of antimicrobial use in the wider companion animal population (Buckland et al., 2016; Singleton et al., 2017). In the United Kingdom (UK), antimicrobials are routinely prescribed for companion animals: over a two-year period, 25.2% of dogs and 20.6% of cats attending a veterinary clinic were given at least one antimicrobial treatment, with HPCIAs accounting for around five percent of antimicrobial prescribing events in dogs (Buckland et al., 2016). Unlike the livestock sector (O'Neill, 2016; Veterinary Medicines Directorate, 2019), there are no published target levels for appropriate antimicrobial use in companion animals; however, professional bodies such as the British Veterinary Association (2015) and the British Small Animal Veterinary Association (2018) advise that HPCIAs should not be routinely used as first line treatment. Variation in the use of HPCIAs could act as a surrogate measure for 'appropriate' antimicrobial use with a low proportion of HPCIA events amongst antimicrobial events presumed to be following this advice. This could offer potential opportunities to benchmark companion animal veterinary clinics in the future.

In addition to companion animal and veterinarian characteristics (Radford et al., 2011; Hughes et al., 2012), veterinary organisational structure has been associated with antimicrobial use. For example, the proportion of companion animals receiving antimicrobials varies approximately twofold between UK practices (Radford et al., 2011). Singleton and colleagues (2017) investigated longitudinal changes in HPCIA utilisation in veterinary consultations via a model that included practice (a single veterinary business) and premises (branches that form a practice) as random effects. They identified similar amount of variance at practice (0.225) and premise level (0.175) but did not explore the impact of belonging to different large veterinary groups. Across the UK companion animal veterinary sector, there has been increasing corporatisation in recent years with approximately half of all UK practices now belonging to large groups (Wedderburn, 2017). Understanding the context in which a growing number of companion animal veterinarians work may provide insights into where best to focus effective antimicrobial stewardship interventions. For example, identifying the organisational level at which antimicrobial use is most tightly clustered could indicate the most effective leverage point at which to intervene to change prescribing habits.

The social sciences are recognised to play a crucial role in understanding antimicrobial utilisation (Chandler et al., 2016). Often cast as 'irrational' and 'inappropriate', the methods and theories of anthropology offer a means by which to ask*, "what makes common sense here, and why?"* in order to develop situated accounts of antimicrobial use (Denyer Willis and Chandler, 2018). The cornerstone of anthropological methods is ethnography, involving participant observation to study enacted practice – both conscious and subconscious. Such an approach can provide additional insights to extend existing understandings of antimicrobial use, especially in companion animals, which has mostly relied on surveys that can only describe self-reported behaviour (Will, 2018). Ethnographic studies have been promoted in One Health for their ability to explicate the messy complexities of everyday lives whilst situating them in their broader political, economic, historical and social contexts (Wolf, 2015). This is crucial for a deeper understanding of the wider influences on antimicrobial use, beyond the moment of prescribing. Furthermore, anthropological approaches can address calls for the exploration of issues of power, professional identity and reputation with respect to veterinary prescribing of antimicrobials that, to date, remain under-scrutinised (Wood, 2016).

This mixed-methods study harnesses the complementary strengths of epidemiology and anthropology. This enables the painting of a more complete picture of antimicrobial use in companion animals, one that is, *"greater than the sum of the parts"* (O'Cathain et al., 2010). The goal of this research is to help inform the design of antimicrobial stewardship efforts in the companion animal veterinary sector. Therefore, the aims of this study are i) to epidemiologically analyse the variation in the percentage of antimicrobial events comprising of HPCIAs in companion animal dogs attending clinics belonging to large veterinary groups and, ii) to analyse how the organisational structure of companion animal veterinary medicine influences antimicrobial use, based on insight gained from anthropological fieldwork.

Materials and methods

Epidemiological study

Design

A VetCompass$_{TM}$ dataset spanning June 2012 to June 2014 inclusive that had previously been used to quantify UK antimicrobial use (Buckland et al., 2016) was analysed. Due to the time constraints of this PhD project, the study population was limited to dogs, the most common UK companion animal species (O'Neill, 2013). The percentage of antimicrobial dispensing events comprising of HPCIAs was selected as the outcome measure, given the interest in these agents (Veterinary Medicines Directorate, 2019). In addition to the previously applied inclusion and exclusion criteria (Buckland et al., 2016), only data from corporate veterinary groups with over thirty clinics were retained (Fig. 1). Supplementary material 1 describes the full study inclusion and exclusion criteria.

[Figure 1 - The flow of data through the VetCompass$_{TM}$ epidemiological study including the hierarchical models]

Data cleaning and processing

Buckland et al.'s (2016) definition of an antimicrobial agent and application to the dataset were re-used (Supplementary material 1). In brief, these were medicines that destroy or inhibit the growth of bacterial microorganisms and authorised for systemic use. Additional

HPCIA coding based on the WHO's definition (2019) was added. As per Buckland et al.'s approach, an antimicrobial event was defined as an independent record (line) in the treatment data field of the EPR-derived dataset and, consequently, multiple events could arise from a single consultation or across multiple visits.

The variable 'any HPCIA' was generated and coded as positive for all antimicrobial events linked to a unique dog identity number if one or more of these events comprised of an HPCIA. Dog age was calculated as the period between the birth date and the antimicrobial dispensing date; ages <0 or >24 years were coded as missing. Age was grouped *a priori* into quartiles to allow for non-linearity of effects and to facilitate interpretation. Dog sex was coded as male, female or missing. The 20 most prevalent dog breeds in the dataset were taken as categories, the remaining pure breeds were pooled together ('other purebreds') as were 'cross breeds'. The clinic postcode was used to derive its region in the UK.

Descriptive and univariable analyses

Counts and percentages were calculated for each categorical variable (dog sex, breed, clinic region). Dog age was summarised for each quartile using median and interquartile range (IQR) after reviewing its distribution. The Pearson chi-square test and the Mann Whitney U test, as appropriate, checked for differences between the sample characteristics of each veterinary group (Kirkwood and Sterne, 2003).

The total and average (mean, median) number of antimicrobial events and HPCIA events per dog were calculated. From the total number of antimicrobials events, the continuous outcome measure of the percentage of events compromising of HPCIAs was calculated at dog, clinic and veterinary group levels along with 95% confidence intervals (95% CIs). The distribution of the percentage of HPCIA events at a clinic level was plotted graphically. The composition of HPCIA events by veterinary group was investigated using percentages and 95% CIs.

Hierarchical modelling

A multilevel logistic regression model was built for the binary outcome of whether an antimicrobial event comprised of a HPCIA (yes versus no) using complete cases (antimicrobial events with full data on dog identification number, dog age, dog sex, dog breed, clinic identification number, clinic region, veterinary group identification number) in the dataset. This was with the aim of investigating the clustering of HPCIA use within dogs, clinics and veterinary groups. Data at individual veterinarian level were not available. Dog identity number and clinic identity number were added as random effects whilst veterinary group was included as a fixed effect. Clinic and animal identities were included as random effects due to the large number of individual identities at both levels and where the interest was in adjusting for clustering at these levels rather evaluating individual animal or clinic differences. A screening criterion of a univariable p-value <0.25 was applied when considering the inclusion of additional fixed effects (dog age, sex, breed, clinic region) (Hosmer and Lemeshow, 2004).

Model development used a manual backwards stepwise elimination approach. Models without dog identity number, clinic identity number or veterinary group were not considered as this would have prevented the investigation of HPCIA use at these levels. Likelihood ratio tests were used to compare the performance of the new, smaller model to the original. The estimated coefficients of the remaining variables were compared to those from the full model with all variables included to check there was no sizable change in their magnitude (Hosmer and Lemeshow, 2004). Pair-wise interaction effects between age quartile and percentage of HPCIA events in each veterinary group were evaluated. However limited computational power prevented the inclusion of an interaction term in the hierarchical modelling.

Model performance was assessed using Receiver Operator Curve (ROC) statistics and Hosmer Lemeshow residuals (Hosmer and Lemeshow, 2004; Statalist, 2017). Odd Ratios

(ORs) and 95% CIs were calculated for each fixed effect variable. The intraclass correlation coefficients (ICCs) at a dog and clinic level were calculated to assess the clustering of HPCIA use, that is the correlation among observations within the same cluster (Dohoo et al., 2003).

Due to the imbalanced structure of the dataset with most dogs having a single antimicrobial event, the analyses were re-run i) in the same model using a dataset limited to dogs with multiple antimicrobial events only (model 2) and ii) a model with a binary outcome of whether a dog received any HPCIA (model 3) (Fig.1). The ICCs and performance of these models were compared to the main model (model 1) to assess the robustness of the estimates produced.

Data analyses were conducted in Stata 16 (StataCorp, Texas, USA) and statistical significance was set at the 5% level. These analyses were covered by the VetCompassTM research ethics approval from the Royal Veterinary College's Ethics and Welfare Committee (SR2018-1652).

Anthropological study

Data collection

Fieldwork was undertaken by the lead author (AT) over nine months in 2019 at three UK companion animal clinic sites belonging to different large veterinary groups (two commercial and one charitable). The extended nature of placements enabled the researcher to become embedded in the clinic teams who became less conscious of being 'studied'. All aspects of daily clinic life were observed including consultations, surgical procedures, administrative and reception duties. The researcher's non-veterinary background facilitated a 'fresh pair of eyes' (an 'etic' view) on taken-for-granted situations, illuminating the unwritten rules surrounding companion animal veterinary work that become self-evident from an 'emic' view (Russell Bernard, 1985). Within these observation periods, informal interviews were undertaken with veterinarians, support staff and owners to clarify arising issues. Detailed field notes describing relations, language, metaphors, and sense-making between those actors at the interface of antimicrobial use were made with attention paid to both verbal and non-verbal gestures. Additional written data sources included clinic and veterinary group policies and media articles from the mainstream and veterinary press. Semi-structured interviews were also conducted with veterinarians working at fieldwork clinics. These followed a topic guide (Supplementary material 2) but with flexibility to follow up issues raised by interviewees. The formal interviews were audio-recorded and transcribed.

Data analyses

The software NVivo 12 (QSR International Pty Ltd, USA) was used to organise the qualitative data and facilitate thematic coding. Initial, low level codes situated in the data – such as the activity being undertaken or topic being discussed - were developed into more abstract themes (Ziebland and McPherson, 2006). Analysis involved comparing clinics to draw out similarities and differences. Moving to a new physical space - and shifting between emic (insider) and etic (outsider) perspectives - rendered visible the enacted 'common sense' and supporting infrastructures (Chandler, 2019) in each location. Analyses were conducted by the first author and interim findings were discussed amongst the multidisciplinary research team.

The empirical fieldwork data was considered in response to - and building on - the existing theoretical literature. Anthropologists emphasise that researchers always operate from a particular theoretical position that informs the inflection of the research: It shapes the lines of inquiry, what is tuned into in conversations, what captures the fieldworker's gaze during observations and what is deemed noteworthy. The theoretical orientation informing this study arises from the research in anthropology and science and technology studies, influenced by the ontological turn in the social sciences, which moves from distinctions of 'nature' and 'culture' to understanding 'naturecultures' (Haraway, 2003). Anthropologists strive to ‘take seriously’ their interlocutors and give voice to traditionally marginalised or overlooked groups. As such, this study sought to move beyond blaming veterinarians for being irrational users of antimicrobials and beyond blaming owners for demanding antimicrobials. Instead this project wanted to understand antimicrobial prescribing as an emergent and contingent practice that is enacted under particular economic, social and material conditions (Reynolds Whyte et al., 2002). It was informed by sensory accounts of multispecies encounters (for example Kirksey and Helmreich, 2010) and material semiotic approaches that have previously been used to study care in veterinary work (Law, 2010).

All study participants gave informed consent. The anthropological study was approved by the research ethics committee of London School of Hygiene and Tropical Medicine (16126).

Results

Epidemiological study

Descriptive results

The cleaned dataset contained 468,665 antimicrobial events across 240,998 dogs with 294,016 (62.7%) of these events arising from veterinary group C (Table 1). Of the total antimicrobial events, 29,984 comprised of HPCIAs (6.4%, 95% CI: 6.3; 6.5%): this percentage differed between veterinary groups ranging from 4.9 % (95% CI: 4.8; 5.0) in group B to 15.6% (95% CI: 15.2%; 16.1%) in group A ($p<0.001$). However, the canine and clinic characteristics of antimicrobial events also varied between veterinary groups (Supplementary material 3), potentially confounding this univariable finding although this is accounted for in subsequent multivariable analyses.

The types of HPCIA used varied between veterinary groups. The higher percentage of HPCIA events in group A was largely composed of fluoroquinolone use which contributed 13.4% (95% CI: 12.9;13.8%) to the total antimicrobial events in this group; This compared to 4.5% (95% CI: 4.4; 4.7%) in group B and 4.2% (95% CI: 4.2; 4.3%) in group C. Group B –

which had the lowest percentage of HPCIA events - had six uses of third generation cephalosporins (0.0% of antimicrobial events), suggesting they were not routinely stocked by clinics in this group. The corresponding results in groups A and C were 2.1% (95% CI: 2.0; 2.3%) and 1.9% (95% CI: 1.9; 2.0%) respectively. Macrolide use was low across all groups (n = 1,137 0.2% of antimicrobial events).

At a clinic level (n = 367), the median percentage of HPCIA events was 5.9 (IQR: 3.4 – 10.4%) with a range of 0.0% (10 clinics) to 69.9% (1 clinic). When plotted graphically, a positively (right handed) skewed distribution with a long tail was revealed (Fig. 2). The median number of antimicrobial events per dog was 2 (IQR: 1 - 4, range: 1 - 60), whilst the median number of HPCIA events was 0 (IQR: 0 - 0, range: 0 - 60).

[Figure 2 - The distribution of the percentage of antimicrobial events comprising of highest priority critically important antimicrobials by clinic (n = 367)]

Hierarchical modelling results

All variables met the univariable screening criterion for inclusion in the multivariable model building stage. At this point dog sex was not statistically significant and, therefore, the models comprised of clinic and dog as random effects, and corporate veterinary group, age quartile, breed and clinic region as fixed effects.

Table 2 reports the main model (model 1) results: The OR of an antimicrobial event comprising of a HPCIA was statistically significantly different between veterinary groups ($p<0.001$) whilst and was positively associated with increasing quartiles of age. The nine breeds with the greatest OR of an HPCIA event were classified as 'small' (Kennel Club, no date). Compared to the South East, the OR of an event comprising of a HPCIA in Scotland was reduced (0.26, 95% CI: 0.14; 0.49) whilst the corresponding figure for an event at clinics in the north west was 0.47 (95% CI: 0.30; 0.73). In other regions, there was no statistically significantly difference.

The area under the ROC for the main model (model 1) was 0.983 (95% CI: 0.983; 0.984) and the Hosmer-Lemeshow test was non-significant (p=0.314) suggesting an acceptable model fit. When dog identity number was removed as a random effect from the main model (model 1), the area under the ROC fell to 0.712 (95% CI: 0.709; 0.715, Hosmer-Lemeshow p-value 0.231) suggesting that the information contained with dog identity number variable makes a sizeable contribution to the model's performance.

Comparison of the ICCs in the main model (model 1) suggests HPCIA use is more strongly clustered within a dog (0.710, 95% CI: 0.710; 0.719) than within a clinic (0.089, 95% CI: 0.076; 0.104). These estimates were broadly similar across the models 1 to 3 (Supplementary material 4). The removal of veterinary group identity number from the main model (model 1) increased the clinic level ICC only slightly to 0.118 (95% CI: 0.102; 0.136).

Anthropological study

The statistical model presents a representation of the companion animal veterinary work in which a dog attends a single veterinary clinic and that each clinic is a neatly bounded entity under the umbrella of a corporate veterinary group. Time in the field revealed more fluid structures which are described below. These are presented in an order to reflect the levels of the statistical model.

"Highest priority what?"

HPCIA – the quantitative outcome classification used in the statistical model - had little meaning 'on the ground'. For example, antimicrobials were organised in clinic based on their formulation type (tablet, injectable) rather than other categorisations. They were referred to by their brand names amongst staff, for instance there was awareness regarding the pressure to restrict use of Convenia (Zoetis), a third-generation cephalosporin. When outlining treatment plans to owners, it was unusual for veterinarians to present choices between different antimicrobials or describe their HPCIA status. More typically a yes/no option was proposed: 'antibiotics' were offered or, in some cases, suggestions were made that they should be withheld – at least initially – due to concerns about antimicrobial resistance. The reasoning behind the selection of the antimicrobial agent offered to pet owners was rarely articulated by the veterinarians.

"He's just not himself"

Whether a dog received antimicrobials was shaped by a complex interplay of canine and owner characteristics. Owners determined if - and when - their dog attended the veterinary clinic and therefore could potentially access antimicrobials. Some owners presented at the first sign of trouble whilst others had to make tricky decisions about when to seek help based on limited financial and time resources. The epidemiological modelling did not investigate this entanglement of biological and social factors.

Furthermore, these canine-owner knots also influenced prescribing decisions by veterinarians who assessed whether owner characteristics, such as frailty, mobility or financial hardship, may hamper antimicrobial administration or prevent return to the clinic in case of problems. Frontline veterinarians had to balance the immediate welfare needs of the animal in front of them with the less tangible risk of antimicrobial resistance. In such circumstances, the use of long-acting, injectable agents such as Convenia (Zoetis) given then and there 'made sense'.

"Oh no – here comes the antibiotics police"

Due to the anonymization of information available in VetCompass™, it was not possible to quantitatively investigate variation in HPCIA use at an individual veterinarian level.

Observations revealed that this is important with several younger veterinarians taking on the role of local antimicrobials champion. They advised and, in some cases, cajoled their co-workers regarding more appropriate use. However, these champions revealed that they did not feel able to challenge all of their colleagues, in part due to their relative positions in the clinic hierarchy.

"We're like ships that pass in the night"

Modern ways of working challenge the notion of the veterinary clinic as a bounded unit with a stable workforce and shared practices. Shortages of qualified staff presented ongoing challenges in the fieldwork sites with rota gaps being filled by veterinarians from other clinics or locum staff. In some cases, out-of-hours work was contracted out to separate businesses. However, the flow of staff offered opportunities to share best practice between clinics.

Staffing patterns could pose issues in terms of continuity of care with pet owners no longer having a 'usual' veterinarian. For example, veterinarians were sometimes placed in awkward situations if pet owners had previously been seen by colleagues who had set a precedent by prescribing antimicrobials in conflict with guidelines.

"There's not enough hours in the day"

Belonging to a large veterinary group presented the potential to share some of the workload associated with antimicrobial stewardship. It was difficult for frontline veterinarians to personally carve out time to undertake such activities because clinical and revenue generating activities take priority under existing business models. At one fieldwork clinic, the corporate headquarters distributed template stewardship materials for completion; however, there was limited local capacity for this work in terms of time and personnel. In another group, a single 'top-down', business-wide policy regarding 'appropriate' use was introduced but there was muted buy-in at a clinic level. The level of clinic autonomy – for example deciding which drugs to stock – varied between veterinary groups whose organisational cultures differed.

Discussion

This study is the first to combine epidemiological and anthropological approaches to provide insights into antimicrobial use in the companion animal veterinary sector to help inform the design of sustainable stewardship interventions for this setting. Based on a large VetCompassTM dataset, the study quantified the variation in the percentage of antimicrobial events comprising of HPCIAs between clinics and three different veterinary groups. It also identified that relative HPCIA utilisation was more strongly clustered within dogs than within clinics. The anthropological fieldwork highlighted how the organisational structure of the companion animal veterinary sector was more fluid than that depicted in the statistical model, identifying opportunities and challenges when seeking to intervene regarding antimicrobial use. Table 3 provides a summary of the recommendations for antimicrobial stewardship schemes in companion animal veterinary practice arising from this study.

The main hierarchical model suggests that the cost influences antimicrobial choice: the odds of an antimicrobial event comprising of a relatively costly HPCIA were higher in low weight breeds in which smaller – less expensive - doses are indicated. In the future, a minimum price could be applied to a HPCIA dispensing event, deterring their use in smaller dog breeds. Recognising that companion animal veterinarians make decisions based on more than clinical factors alone is important when considering how to alter antimicrobial use. Previous research has used clinical vignettes to assess 'appropriate' antimicrobial utilisation (Barzelai et al., 2017; Hardefeldt et al., 2017; Van Cleven et al., 2018). However, such methods overlook the day-to-day complexities faced by frontline veterinarians when making choices about antimicrobial use. The model also revealed that the odds of an antimicrobial event comprising of a HPCIA increased as dogs ages. This could be partially explained by the contraindication for fluoroquinolones in young dogs (BSAVA, 2018) or by longitudinal changes in the common conditions treatable using antimicrobials across a dog's life course.

The quantitative study estimated that the odds of an antimicrobial event comprising a HPCIA was more tightly clustered at a dog level, perhaps reflecting their deployment in dogs with ongoing conditions. Less clustering was calculated at a clinic level suggesting that companion animal veterinarians working in the same clinic do not automatically share ways of working with antimicrobials. It was considered unlikely that within-clinic specialisation by veterinarians may have contributed to this limited within-clinic clustering, such that one clinician may be more likely to deal with dermatological conditions, for example, whilst another specialised in gastro-intestinal disorders. Within VetCompass the vast majority of work is primary care veterinary medicine with little internal referral and, as such, individual veterinarians are likely to treat the spectrum of conditions that present to a clinic. This limited clustering was echoed by the fieldwork finding that the 'clinic' was not found be the bounded, stable unit modelled in epidemiological studies as well as by work by Singleton et al (2017, supplementary material) where clinic premises explained little of the variance reported.

A limitation of this study is that the quantitative data was from 2012 to 2014and it is unclear to what extent these patterns of antimicrobial use persist. This study period was chosen due to the presence of a pre-existing, cleaned VetCompass dataset that facilitated the undertaking of this analysis. A UK-based SAVSNET study found the percentage of HPCIA events increased slightly between 2014 and 2016 (Singleton et al., 2017). Meanwhile, in the Netherlands, a statistically significant decrease in HPCIA use was measured between 2012 to 2014; however inter-clinic variation became more pronounced (Hopman et al., 2019a), perhaps suggesting differential uptake of antimicrobial stewardship messaging around HPCIA use. Subsequent to these quantitative data, the British Small Animal Veterinary Association (2018) introduced its UK stewardship campaign which included developing clinic level antimicrobial use policies. It will be interesting to assess whether the clinic level clustering of HPCIA use has subsequently changed.

From the anonymised clinical data shared with VetCompass™, it was not possible to quantify the clustering of HPCIA use at an individual veterinarian level or include the influence of owner characteristics. Future studies could quantitatively investigate these factors. However, time spent in clinic demonstrated that the decision to use an antimicrobial arose from complex interactions including those between the consulting veterinarian and the companion animal owner, highlighting the benefits of a mixed-methods approach. A previous qualitative study reported that veterinarians feel under pressure from owners to prescribe antimicrobials; however, owners reported that it was the veterinarians themselves who encouraged their use (Smith et al., 2018). Social scientists, meanwhile, have argued that focussing on who to blame overlooks the broader structural factors supporting the continued use of antimicrobials (Chandler, 2019). Future research should further investigate the entangled roles of these actors whilst considering the context in which they operate.

The percentage of antimicrobial dispensing events comprising of HPCIAs varied widely between veterinary groups largely due to variation in fluoroquinolone use. At a clinic level, a skewed distribution was observed. In the Dutch livestock sector, when defined daily antimicrobial dose per animal was plotted by farm a similarly skewed pattern was noted (Bos et al., 2015). The Netherlands Veterinary Medicines Authority used this as a basis to benchmark establishments and require that any above the 75th percentile – an arbitrary threshold – worked with their veterinarian to reduce their antimicrobial use. A similar approach could be adopted in the companion animal veterinary sector to tackle the 'long tail' of clinics using a higher proportion of HPCIAs. However, careful attention should be paid to the selection of any future benchmarking metric: for example, a clinic may have a high percentage of antimicrobial events comprising of HPCIAs despite a relatively small denominator (total antimicrobial events), thus masking a limited frequency of HPCIA events.

Alternatively, veterinarians might be careful users of HPCIAs but frequently prescribe other antimicrobials. Future benchmarking could account for both absolute as well as relative usage of antimicrobials overall as well as HPCIAs.

On-the-ground, antimicrobial stewardship activities have to be fitted around existing, income generating workloads. Large veterinary groups may be able to shoulder some of this stewardship burden. However, the fieldwork indicates that careful reflection should be given to considering how best to ensure 'buy-in' by frontline veterinarians. Furthermore, the organisational culture of each veterinary group varied, suggesting an 'off-the-shelf' approach might have limited impact. Whilst recent graduates may be willing to act as local champions for appropriate antimicrobial use, consideration is required of how the hierarchies and gender roles at play in veterinary work (Knights and Clarke, 2019) may help or hinder these activities.

To date, there has been little published research evaluating the effectiveness of interventions seeking to alter antimicrobial use in the companion animal veterinary sector although several projects are underway. Two studies (Weese, 2006; Sarrazin et al., 2017) focused on the introduction of prescribing guidelines; however, the interpretation of their findings is hampered by methodological issues such as lack of contemporaneous control groups or, in the case Sarrazin et al. (2017), the short follow-up period. Targeting the behaviour of individuals - such as prescribers - is a popular stewardship approach but also one which often has limited impact as it fails to address broader contextual issues supporting the continued use of antimicrobials (Denyer Willis and Chandler, 2019). The current study provides valuable insight into these contextual issues that, to date, have be largely overlooked when seeking to optimise antimicrobial use in the companion animals.

A more recent trial (Hopman et al., 2019b) tested a multicomponent stewardship approach – which include benchmarking activities, social pledges, veterinarian education and owner information sheets. Total antimicrobial use was reduced by 15% although there was no statistically significant reduction in HPCIA use. Clinics were reimbursed for their involvement which required considerable veterinarian participation. If Hopman et al.'s intensive approach were to be rolled out more widely, the current study suggests that financial reimbursement or provision of veterinary staff to cover clinical duties could be crucial in supporting the completion of stewardship activities. Outside of a research context, it is unclear which commercial, professional, or governmental bodies would provide these.

To conclude, this rigorous mixed-methods study has provided fresh insights into antimicrobial use in the companion animal veterinary sector. In doing so, it demonstrates the strengths of working across traditional disciplinary silos to better understand and intervene in this area. By using both quantitative and qualitative approaches, it has enabled a deeper understanding of the organisational structure in which an increasing number of companion animal work and how this can influence antimicrobial use. These findings will help inform the design of sustainable stewardship interventions for this setting.

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Conflicts of interest statement

The authors declare no conflicts of interest.

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Table 1. The distribution of antimicrobial and HPCIA events by veterinary group in a VetCompassTM UK dataset from 2012 -2014. Distribution is reported in total and at a clinic level (No.: Number; HPCIA: Highest priority critical important antimicrobial; CI: confidence interval; IQR: interquartile range)

Vet. Group	No. dogs (%)	No. antimicrobial events (%)	No. HPCIA events (%)	Percentage of antimicrobial events comprising of HPCIAs (95% CI)	No. clinics (%)	Median clinic percentage of antimicrobial events comprising of HPCIAs (IQR)
A	12,565 (5,2)	25,909 (5.5)	4,044 (13.5)	15.6 (15.2;16.1)	90 (24.5)	13.8 (10.9;19.9)
B	83,754 (34.8)	148,740 (31.7)	7,280 (24.3)	4.9 (4.8;5.0)	117 (31.9)	3.7 (2.1;6.1)
C	144,679 (60.0)	294,016 (62.7)	18,660 (62.2)	6.3 (6.3;6.4)	160 (43.6)	5.3 (3.6;7.7)
Total	240,998 (100.0)	468,665 (100.0)	29,984 (100.0)	6.4 (6.3;6.5)	367 (100.0)	5.9 (3.4;10.4)

Table 2. The results of the main hierarchical model (model 1) investigating HPCIA events in a VetCompass™ UK dataset of antimicrobial events from 2012 -2014 (n = 458,599) (No.: Number; HPCIA: Highest priority critical important antimicrobial; CI: confidence interval)

Variable		**No. (%)**	**Odds of HPCIA Exposure (95% CI)**	**p-value**
Veterinary group	B	146,802 (32.0)	1.00	<0.0001
	A	25,417 (5.5)	7.34 (5.14;10.49)	
	C	286,380 (62.4)	2.04 (1.56;2.70)	
Age quartile	<1.5 years	113,060 (24.7)	1.00	<0.0001
	1.5 to <4.3 years	116,388 (25.4)	2.12 (1.97;2.29)	
	4.3 to <8.2 years	113,029 (24.6)	2.95 (2.73;3.18)	
	8.2 years and over	116,122 (25.3)	5.02 (4.64;5.43)	
Breed	Crossbreed	94,069 (20.5)	1.00	<0.0001
	Staffordshire bull terrier	27,753 (6.1)	0.74 (0.65;0.84)	
	Border collie	10,330 (2.3)	0.83 (0.68;1.01)	
	Rottweiler	5,947 (1.3)	0.95 (0.74;1.23)	
	Labrador retriever	35,097 (7.7)	0.96 (0.86;1.08)	
	German shepherd dog	14,686 (3.2)	1.03 (0.87;1.22)	
	Golden retriever	7,350 (1.6)	1.04 (0.84;1.30)	
	Springer spaniel	7,708 (1.7)	1.22 (0.98;1.51)	
	Jack Russell	22,303 (4.9)	1.28 (1.13;1.45)	
	English springer spaniel	6,228 (1.4)	1.39 (1.11;1.74)	
	Boxer	9,463 (2.1)	1.48 (1.22;1.79)	
	All other pure breeds	107,008 (23.3)	1.55 (1.43;1.68)	
	Border terrier	5,234 (1.1)	1.70 (1.34;2.15)	
	Cavalier King Charles spaniel	11,941 (2.6)	1.85 (1.57;2.18)	
	Cocker spaniel	19,289 (4.2)	1.98 (1.73;2.26)	
	Bichon fries	7,611 (1.7)	2.09 (1.72;2.54)	
	Lhasa apso	6,490 (1.4)	2.31 (1.89;2.84)	
	West highland terrier	18,115 (4.0)	2.47 (2.17;2.81)	
	Shih tzu	12,618 (2.8)	2.61 (2.24;3.03)	
	Yorkshire terrier	14,634 (3.2)	2.83 (2.47;3.23)	
	Pug	5,849 (1.3)	3.12 (2.52;3.86)	
	Chihuahua	8,836 (1.9)	3.31 (2.80;3.92)	
Clinic region	South East	78,224 (17.1)	1.00	0.0017
	Scotland	18,765 (4.1)	0.26 (0.14;0.49)	
	Northern Ireland	5,567 (1.2)	0.41 (0.17;1.01)	
	North West	45,192 (9.9)	0.47 (0.30;0.73)	
	North East	42,324 (9.2)	0.69 (0.41;1.14)	
	West Midlands	46,924 (10.2)	0.71 (0.45;1.11)	
	East Midlands	54,458 (11.9)	0.71 (0.45;1.11)	
	Greater London	41,402 (9.0)	0.74 (0.49;1.11)	
	East of England	65,092 (14.2)	0.80 (0.55;1.16)	
	South West	45,011 (9.8)	0.88 (0.59;1.40)	
	Channel Islands	926 (0.2)	0.98 (0.14;6.80)	
	Wales	14,714 (3.2)	1.02 (0.53;1.96)	

Table 3. Recommendations for antimicrobial stewardship schemes in companion animal veterinary clinics

Tailor language to reflect target audiences.
Address the structural influences supporting antimicrobial use (for example their physical accessibility in clinic).
Provide tools to support vet-owner discussions regarding antimicrobials.
Make stewardship activities inclusive to all staff including those working part-time, as locums or hour-of-hours.
Support antimicrobial champions by strengthening the evidence base regarding clinical outcomes when adhering to prescribing guidelines.
Incorporate mandatory antimicrobial stewardship training in CPD requirements.
Encourage benchmarking by the provision of accessible benchmarking tools and services such as SAVSNET-AMR (Radford et al., 2017).

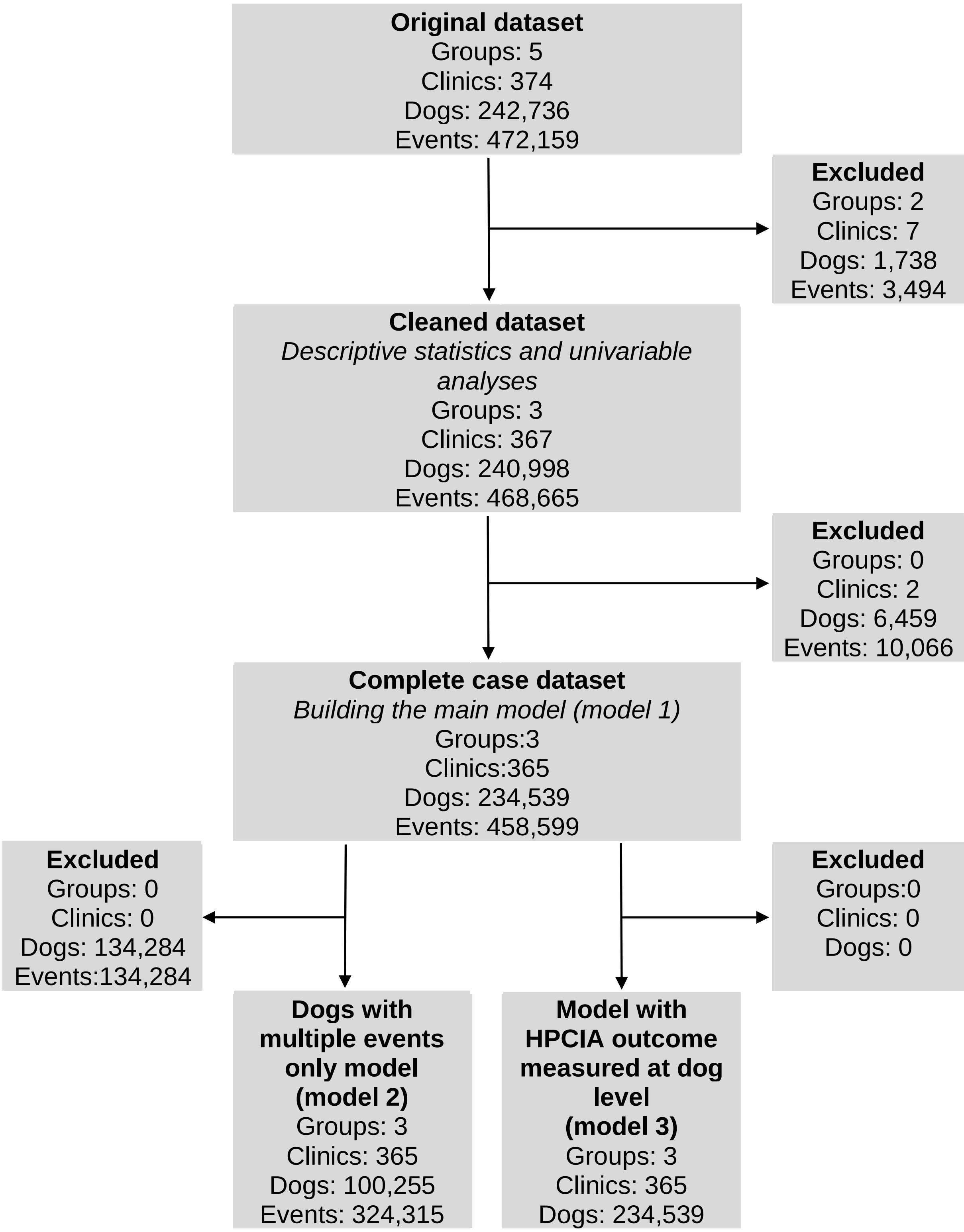

Figure 1 - The flow of data through the VetCompass$_{TM}$ epidemiological study including the hierarchical models

Figure 2. The distribution of the percentage of antimicrobial events comprising of highest priority critically important antimicrobials by clinic (n = 367)