ANTIMICROBIAL STEWARDSHIP AND PETS

EVALUATING AND OPTIMISING ANTIMICROBIAL USE IN DUTCH COMPANION ANIMAL CLINICS






Nonke E.M. Hopman

Haley van Zanten heeft dit proefschrift kleur gegeven. Zij heeft in haar jonge leven al (te) veel chemotherapeutische behandelingen gehad. Dit was onmogelijk geweest zonder werkzame antibiotica.

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Antimicrobial Stewardship en Gezelschapsdieren

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in Nederlandse Gezelschapsdierenpraktijken
(met een samenvatting in het Nederlands)

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The most important things in life aren't things

Voor mijn lieve oma

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Chapter 1

General introduction

The discovery of antibiotics

The discovery of antibiotics in the previous century, with penicillin by Sir Alexander Fleming in 1929 being the first one [1,2], is one of the most important advancements in human medicine. Antibiotics have made a major contribution to extending life expectancy. Without effective antibiotics, the core of modern medicine and treatment of bacterial diseases are threatened; intensive care and organ transplants, the application of cancer chemotherapy, common surgical procedures, and treatment of basic bacterial infections rely on our worthy ally: effective antibiotics [3-5]. Animal health and welfare rely on access to effective antibiotics as well. Antibiotics save lives and there may be negative effects on animal health and welfare when diseases can no longer be treated [6].

Clarification of used terms

Microorganisms, also called microbes, include bacteria, viruses, fungi and protozoa. An antimicrobial is "any substance with a direct action on microorganisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and antiprotozoals". Antibiotics are "any substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious diseases" [3,7].
In this thesis, the term antimicrobial (AM) will be used to refer to antibiotics. There are several different classes of antimicrobials, mostly differentiated by chemical structure. AMs within a class will generally have a similar mechanism of action and pattern of activity. Antimicrobial resistance (AMR) is the ability of a microorganism to resist the action of one or more AMs and to be able to replicate in the presence of these AMs. When AMs belong to the same class, resistance to one specific AM out of that class, often leads to resistance to all members of the same class of AMs.

Emergence of antimicrobial resistance

As soon as antimicrobials were introduced, resistance emerged as well. During his Nobel Lecture in 1945, Sir Alexander Fleming already warned that inappropriate use of antimicrobials would lead to the development of resistance [8]; "Mr. X. has a sore throat. He buys some penicillin and gives himself not enough to kill the streptococci, but enough to educate them to resist penicillin". Bacteria respond rapidly to their environment, enabling them to survive in disadvantageous environments, e.g., under the pressure of AMs [9].

Pathogens can have an innate or intrinsic (multidrug) resistance, but they can also acquire resistance. Acquired AMR is a consequence of natural selection and genetic mutation. Such a mutation might then be passed on conferring resistance. This natural selection process is exacerbated by factors such as inappropriate antimicrobial use (e.g., unnecessary use of AMs for viral infections, use of AMs to which the pathogen is resistant or use of an overly broad-spectrum AM to treat a susceptible bacterium) [9-12]. The commonly accepted two major drivers for AMR are antimicrobial use (both appropriate and inappropriate use), "the more you use them, the more you lose them", and transmission of antimicrobial resistant microorganisms (and genes) between humans, animals and the environment, including food [9, 13, 14].

Consequences of AMR in human medicine

The burden of disease as consequence of AMR is difficult to assess. However, in the European population in 2015, infections with antimicrobial resistant bacteria were estimated to account for an estimated 33,110 attributable deaths. The number of disability-adjusted life years was estimated to be 874,541 and the contribution of antimicrobial resistant bacteria to infections has increased since 2007 [15, 16]. Centers for Disease Control and Prevention (CDC, USA) estimate that in the USA each year, at least 23,000 people die as a direct result of antimicrobial resistant infections and at least 2 million people acquire serious infections with resistant bacteria. The number of people dying from other conditions, but complicated by an antimicrobial resistant infection, was estimated to be considerably higher [17].

No major new class of AMs has been discovered since 1987 and no more than only a few agents are in the development pipeline for the next 5-10 years [4]. This is why action is needed to keep new resistance from developing and to prevent resistance from spreading. The theme of World Health Day 2011 was "antimicrobial resistance: no action today, no cure tomorrow" [10, 18].

Turning the tide

There are many efforts and action plans to decrease AMR and to increase the development of new AMs. One of these action plans is from the World Health Organisation (WHO) [4], which outlines five objectives:

1) Improving awareness and understanding of AMR;
2) To strengthen the knowledge and evidence through surveillance and research;
3) To reduce the incidence of infections;
4) To optimise antimicrobial use (AMU) both in human and animal health;
5) To develop an economic situation in which sustainable investments take into account

the needs of all countries (i.e. low, middle and high-income countries), to promote the investment in new drugs, diagnostic tests, vaccines and other interventions to fight AMR.

In general, three main strategies are proposed to preserve antimicrobials as resources for future generations [9, 19]:

1) Infection control and prevention strategies to prevent the spread of (resistant) bacteria, since every infection prevented is one that needs no treatment. Without proper infection control and prevention strategies, other interventions will not yield the optimal effect [20];

2) Stimulate research and development of new (classes of) AMs and other treatment options effective against resistant strains;

3) Secure the efficacy of the existing antimicrobial treatment options, including ensuring access.

Antimicrobial stewardship

Antimicrobial stewardship mainly focuses on the third strategy. The term "antimicrobial stewardship" first appeared on Pubmed in 1996 and has many definitions, one of which is "being a coherent set of actions which promote responsible use of AMs to ensure access to effective AMs for all who need them, today and tomorrow" [21]. The primary goal of antimicrobial stewardship is to optimise clinical patient outcomes while minimising unintended consequences of AMU, including toxicity, the selection of pathogenic organisms (such as *Clostridium difficile)* and the emergence of AMR [22]. "As little as possible and only as much as necessary". Antimicrobial stewardship involves actions balancing the need of any individual for appropriate treatment and the longer-term need for society for sustained access to effective AM therapy in the future [21].

In human medicine, many initiatives at international, national and local level have been launched to fight AMR and many antimicrobial stewardship programmes (ASPs) were developed and implemented to promote responsible AMU [23-31]. Before implementing an ASP, it is necessary to know which factors influence AM prescribing behaviour, which factors facilitate appropriate AM prescribing and which factors are possible barriers. These influencing factors have been studied extensively in different clinical settings [32-35].

Responsible antimicrobial use in veterinary medicine

Most classes of AMs are used in both humans and animals. Although we do not know the exact attribution of human and veterinary AMU, any use of antimicrobials selects for AMR. Therefore, responsible use of AMs should not only be promoted in human medicine, but also in veterinary medicine [4, 36].

Increased attention on AMU, companion animals should follow suit

In the Netherlands, from 2008 onwards, AMU in food-producing animals received increasing attention. Actions were taken at different levels and AMU was reduced considerably [37-41]. Most actions addressed food-producing animals, because the majority of AMs were and are used in these sectors and it represents a significant higher number of animals (and resulting mass). However, in 2011, the advisory report of the Health Council of the Netherlands on the use of AMs in food-producing animals, also mentioned the presence of highly resistant microorganisms (HRMO) in companion animals as a real concern [42]. Legislation on mandatory susceptibility testing for use of 3rd choice AMs since January 2013, and classification of AMs in 1st, 2nd and 3rd choice AMs, also hold for companion animals [43, 44].

In the context of all actions against the emergence of AMR, a more responsible and restricted use of antimicrobials in companion animals can not be disregarded [45, 46]. Everyone involved in using AMs has a responsibility to use them judiciously, including companion animal veterinarians. After all, "the spread of resistant bacteria changes the problem from an individual to a collective one" and as a result, turns it into a public health issue [47].

Classification of antimicrobials

To support responsible AMU, WHO compiled a list of AMs that are critically important for human medicine, the so-called CIA-list (Critically Important Antimicrobials). Very recently, the 6th revision of this 'CIA-list' has been released [48]. AMs are categorised and prioritised as Critically Important (with a subgroup indicated as "highest priority" and a subgroup "high priority"), Highly Important and Important. E.g., cephalosporins (3rd and higher generations) and quinolones are highest priority CIAs for human medicine [48]. WHO recommends an overall reduction in use of all classes of medically important AMs in food-producing animals [49]. The ranking of WHO can be used when risk management strategies are developed for non-human use of AMs.

In the Netherlands, AMs for veterinary use are classified according to the Dutch policy on veterinary AMU (Table 1) [43, 44, 50]. During development of the Dutch policy on veterinary AMU, earlier versions of this WHO list were taken into consideration, as well as the advisory report of the Health Council of the Netherlands [42].

Table 1: Classification of veterinary AMU according to Dutch policy on veterinary AMU.

Classification	Reasoning	Main classes of AMs
1st choice	Empirical therapy; Do not select for (to current knowledge), nor are specifically meant for treatment of ESBL-producing micro-organisms.	Tetracyclines, nitroimidazoles, narrow-spectrum penicillins, trimethoprim, sulfonamides, lincosamides and phenicols.
2nd choice	All AMs not classified as 1st or 3rd choice AMs; Use of these AMs might select for ESBL-producing bacteria or is specifically indicated in case of an ESBL-infection.	Aminopenicillins (with/without beta-lactamase inhibitors), 1st generation cephalosporins, aminoglycosides and colistin.
3rd choice	A selection of highest Priority Critically Important AMs for human medicine according to WHO; By Dutch law restricted to use only in individual animals and after culture and susceptibility testing.	Fluoroquinolones, 3rd and 4th generation cephalosporins.

Antimicrobial use in companion animals

Compared to food-producing animals, data on AMU in companion animals are scarce. However, available data show that there is room for improvement of AMU. E.g., aminopenicillins (with or without clavulanic acid), cephalosporins and fluoroquinolones are widely used as empiric “first-line” agents in dogs and cats, including treatment of mild or even self-limiting infections [51-55]. A survey in the Netherlands (2009-2011) showed that in companion animals only 5% of prescribed AMs represented 1st choice AMs (i.e. empirical therapy, Table 1), whereas 18% of calculated AMU was characterised as long acting 3rd generation cephalosporines (10%) and fluoroquinolones (8%) [56].

Antimicrobial resistance in companion animals

The relevance of responsible and rational AMU in companion animals is also demonstrated by increasing resistance rates in bacteria isolated from companion animals and their owners. In companion animals an increasing incidence of methicillin resistant *Staphylococcus pseudintermedius* (MRSP) has been reported [57-60].

Extended Spectrum Beta-Lactamase (ESBL)-producing Enterobacteriaceae have been isolated from clinical cases in companion animals and about half of the healthy dogs is shown to be carrier of ESBL-producing *Escherichia coli* (*E. coli*) in a pilot study in the Netherlands [61, 62]. Another study also shows a high prevalence of ESBL-producing Enterobacteriaceae among healthy dogs in the Netherlands [63]. Routine treatment of dogs with beta-lactam AMs or fluoroquinolones is shown to be associated with increased detection of important phenotypic and genotypic AMR faecal *E. coli* [64].
Worrisome are recent publications about the presence of carbapenemase producing Enterobacteriaceae in companion animals [65-67]. This increasing resistance incidence might pose a threat for public health [68, 69].

The direct and close contact between companion animals and humans provides opportunities for interspecies transmission of (resistant) microorganisms [70, 71]. Transmission between companion animals and their owners has indeed been shown for *Staphylococcus pseudintermedius* and methicillin resistant *Staphylococcus aureus* [72-75]. For *E. coli* the presence of homologous strains in humans and companion animals in the same household has also been documented [76]. Besides a possible risk for humans, AMR also has a direct impact on animal health and welfare, because infections with (multi-)resistant microorganisms can be difficult to treat which may lead to worse clinical outcomes.

Use of guidelines

According to the Dutch Working Party on Antibiotic Policy (SWAB) one of the two pillars of good antibiotic policy are guidelines on restrictive AMU. In human medicine, there are many national guidelines on use of diagnostics, restrictive AMU and infection prevention [77-80].

In the Netherlands since 2014, there are three guidelines published for companion animals by the Royal Dutch Veterinary Association (KNMvD) on the diagnostic work-up and treatment of urinary tract infections, skin infections and otitis externa (2014-2015) [81]. Guidelines do not indicate which AM to use; this is indicated in the formulary for companion animals [50, 81]. In 2013 and 2018, the formulary was revised (the formularies are revised every 3-5 years in general). For the development of these guidelines and the formulary, less scientific literature is available compared to human medicine. Dissemination, implementation and use of these guidelines and formulary is relatively new in veterinary medicine. It is unlikely that the development and publication of guidelines and a formulary alone will be sufficient to optimise AMU in companion animals.

"Antibiotic Stewardship and Pets"-project

In 2014, the research project described in this thesis was started with the aim to develop, to implement and to evaluate the effectiveness of an "intervention programme" to optimise AMU in companion animals, to protect both human and animal health. This project received the acronym "ASAP-project"; Antibiotic Stewardship and Pets.

One of the many explanations of antimicrobial stewardship is a multifaceted and dynamic approach to preserve the clinical efficacy of AMs by optimising AMU while minimising the emergence of AMR and possible other adverse effects [55, 82, 83]. One of the many approaches to optimise AMU, specifically focussed on veterinary AMU, is the 5 Rs-approach to antimicrobial stewardship, described by Page et al. [83]:

1) **Responsible** AMU in which the prescriber accepts responsibility for the decision to prescribe AMs, with possible adverse consequences;
2) **Reduction** of AMU, which may result, e.g., from enhanced infection prevention and vaccination, but also from reduced treatment course lengths;
3) **Refinement** of AMU to ensure the likelihood that the selection of AMR is minimised while the likelihood of clinical efficacy is maximised;
4) **Replacement** of AMs by an alternative treatment whenever possible and available;
5) **Review** of antimicrobial stewardship initiatives should be performed regularly.

It is important to notice that antimicrobial stewardship in veterinary medicine is slightly differently perceived and defined compared to human medicine. In veterinary medicine, antimicrobial stewardship is generally associated with country-wide surveillance on AMR and development of (inter)national guidelines on AMU. Whereas in human medicine, this term is usually used to describe specific programmes or series of interventions to monitor and direct AMU at hospital level [55].

Aims and outline of this thesis

To be able to develop, implement and evaluate the effectiveness of an antimicrobial stewardship programme, some questions need to be addressed first.

Therefore, in Chapter 2, the central question "which factors influence antimicrobial prescribing in companion animal clinics in the Netherlands" is addressed, using qualitative research.

In Chapter 3, attitudes and perceptions of companion animal veterinarians towards AMU and AMR are quantitatively investigated to identify associations with demographic characteristics as possible explanatory variables.

In Chapter 4, systemic AMU is quantified based upon procurement data of 100 Dutch companion animal clinics, to explore applied antimicrobial classes and to identify differences in prescribing patterns over time and between veterinary clinics. A method to quantify AMU is introduced as well, using the number of Defined Daily Doses for Animals (DDDA).

In Chapter 5, systemic AMU, based upon prescription data of 44 Dutch companion animal clinics, is described over a 3-year time period (2012-2015). Time trends, seasonality and the influence of a few determinants of AMU are explored. These data and used calculation method will serve as starting point for a follow-up study.

In Chapter 6, a customised antimicrobial stewardship programme is implemented in these 44 Dutch companion animal clinics, using a stepped-wedge design. The effectiveness of this ASP on AMU is evaluated over a follow-up period of 12 months.

In Chapter 7, the general discussion, the main findings of this thesis are summarised and a number of key issues related to AMU in companion animal clinics is discussed and followed by recommendations.

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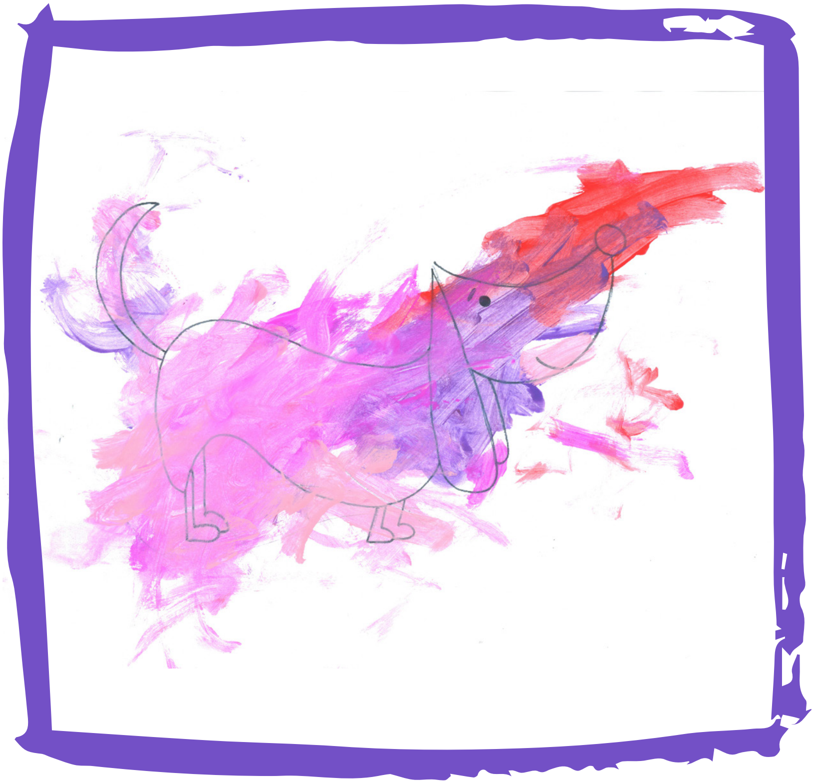

Chapter 2

Factors influencing antimicrobial prescribing by Dutch companion animal veterinarians: A qualitative study

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Abstract

Use of antimicrobials selects for antimicrobial resistance, and this poses a threat for both human and animal health. Although previous studies show that total antimicrobial use in Dutch companion animal clinics is relatively low and decreasing, the majority of antimicrobials prescribed are categorised as critically important for human medicine by the World Health Organisation (WHO). Large differences in use between clinics are also observed. Identification of factors that influence the prescribing behaviour of veterinarians is needed to tailor future interventions aimed at promoting prudent use of antimicrobials in companion animals. The aim of this study was to explore factors influencing the antimicrobial prescribing behaviour of companion animal veterinarians in the Netherlands.

Face-to-face, semi-structured interviews were used to interview 18 Dutch companion animal veterinarians. Interviews were held until theoretical data saturation was reached. An interview guide was used to structure the interviews, and ATLAS.ti 7.5 was used to manage and analyse the qualitative data. An iterative approach was applied to develop a conceptual model of factors that influence antimicrobial prescribing behaviour.

The conceptual model shows four major categories of factors that influence the antimicrobial prescribing behaviour: veterinarian-related factors, patient-related (i.e. owner- and pet-related) factors, treatment-related factors (i.e. alternative treatment options and antimicrobial-related factors) and contextual factors (i.e. professional interactions, further diagnostics and environmental factors). All four major categories of influencing factors should be addressed to improve awareness on antimicrobial prescribing behaviour and to develop an antimicrobial stewardship programme for companion animal clinics.

1. Introduction

The global increase in antimicrobial resistance (AMR) is recognised as a threat for both human and animal health [1-3]. As any use of antimicrobials selects for antimicrobial resistance, prudent use of antimicrobials (AMs) in humans and animals should be promoted [4]. To support prudent antimicrobial use (AMU) the World Health Organisation (WHO) compiled a list of AMs that are critically important for human medicine, the so-called CIA list [5]. Recommendations on restricted AMU focus primarily on AMU in food animals, but due to the close contact between companion animals and their owners and therefore the potential transmission of resistant bacteria, these recommendations should likewise hold for companion animals [1, 6-11].

In comparison with food animals, data on AMU in companion animals are scarce. Studies in the UK and New Zealand showed that the majority of AMs used in dogs and cats were classified as critically important (CIA) to human health [12, 13].
A survey on purchase data from 100 Dutch veterinary clinics providing care for companion animals (2012-2014) showed that the majority of AMs were on the CIA list, while the highest priority AMs (i.e. 3rd generation cephalosporins and fluoroquinolones) accounted for 7% of total AMU in 2014. Total AMU was relatively low (compared to AMU in livestock) and a decrease was seen over the study period. Large differences between clinics were observed (e.g. a 13-fold difference in total use between clinics in 2014), indicating that there is room for improvement [14].

Several international and national guidelines to promote prudent AMU in companion animals have been developed in recent years [15-19], but the implementation of these guidelines and antimicrobial stewardship programmes in companion animals are limited.
Over the past few decades, antimicrobial stewardship programmes have been implemented in human medicine to optimise AMU [20]. Before implementing a stewardship programme, it is necessary to know which factors influence antimicrobial prescribing behaviour. In human medicine, these determinants have been studied extensively in different clinical settings [21-23]. In veterinary medicine, only a few qualitative studies exploring AM prescribing behaviour of veterinarians have been performed, primarily in production animals [24-27]. As part of a larger research project on antimicrobial stewardship in Dutch companion animal clinics (the ASAP-project: Antimicrobial Stewardship and Pets), the present study aimed to identify factors influencing AM prescribing in companion animal clinics in the Netherlands. This information will act as a starting point for the development and implementation of an antimicrobial stewardship programme for companion animal clinics.

2. Material and methods

2.1. Study design

Face-to-face interviews were used to qualitatively examine the spectrum of factors that might influence AM prescribing behaviour of Dutch companion animal veterinarians.
A semi-structured interview guide was developed by the authors (NH, MH, DS and EB) based upon their field experience as well as the models of Hulscher et al. [28] and Flottorp et al. [29] (Appendix A). Three pilot interviews were conducted to validate and adjust the guide where necessary. Interviews were started with a general 'warm-up' question about the clinic. Subsequently, participants were asked to describe a recent clinical case in which they prescribed AMs and a case in which they doubted about prescribing AMs. Next, the remaining topics from the interview guide were discussed.
The following topics were covered during the interviews (in free order): prior knowledge on use and legislation of antimicrobials; opinions and behaviour of the veterinarian influencing AMU; cultural and socioeconomic context; behaviour of the companion animal owner and organisation of care within the veterinary clinic (Appendix A). Participants were encouraged to reflect on their opinion in detail and to discuss the topics freely.

Interviews were held between January and April 2015 by NH (researcher and DVM). Interviews were recorded and subsequently transcribed verbatim by an independent transcription company. Interviews were analysed as soon as possible, enabling an iterative process with minor changes of the interview guide based upon emerging themes and potential missing information.

2.2. Selection of participants

An exhaustive list of all Dutch veterinarians (from the Royal Netherlands Veterinary Association, KNMvD) was used for the selection of companion animal veterinarians. Inclusion criteria were: practising veterinarians with a primary focus on companion animals (i.e. dogs, cats, rabbits and other small pets, including birds and exotics). Selection of veterinarians was done purposefully to ensure variation in gender, age, years of professional experience, clinical setting (e.g. solo versus group practice and referral versus first opinion clinics) and geographical location.

Interviews were held, and veterinarians were invited on an ongoing basis, until theoretical data saturation was reached, i.e. no new information could be identified from the last three consecutive interviews. Veterinarians were invited via e-mail first, followed by a phone call to answer questions and to arrange a time and place for the interview. Interviews took place at a convenient location for the veterinarian, which could be at their clinic or home or at the researcher's workplace.
Before enrolment, all veterinarians received written information describing the purpose of the

interview and the voluntary nature of participation. All interviewed veterinarians signed an informed consent to assure confidential handling of the data and permission to record the interviews. Interviewed veterinarians were financially compensated for their time investment.
This study was exempt from ethical approval according to Dutch legislation (Law on Medical Scientific Research with People) because no patients were involved.

2.3. Data analysis

ATLAS.ti 7.5 (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany) was used to manage and analyse the qualitative data. An iterative approach was used to analyse interview notes and interview transcripts on an ongoing basis. Two questions were leading during the analysis of the data '*which factors influence the decision to prescribe antimicrobials*' and '*which factors influence which antimicrobial to prescribe*'.
Interviews were conducted in Dutch and analyses of the transcripts were also performed in Dutch. A native English speaker translated quotations used in the manuscript.

All interview transcripts were coded and analysed by NH in a stepwise fashion as prescribed by van Buul et al. (2014) [23]. Eight randomly selected transcripts were independently analysed and coded by two other researchers (HG and EB, four transcripts each). The double-analysed transcripts were used for validation purposes and to discuss the coding process. During the coding and analysis of the remaining transcripts (by NH) several meetings (with HG and EB) took place to discuss the transcripts and coding process until consensus was reached. Emerging themes and patterns were discussed as well.

After the analysis of all transcripts, factors influencing AM prescribing behaviour were discussed with HG, EB and MH until consensus was reached. Finally, a draft conceptual model presenting these factors was developed. This model and observed patterns were critically evaluated (15 October 2015) by the ASAP project group, which consisted of stakeholders from veterinary and human medicine. Finally, the model was revised during the writing process.
The consolidated criteria for reporting qualitative research (COREQ) and the standards for reporting Qualitative Research (SRQR) were used as checklists to guide a comprehensive reporting of the study [30, 31].

3. Results

3.1. Demographic data

Theoretical data saturation was reached after 18 interviews. This number of interviews was reached by inviting 25 companion animal veterinarians; 7 veterinarians were not willing to participate, mainly due to lack of time or interest. Duration of the interviews varied from

50 to 90 minutes. The interviewed veterinarians worked in different clinics and settings, spread throughout the Netherlands. One veterinary European Board-Certified specialist was included, one veterinarian mainly working in shelters, one veterinarian working in a holistic clinic and two veterinarians working in a corporate chain of veterinary clinics. Except for one, all veterinarians treated companion animals only. Table 1 shows additional demographic information of the interviewed veterinarians.

Table 1: Demographics of interviewed companion animal veterinarians (n=18).

Demographic		Veterinarians (n=18)
Gender	Male	5
	Female	13
Years since graduation	Mean (range)	18.2 (2 - 38) yrs
	< 10 yrs	5
	10 – 20 yrs	6
	21 – 30 yrs	4
	> 30 yrs	3
Country of graduation	The Netherlands	16
	Belgium	2
Age	Mean (range)	45.9 (26 - 68) yrs
	< 30 yrs	2
	30 – 40 yrs	3
	40 – 50 yrs	5
	> 50 yrs	8
Position	Employer/practice owner	8
	employee	10

3.2. Factors influencing antimicrobial prescribing behaviour

In the conceptual model, factors influencing AM prescribing behaviour were divided into four major categories: 1) veterinarian-related factors, 2) patient-related factors (owner- and pet-related factors), 3) treatment-related factors (i.e. alternative treatment options and antimicrobial-related factors) and 4) contextual factors (i.e. professional interactions, further diagnostics and environmental factors). Figure 1 shows the conceptual model of factors that influence the AM prescribing behaviour of Dutch companion animal veterinarians. It shows the relation between intrinsic (veterinarian related) and external factors.

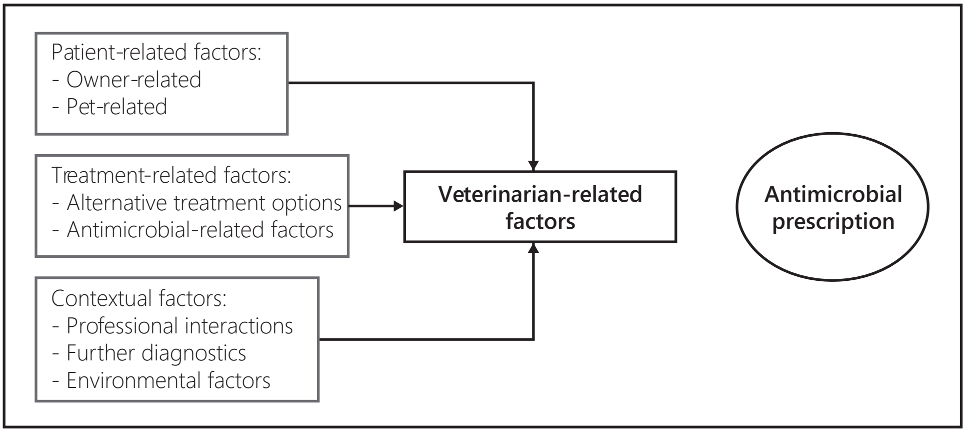

Figure 1: Conceptual model of factors influencing antimicrobial prescribing behaviour.

3.2.1. Veterinarian-related factors

By law, a veterinarian is the authorised person for prescribing AMs for veterinary use. All prescriptions of AMs for veterinary use are therefore made by a veterinarian, which is why 'veterinarian-related factors' is centred in Figure 1. Interviews showed several intrinsic factors related to the companion animal veterinarian that influence AM prescribing behaviour.

3.2.1.1. Personal beliefs on AMU, opinions, preferences, aversions, experiences and habit

Personal beliefs, opinions and preferences influenced the decision whether to prescribe an AM or not. Personal preferences were regularly stated as a reason to choose a specific AM: "*never change a winning team, as then everything always works out*" (P8). These preferences could be in line with theoretical knowledge, evidence-based veterinary medicine (EBVM) and current guidelines, but they could also be conflicting. Previous experiences (positive and negative) with prescribing or non-prescribing of AMs appeared to contribute to current decisions, regardless of argumentation based on theory and EBVM. Some veterinarians mentioned prescribing AMs in situations where other veterinarians would seldom prescribe, e.g. peri-operatively in elective surgery. Some veterinarians never prescribed AMs during or after elective surgery: "*in my view, if you always work meticulously and have a clean operating theatre, then there is no need to prescribe AMs*" (P18), whereas others used AMs routinely. Regarding the type of AM chosen, several veterinarians stated mainly choosing AMs according to habit and not so much on the basis of EBVM or guidelines.

Besides differences in AMU habits, there were remarkable differences in opinions on the importance of AMR. A considerable number of interviewed veterinarians recognised the need for a more prudent AMU, not only in large animal practice but also in companion animal practice: "*it is nothing short of logical that we have become reserved in the use of AMs.*

Partly because .... Hardly any new AMs are being developed [....] So that is the responsibility that we have" (P12). However, other veterinarians questioned the contribution of AMU in companion animals to problems with AMR seen in human medicine. These veterinarians pointed at AMU in large animals and/or in human medicine as main contributors: "*I think that every bit helps, but I think the bits from pets are very small. However, if you were talking about farm animals and would say 'you cannot simply use that anymore', then I could understand your perspective because they administer such vast amounts. But in the case of just 0.3cc for a cat, I would think 'oh, well'......*" (P8). A minority of veterinarians questioned the effectiveness of prudent AMU in Dutch companion animals, as long as in other countries AMs are widely available even without prescription. Some veterinarians admitted ignoring current guidelines for companion animals occasionally, because of lack of a real 'problem recognition'.

3.2.1.2. Personal 'guideline' beliefs, opinions, preferences, aversions, experiences and habit

Under Dutch law, the use of fluoroquinolones and 3rd and 4th generation cephalosporins (i.e. third choice AMs) in animals is restricted to infections caused by bacteria with susceptibility results indicating no susceptibility to any other AM. Besides legislation, there are several Dutch guidelines on AMU in companion animals (www.wvab.nl & www.knmvd.nl). Some veterinarians used the Dutch guidelines to promote prudent AMU as a reminder or back-up. A younger veterinarian stated: "*I think that especially when you have just started, you have to deal with so many different things that you simply cannot remember everything*" (P9). Some used the guidelines as a pressure tool to convince an owner that AMs were not indicated or that further diagnostics had to be performed first. "*Yes, I'm sorry, the legislation has changed, I can't give you anything. Just turn on your TV and you'll see the criticism we are facing as vets. And there are good reasons for that, I'm... simply not allowed to*" (P13).

Not all veterinarians were familiar with the guidelines, while others indicated that the guidelines were unclear or impractical. Some veterinarians indicated being afraid of reprisal when prescribing fluoroquinolones or 3rd or 4th generation cephalosporins: "*and to be honest, I hardly dare to use it anymore, in fact only after a positive susceptibility test*" (P3), whereas others indicated to use these AMs on a regular basis, even without meeting the legal requirements for use.

3.2.1.3. Veterinarians' knowledge of infectious diseases, antimicrobials and pharmacokinetics

In some cases, theoretical knowledge of infectious diseases and antimicrobials was explicitly mentioned as an influencing factor. Especially when choosing a specific AM, knowledge of the spectrum of activity and sometimes the pharmacokinetics was applied. Veterinary literature and continuing education were also mentioned as influencing factors. However, in some cases, the content of courses or (international) literature conflicted with Dutch legislation.

3.2.1.4. Perceived risks of (non-) treatment and perceived risks of treatment with specific antimicrobials

Fear of complications or an unsatisfied owner after not prescribing AMs was often mentioned as a reason to prescribe: "*yes, I think it is because it has become a habit and because one is afraid to leave it out in case it would then go wrong*" (P10). Some veterinarians prescribed AMs post-surgery because of a fear of complications due to a lack of hygiene during surgery: "*then just to be sure, I will prescribe AM tablets for the cat, because I cannot guarantee that I have worked meticulously and sterilely enough. And that is not a risk I am willing to take*" (P4).
On the other hand, some veterinarians mentioned fear to prescribe AMs because of harmful side effects: "*as otherwise those AMs might cause more harm than the problem they will solve*" (P1). Some veterinarians clearly expressed their fear of adverse clinical side effects related to specific AMs. This fear could be based on personal experiences, but also on 'hearsay'. Trimethoprim/sulphonamide combinations were often mentioned in this context: "*in such a case, I am so worried about a keratitis sicca that I then deliberately do not do it*" (P15).

3.2.1.5. 'Just give it a try' and 'quick fix'

In some cases, veterinarians were uncertain (about a diagnosis and/or which AM to choose) and decided to "give it a try", without a very strong reason or argument. In these cases "It does not hurt to try" was sometimes the driving factor for prescribing AMs. In other cases, a 'quick fix' (for the veterinarian and/or owner) was stated as a driving factor.

3.2.2. Patient-related factors

In veterinary medicine, a pet is almost always accompanied by an owner or caretaker. In the conceptual model, both the pet and owner were identified as influencing factors.

3.2.2.1. Pet-related factors

3.2.2.1.1. Pet characteristics

Interviews indicated that AMU was influenced by pet characteristics, e.g. animal species, breed, age, living conditions, weight, coat type and character of the pet. In the case of a non-cooperative or aggressive animal, veterinarians tended to more frequently choose a therapy with AMs, even when AMs were not necessarily indicated. This was mainly because a physical and/or further examination was not feasible and because alternative treatment options were not applicable. In the case of an aggressive animal, veterinarians seemed to prefer injectable AMs and long-acting AMs. Living conditions were also mentioned as an influencing factor, e.g. a household with young children for which the veterinarian was concerned about the possible spread of bacteria to the children and therefore preferred AMs above alternative treatment options. In the case of a large or heavy animal, veterinarians sometimes chose another type of AM to keep down the costs or the number of tablets that had to be administered to the animal.

3.2.2.1.2. Current clinical situation and history

The current clinical situation, as well as the clinical history, influenced the prescribing decision. The interviews showed that AMs were predominantly prescribed on the basis of presumed diagnoses: *"more often than not, you do not have a 100% diagnosis but instead a probable diagnosis, and that is what you act on"* (P12). 'Only mild' signs were regularly stated as a reason not to prescribe AMs, 'severe' clinical signs and especially pyrexia were mentioned as a reason to prescribe; "*a fever of 41 degrees Celsius, was severely ill*" (P1). Comorbidities and previous episodes of similar symptoms were also mentioned as influencing factors. The localisation of an injury or type of surgery, organ(s) involved, possible causal agents and the severity of complaints also influenced the AM chosen: "*what kind of inflammation it is, where it is located, the severity…. and uhm…. Possible causal agents you might think of…*" (P4).

3.2.2.2. Owner-related factors

3.2.2.2.1. Owner demands

In several cases, veterinarians mentioned perceived pressure from owners to prescribe AMs. Some owners were very clear in their request: "*they simply say in no uncertain terms: I want AMs, full stop. You may only look further once we have tried this because I am convinced it works simply because it has worked in the past*" (P13). In other cases, the pressure was less clear: "*sometimes I do think: I'll just prescribe [an AM] as otherwise they will simply not be satisfied, even though it would be better for the dog not to and it is not necessary either*" (P4). Some veterinarians also mentioned perceiving pressure not to prescribe AMs: "*that they just don't want [to use AMs] at all, because they do not want to vaccinate either*" (P16). Breeders were specifically mentioned as quite demanding regarding the prescribing of AMs: "*some breeders who are very demanding and who even think that they know when they need AMs*" (P14).

3.2.2.2.2. Owner convenience and costs

The choice for a specific AM could also be influenced by the owner. Convenience for an owner and expected compliance of a proposed therapy were explicitly mentioned as influencing factors. Costs of and the willingness to pay for treatment were also influential. In some cases, owners refused or did not want to pay for any further diagnostics limiting the veterinarians' options to make a proper diagnosis. In some cases, when owners had a pet insurance, additional diagnostics were performed more easily or a more expensive AM was given.

The familiarity with an owner and the veterinarian's assessment of the capacity of an owner or caretaker to take care of an animal and to notice deterioration on time were also mentioned as influencing factors: "*I know them quite well, and then I think… well…. If you don't trust it, just come and see me immediately, but in this case, I thought, if it goes wrong, they will not even notice it…*" (P5).

3.2.3. Treatment-related factors

3.2.3.1. Alternative treatment options

The interviews showed that alternative treatment options, defined here as 'all non-antimicrobial treatment options' could influence the decision 'to prescribe AMs'. In several cases, veterinarians appeared to be willing to try non-antimicrobial (supportive) treatment options, but when an alternative option 'appeared' ineffective (based upon earlier experience and expectation) or when an owner had to be convinced to apply an alternative option, veterinarians tended to choose for AMs. The application of alternative treatment options had to be feasible for an owner, for example when using local skin shampoos instead of systemic AMs in case of dermatologic problems. The use of alternative treatment options also depended on the experience with these options and preference of the veterinarian.

Some combination products containing AMs were perceived to be more user friendly and/or cheaper compared to products not containing AMs, e.g. local skin or ear products with AMs and steroids: "*on the face of it, those AMs in that skin product are often not even necessary. However, the one without AMs is a spray and the one with AMs is an ointment, and there is a difference in costs as well. I believe the spray is at least twice as expensive*" (P17).

3.2.3.2. Antimicrobial-related factors

Antimicrobial- and formulation-related factors appeared to have an important influence on deciding 'which antimicrobial to prescribe'. Practical considerations, side effects, spectrum of action, AM classification (first, second or third choice according to Dutch policy on AMU), route of administration, duration of action, immune-modulating effects, instructions for use, expiration date, package size and costs of specific products containing AMs were mentioned as influencing factors.

Practical considerations were often mentioned as motivating factors. Reasons from one veterinarian to choose amoxicillin in a specific situation: "*because it is cheap, easy to dose, is a fine second choice AM, I can inject it…*" (P2). Taste and acceptance by the animal were also mentioned as reasons to choose for a specific AM. Other practical considerations were also mentioned: "*I really look at what I think is a nice product, what I think is a suitable packaging, what I find easy to use and what I think from my impressions of the owner will be good and easy for them to administer*" (P18).

The duration of action was often mentioned as a driver to choose for a specific AM. When choosing a long-acting injectable AM, the AM class seemed to be of secondary importance compared to the duration of action and the route of administration. One specific long-acting injectable preparation containing cefovecin was regularly chosen because of the convenience (for veterinarian and owner), the compliance and as a solution for non-cooperative animals. However, some veterinarians had an aversion to long-acting AMs: "*but that injection works for 48 hours, which I am not entirely happy with anyway, because it is such a slow release AM that only releases a bit of AM once in a while*" (P7).

3.2.4. Contextual factors

In the conceptual model, several contextual factors influencing AM prescribing were identified. These factors were mainly linked to the workplace and colleagues at work.

3.2.4.1. Professional interactions

Veterinarians mentioned influence from direct colleagues on AM prescribing. Some clinics had strong habits and (written) policies regarding AMU, whereas in other clinics these were absent. In some clinics, veterinarians perceived pressure from other colleagues to prescribe AMs: "*look, I am always happy to talk about the matter, but it remains his word. Nevertheless, to put things bluntly, I must do what he says if I want to keep my job*" (P7). On the other hand, younger and/or recently graduated veterinarians were reported to have an influence on older veterinarians as well: "*every so often, when a new colleague comes, such as XXX, then they might suggest 'why don't you try this?' And then I think to myself, that is another viable option, of course*" (P3). Some veterinarians indicated that newly graduated veterinarians tended to be more prudent in AM prescribing compared to older veterinarians: "*I have to be honest that the younger veterinarians are quite strict, but that we also have some older colleagues who somewhat more easily say, well…. let's just do it. And that is a bit of a discussion here*" (P14).
Not only differences between colleagues within the same clinic, but also differences in AM policies between clinics were mentioned: "*and then they leave and go to another veterinarian where they can get the injection, and that's fine with me*" (P2). Even though different policies between clinics were explicitly mentioned, most veterinarians indicated that they adhered to their own policies: "*and then you have a few who say: then I'll just go and get it somewhere else. And then it is the responsibility of the veterinarian who does that*" (P12). Veterinary specialists and human doctors were also mentioned as factors influencing AM prescribing behaviour. In some cases, however, the advice of specialists appeared to conflict with Dutch legislation.

3.2.4.2. Further diagnostics

In addition to bacterial culture and sensitivity testing, blood work, radiographs, urinalysis, cytology (mainly skin or ear samples), ultrasound and other forms of further diagnostics were mentioned as influencing the prescribing decision: "*I believe that the rule is that you must diagnose first; there must be a clear evidence-based diagnosis and, whenever possible, you have to test susceptibility or take a first choice AM*" (P12) and "*if, for example, there was a lot of blood, leucocytes and proteins on my urinary stick, then I would prescribe AMs*" (P9).

3.2.4.3. Environmental factors

3.2.4.3.1. Time

In some cases, time was a limiting factor for performing further diagnostics and/or evaluating a patient thoroughly. In these cases, prescribing AMs appeared to be a quick solution. Time needed to obtain laboratory results, especially in the case of bacterial culture and sensitivity testing, was regularly mentioned as a limiting factor for performing further diagnostics.

3.2.4.3.2. Availability

A specific type of AM can only be prescribed if it is available, both in the clinic as well as from the wholesalers. In some cases, for example, only amoxicillin with clavulanic acid was available in the clinic. As a result, veterinarians were not able to prescribe amoxicillin without clavulanic acid even if this was preferred. Another regularly mentioned example was the limited availability of topical formulations with corticosteroids but without AMs. When a specific AM was not in stock, it could not be prescribed, even when an owner specifically asked for it. Here it could serve as an argument to convince an owner to try another type of AM or an alternative treatment option.

3.2.3.4.3. Commercial drivers

A very small number of veterinarians stated that financial gain could influence AM prescribing. In the case of shelter medicine, it was recognised that AMs were sometimes prescribed to decrease the number of days that a dog or cat had to stay in isolation and with that costs for the shelter. Only a few veterinarians mentioned that violating regulations and guidelines (e.g. prescribing fluoroquinolones without susceptibility testing) could attract new clients: "*yes, and it can also get me clients sometimes*" (P5).

4. Discussion

This study explored the spectrum of factors influencing Dutch companion animal veterinarians in the decision-making process on prescribing AMs. In the conceptual model, four major categories of influencing factors could be identified: 1) veterinarian-related factors, 2) patient-related factors, 3) treatment-related factors and 4) contextual factors. Many of the factors described are related, but ultimately the companion animal veterinarian is authorised to prescribe AMs.

The decision-making process of companion animal veterinarians on AM prescribing appeared to be complex, which is recognised both in human and veterinary medicine [23, 25, 26, 28]. Many factors other than theoretical knowledge and clinical reasoning appeared to play a role. Other qualitative studies on AM prescribing behaviour have also shown this [24, 27, 28, 32, 33]. As the person authorised to prescribe AMs, the companion animal veterinarian appeared to play a central role in the decision-making process.

Over the past few decades, numerous clinical practice guidelines have been developed and implemented in human medicine (e.g. www.escmid.org). These comprehensive guidelines are usually based on substantial amounts of scientific evidence. In veterinary medicine, guidelines are less well established, and for several infections the level of scientific evidence on optimal AM treatment strategies is limited [34]. Dutch legislation on veterinary AMU was revised in the period 2012-2013 and guidelines on prudent AMU have been developed. This study showed that the familiarity with and implementation of these guidelines for a prudent AMU in companion animals differed considerably among the veterinarians interviewed. Other studies have also confirmed this finding [35, 36].

Although our study was not designed for a quantitative exploration of influencing factors, newly graduated companion animal veterinarians seemed to be more familiar with the guidelines compared to more experienced veterinarians. This is possibly because policies and guidelines on AMU are now embedded in education. Guidelines seem to support younger veterinarians in daily practice, whereas more experienced veterinarians seem to be less willing to adjust their daily routines [37]. Studies are needed to measure and improve implementation of and compliance to current guidelines. Guidelines should also be evaluated and updated regularly taking results from qualitative studies into account. For example, in our study (perceived) risks of antimicrobial treatment or the opposite (perceived) risks of no antimicrobial treatment were mentioned quite often.

Opinions on the importance of AMR and prudent AMU in companion animals appeared to differ considerably between the veterinarians interviewed. These differences in opinions were also observed among Dutch farm animal veterinarians [37]. Evidence-based information on the importance of prudent AMU in companion animals and improved awareness are needed to optimise AMU.

Patient-related factors appeared to be important as well, which is in line with other studies confirming the differences in type of AM chosen and the route of administration between dogs and cats [13, 38]. Especially in the case of the use of cefovecin in cats, not so much the AM spectrum, but the character of the animal and the product characteristics (injection and long-acting) appeared to be reasons to prescribe this specific AM. Other studies have shown this as well [39, 40]. Animal characteristics are probably difficult to change. However, future research should be based on finding solutions for treating non-cooperative animals in line with prudent AMU principles.

The importance of an animal owner or caretaker regarding AMU is confirmed by other studies on companion animals as well as on farm animals [24-26, 40, 41]. A recent study on AM prescribing in companion animals states that veterinarian's perceptions of client expectations might drive inappropriate AM prescribing [27]. In human medicine, the patient or his/her family can influence the decision-making process as well [23, 42, 43].

These findings show that educating owners, involving owners in prudent AMU and a better explanation of restricted AMU are needed to optimise AMU. International and national veterinary associations have already developed educational posters, but the distribution, practical use and effect of these documents have not been evaluated yet (e.g. FECAVA [44], FVE [45] and KNMvD).

The unwillingness or inability to pay for further diagnostics or therapy was identified as a factor that may lead to inappropriate AMU. In human medicine, especially non-hospital settings, a lack of diagnostic resources was also mentioned as a factor that contributes to diagnostic uncertainty [23, 46]. Further diagnostics are needed to reduce diagnostic uncertainty. In contrast to human medicine, most Dutch companion animal owners do not have a pet insurance, and so the owner has to pay the costs of diagnostics and therapy. Financial barriers play an important role in treatment decisions of veterinarians, as was also shown in previous research [24, 40]. The development of cheaper, faster and more reliable on-site diagnostics might lead to better adherence to current guidelines and a decrease in inappropriate AMU.

Treatment-related factors, especially practical considerations like administration route, lack of adverse effects, and availability turned out to play another important role. Pharmaceutical companies can take more responsibility here, e.g. by producing easy-to-administer first choice AMs (e.g. tasty liquid oral formulations instead of tablets) or smaller packages (to prevent expiration of less often used AMs) and by marketing alternative (non-antimicrobial) treatment options. Registration of new veterinary medicinal products is time-consuming and expensive, but smaller packages of tablets, for example, might be easier to accomplish.

Many contextual factors, especially peer pressure, appeared to influence a companion animal veterinarian. A clear and uniform clinic policy on prudent AMU might increase awareness and decrease differences in treatment regimens between colleagues within a clinic.

This study has various strengths and limitations. Individual interviews were preferred over focus groups to ensure unbiased and truthful answers from participants [47]. During the interview process, answers appeared to be very open and without scruples, which reassured the authors that the answers were honest and unbiased. Veterinarians from different settings, supporting and opposing current policies on AMU, were interviewed. We are therefore confident that we have covered the broad array of influencing factors. Relatively more female veterinarians than male veterinarians were interviewed reflecting the current situation in Dutch companion animal veterinarians.

Because a qualitative strategy was used, it was not possible to quantify the importance of the different influencing factors [48]. However, this qualitative study generated a broad set of factors influencing Dutch companion animal veterinarians and an in-depth understanding of these factors, which was the purpose of this study.

Because legislation and organisation of veterinary care varies between countries, some factors might be restricted to the Dutch situation, other factors might be more generalised. Few qualitative studies have been done on this topic in companion animal medicine, but many factors seem to be similar to factors identified in human medicine and farm animal medicine in different countries.

Findings from the current study will be quantitatively further explored and used to develop tailored interventions to promote responsible AMU in Dutch companion animal clinics within an antimicrobial stewardship programme (ASP). Antimicrobial stewardship is usually defined as a multifaceted and dynamic approach to preserve the clinical efficacy of AMs by optimising AMU while minimising the emergence of AMR and possible other adverse effects [49, 50]. When developing an ASP, the primary focus should be on the companion animal veterinarian. Improving awareness of the importance of prudent AMU and AMU guidelines seems to be a major issue that needs to be taken into account. Companion animal owners should be involved more and practical solutions need to be found to support veterinarians in responsible AMU, also in non-cooperative animals. Reducing barriers for performing further diagnostics might also contribute to a more prudent AMU.

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Submission declaration

This research study has not been previously published elsewhere.

Conflicts of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.prevetmed.2018.07.013

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Chapter 3

Attitudes and perceptions of Dutch companion animal veterinarians towards antimicrobial use and antimicrobial resistance

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Abstract

Antimicrobial use (AMU) in humans and animals facilitates the emergence of antimicrobial resistance (AMR). With increasing AMR being recognised as a major global threat for public health, responsible AMU is strongly advocated in both human and veterinary medicine. Knowledge on factors influencing antimicrobial prescribing behaviour of companion animal veterinarians is needed to promote responsible AMU in companion animals and to improve compliance with current legislation and guidelines. The present study aimed to quantitively investigate attitudes and perceptions of companion animal veterinarians towards AMU and AMR and to identify associations with demographic characteristics as possible explanatory variables. A self-administered questionnaire was developed based upon an earlier qualitative interview study, and 1608 potential participants (i.e. practising companion animal veterinarians) were invited. The questionnaire included questions addressing general descriptives of the respondents and questions with 6-point Likert scale statements, to assess attitudes towards AMU, AMR, factors influencing antimicrobial prescribing, and possible options to support responsible AMU.

The response rate was 32% (22% when complete questionnaires considered). Categorical Principal Component Analysis (CATPCA) was conducted on 76 Likert scale questions. This resulted in a final model with 37 questions explaining 38.7% of the variance of the question scores, with three underlying dimensions ("attitudinal profiles"). Additionally, general descriptives were added to the CATPCA as possible explanatory variables. The first dimension, related to "social responsibility", was positively associated with veterinarians working in clinics dedicated to companion animals, with veterinarians working in a referral clinic, and with more experienced veterinarians. The second dimension was related to "scepticism", which was positively associated with being a male veterinarian and with more experienced veterinarians. The third dimension was related to "risk avoidance", especially regarding surgical procedures, and was negatively associated with veterinarians working in clinics in urban areas and with veterinarians working part-time. Antimicrobial prescribing behaviour was self-reported to be well considered, and respondents did not see economic drivers as important influencing factors. The unwillingness of owners and financial constraints were perceived as important barriers for performing further diagnostics. To improve AMU, a multifaceted approach, taking differences between companion animal veterinarians (e.g., in experience and gender) and differences in work situation (e.g., full-time versus part-time) into account, should be directed at companion animal veterinarians and owners. Moreover, a joint and comprehensive effort of several stakeholders, like veterinary nurses, guideline developers, pharmaceutical industry, and providers of diagnostics, is needed to optimise AMU in companion animals.

1. Introduction

Antimicrobial use (AMU) in humans and animals facilitates the selection and dissemination of antimicrobial resistance (AMR) [1-3]. AMR is a major global threat for public health; thus, responsible AMU is strongly advocated in both human and veterinary medicine [4].

Since 2008, AMU in food-producing animals has received considerable attention in the Netherlands. Nationwide AMU-reducing action plans and several regulations have been implemented, resulting in an overall AMU reduction of almost 68% during 2007-2017 [5-7]. Since January 2013, Dutch legislation requires susceptibility testing prior to prescribing fluoroquinolones and 3rd and 4th generation cephalosporins. This holds for use in all animal species, including companion animals [8]. Besides legislation, policies on veterinary AMU and guidelines on AMU in companion animals were developed [9]. Despite the fact that these guidelines are professional standards, uptake and implementation of these guidelines depends on the individual veterinarian. Research among food-producing animal veterinarians has shown that attitudes and perceptions towards AMU and AMR have changed over the last years, partly because of more and stricter regulations and increased attention for the topic [10-12]. However, little is known about attitudes and perceptions of companion animal veterinarians towards AMU and AMR. Knowledge on factors influencing antimicrobial prescribing behaviour of companion animal veterinarians is needed to promote responsible AMU in companion animals and to improve compliance to current legislation and guidelines. Some qualitative research in companion animals has been done, mainly in the UK [13-15]. In 2015, a qualitative study among 18 Dutch companion animal veterinarians was performed to explore factors influencing antimicrobial prescribing behaviour [16]. The conceptual model of this qualitative study showed four major groups of influencing factors on antimicrobial prescribing: veterinarian-related factors, patient-related factors (i.e. owner- and pet-related), treatment-related factors (i.e. non-antimicrobial treatment options and antimicrobial-related factors), and contextual factors (i.e. professional interactions, further diagnostics and environmental factors). The present study aimed to study these factors in a quantitative way among Dutch companion animal veterinarians by investigating their attitudes and perceptions towards AMU and AMR. A second aim was to identify possible associations between these attitudes and perceptions, and demographic characteristics as possible explanatory variables. The results of this study will be used to provide input for the development and implementation of an antimicrobial stewardship programme in Dutch companion animal clinics.

2. Material and methods

2.1. Study materials

A self-administered questionnaire was developed based on the results of an earlier qualitative study [16]. The questionnaire was divided into three parts: 1) 16 questions addressing general descriptives and demographics, 2) 76 questions with 6-point Likert scale statements (1=completely disagree; 2=disagree; 3=tend to disagree; 4=tend to agree; 5=agree; 6=completely agree) to assess attitudes towards AMU, including factors influencing antimicrobial prescribing behaviour and perceptions on AMR and responsible AMU, and 3) 14 6-point Likert scale questions related to possible options to support responsible AMU.

In one of the questions from part 1 respondents were asked whether they perceived the clinic they worked in as an urban or rural clinic. For some questions, the option 'not applicable' was added.

The design and content of the questionnaire was discussed in detail with experts from human and veterinary medicine and the questionnaire was subsequently piloted amongst veterinarians working in the field and veterinarians working at the Faculty of Veterinary Medicine of Utrecht University. The questionnaire was administered online using SurveyMonkey (SurveyMonkey Inc., San Mateo, California USA, www.surveymonkey.com).

2.2. Study population

The exact number of Dutch veterinarians working with companion animals was estimated to be between 1800 and 2000 at the time of this study (August 2015, personal communication). In total, 1608 unique email addresses of companion animal veterinarians were obtained from the Royal Dutch Veterinary Association (KNMvD) and the Collective of Practising Veterinarians (CPD) for potential enrolment in the study. (KNMvD and CPD are the two major veterinary professional associations in the Netherlands, representing the majority of Dutch veterinarians). This list was not a perfect and complete list. The list contained duplicates (e.g., private and work email address of the same veterinarian), as well as disused email addresses, and email addresses of veterinarians who were not practising anymore. Email addresses of some companion animal veterinarians were obviously missing.

In September 2015, an invitation to participate in the online survey was sent. After 3 and 8 weeks, a reminder was sent to non-responders. The survey was also advertised in newsletters of the KNMvD and CPD. Responses were collected anonymously unless participants voluntarily chose to leave their contact details.

A € 50 voucher was allotted as a financial incentive to one out of every 50 respondents completing the questionnaire. All returned questionnaires were handled confidentially.

2.3. Data analysis

As the aim was to focus on companion animal veterinarians, only respondents who stated that they currently work in a practice and spend more than 50% of their working hours on companion animals were included in the survey.

The 6-point Likert scale questions were described using mean values, mode values, and standard deviations. Mean values, in particular, were used to quantify the central tendency of questions to which most respondents disagreed or agreed.
A Categorical Principal Component Analysis (CATPCA) was performed as described in detail by Speksnijder et al. (2015) [10], to reduce the attitudinal variables (i.e. the single Likert scale questions) to several uncorrelated principal components (dimensions), which reflected the information in the original data. The uncorrelated principal components were further analysed to assess differences in attitudes according to veterinarian's demographics [10, 17]. CATPCA was used because it can manage possibly nonlinearly related variables with different types of measurement levels and is particularly useful to analyse Likert-type variables.

The 76 Likert scale questions from part 2 were included in the CATPCA. For missing values, the default Passive CATPCA option of imputing the modal category after quantification was chosen. Scree plot analysis indicated that a 3-dimension solution was most suitable for analysis of the whole dataset (of originally 76 questions). All variables (i.e. individual Likert scale questions) with a total Variance Accounted For (VAF) of 0.25 or lower were excluded from the final analysis. The CATPCA procedure was repeated until no variables with a total VAF <0.25 remained. Subsequently, component loadings were calculated of which loadings of 0.40 or higher were regarded as sufficient to calculate object scores for each dimension and these were used for further analysis. Based on the component loadings, resulting dimensions were then interpreted as "attitudinal profiles" [10, 17]. Finally, the association between the explanatory variables from part 1 (i.e. demographics of the respondents) and each separate dimension was assessed using linear regression analysis, first univariately (each explanatory variable at a time) and then multivariately. Only those variables with a p-value <0.10 in the univariate analysis were included in the multivariate models, which were reduced in a backward stepwise fashion until only variables with a p-value <0.05 remained. Variables that changed the effect of the other covariates by >10% when removed from the model were considered as possible confounders and therefore retained in the model.

Data were analysed using Microsoft Excel, IBM SPSS Statistics (version 24) and STATA (version 15).

3. Results

3.1. General descriptives

Questionnaires were received from 508 (32%) respondents. Of these, 89 veterinarians indicated in part 1 of the questionnaire that they do not currently work in a companion animal practice or spend less than 50% of their working hours on companion animals. They were therefore excluded. 353 respondents completed part 1 and 2 of the questionnaire, and 350 respondents completed part 3 as well, resulting in a response rate of 22% (based on the 1608 email addresses used). The demographics of the 353 respondents who completed part 1 and 2 of the questionnaire are shown in Table 1.

Table 1: Demographics of respondents who completed parts 1 and 2 of the questionnaire (n=353).

Demographic	Number (%)
Percentage of working hours spent on companion animals:	
50-75%	16 (4.5)
>75%	337 (95.5)
Gender:	
Male	134 (38)
Female	219 (62)
Type of clinic (1):	
Mixed-animals	96 (27.2)
Companion animals only	257 (72.8)
Type of clinic (2)*:	
Rural	143 (40.5)
Urban	210 (59.5)
Work situation (1):	
Clinic owner	202 (57.2)
Working on payroll	132 (37.4)
Other	19 (5.4)
Work situation (2)*:	
Full-time	184 (52.1)
Part-time	169 (47.9)
Work situation (3):	
First opinion	320 (90.7)
Referral	14 (4.0)
Other	19 (5.4)
	Median (min-max)
Year of birth	1969 (1944-1990)
Year of graduation	1997 (1966-2014)
Working experience (years)	(1-46)

* based upon the respondent's own perception of rural versus urban and full-time versus part-time

3.2. Behaviour, attitudes and perceptions

Based on the Likert scale scores (1=completely disagree to 6=completely agree), the 5 questions with a mean score <2 (i.e. majority of respondents disagreed) and the 11 questions with a mean score >5 (i.e. majority of respondents agreed) are displayed in Table 2, as well as all those questions that could be considered as possible barriers to responsible AMU with a mean score >4. The questions with a mean score >5 and <2 show that respondents almost unanimously report their decision-making in antimicrobial prescribing as well considered and not influenced by opinions or pressure from clients and colleagues. The majority of respondents seem to be aware of AMR and practice policies are supportive in using AMs responsibly. With regard to the performance of further diagnostics, reluctance of companion animal owners and their (possibly related) financial constraints were mentioned as possible barriers.

Table 2: Questions with a mean score >5, with a mean score <2 and questions considered as possible barriers to responsible AMU with a mean score >4. Mode values represent the most frequently chosen score per question. SD values represent standard deviations. Questions were scored on a 6-point Likert scale (1=completely disagree; 6=completely agree).

Questions	Mean	Mode	SD
With a mean score >5			
My choice for a specific type of AM* has nothing to do with higher financial profits.	5.49	6	1.075
My choice for a specific type of AM has nothing to do with acquiring more clients.	5.49	6	1.036
In my clinic, we have sufficient possibilities to send in samples to a laboratory for culture and susceptibility tests.	5.39	5	0.645
My choice for a specific type of AM is regardless of my perception of what an owner wants.	5.24	5	0.806
I am okay with the increased attention on AMU in companion animals.	5.21	5	0.874
My choice for a specific type of AM has nothing to do with what an owner wants.	5.15	5	0.853
I think twice before I prescribe AMs.	5.14	5	0.647
In my clinic, sufficient possibilities to perform further diagnostics (other than culture and susceptibility tests) are available.	5.13	5	0.852
When choosing a specific type of AM, I consider which pathogens might be involved.	5.08	5	0.672
My veterinary colleague(s) and I support each other to show restraint in prescribing AMs.	5.06	5	1.037
Our practice policy is committed to showing restraint in prescribing AMs.	5.05	5	1.082
With a mean score <2			
Because a neighbouring clinic is easy in prescribing AMs, I tend to do so as well.	1.97	2	0.9
After most surgical procedures, I habitually prescribe AMs.	1.90	1	1.13

Table 2 continued

With a mean score <2			
Using an AM is fine as long as it causes no harm.	1.69	1	0.825
I quite often experience pressure from colleagues or superiors to prescribe specific types of AMs I disagree with.	1.66	1	1.001
After elective surgery (neuter/spay) without prescribing AMs the risk of complications is too high.	1.61	1	0.923
Considered as possible barriers to responsible AMU, with a mean score >4			
An important hurdle to performing further diagnostics (including culture and sensitivity tests) is that owners do not want to pay for it.	4.55	5	1.107
After negative experiences with a specific type of AM, I tend not to use that type of AM again.	4.06	4	1.084
I regularly encounter companion animal owners urging to try AMs first before performing further diagnostics.	4.04	5	1.355

*AM=antimicrobial

3.3. 3-dimensional CATPCA

The CATPCA resulted in a 3-dimensional solution with 37 variables. The 3-dimensional CATPCA explained 38.7% of the variance of the scores provided by the respondents. Component loadings (as shown in Table 3) for the 3-dimensional solution are correlations (either positively or negatively) between the single Likert scale questions and the dimensions.

Based on the grouping of different variables that have high-value loadings on the different dimensions, three dimensions (latent variables) can be described:

- Dimension 1 is related to “social responsibility”, well-considered antimicrobial prescribing, self-confidence, independence and recognition of the authority/role of the veterinarian in public and animal health, which is not easily influenced by owner’s demands and is related to working in a well-equipped clinic.
- Dimension 2 is related to “scepticism”, as reflected in “no harm done by trying antimicrobials”, risk avoidance related to the individual animal and ignorance of the possible (public health) risks of AMU in companion animals as related to AMR emergence in companion animals, and in general.
- Dimension 3 is related to fear of the possible consequences of not prescribing antimicrobials, a “better safe than sorry” habit, mainly related to possible infections after surgical procedures.

Table 3: Component loadings of 3-dimensional CATPCA. Component loadings (-1 to 1) represent the strength of the correlations between the single Likert scale questions and the dimensions. Dimension 1 is related to "social responsibility", dimension 2 to "scepticism" and dimension 3 to fear of the possible consequences of not prescribing AMs.

Questions	**Dimension**		
	1	**2**	**3**
There is enough evidence proving that alternative treatment options (i.e. non-AM* treatment options) are as effective as treatments with AMs.		-0.546	
Before most surgical procedures, I usually give an AM injection.			0.678
After most surgical procedures, I habitually prescribe AMs.	-0.478		0.607
During standard surgery procedures (neuter and spay), I always work meticulously, and I have a clean operating theatre, which means AMs are redundant.	0.502		-0.486
When choosing a specific type of AM, I take possible adverse events into account.	0.487		
I do not await the results of culture and susceptibility tests or further diagnostics to prescribe AMs, because I think the risk of medical complications is too high.		0.52	
When I know a dog or cat has a comorbidity (e.g. diabetes mellitus), I am more inclined to prescribe third choice AMs.	-0.516		
In general, the risk of complications because of NOT prescribing AMs is bigger than the risk of problems with AMR because of prescribing AMs.		0.62	
After elective surgery (neuter/spay) without prescribing AMs the risk of complications is too high.	-0.465		0.622
Our practice policy is committed to showing restraint in prescribing AMs.	0.518		
The risk of a resistant bacterium spreading as a result of my professional habits is very small.		0.645	
The risk that a specific type of AM that I prescribe can no longer be used in human medicine in the future due to AMR is small.		0.648	
I am okay with the increased attention on AMU in companion animals.		-0.531	
There is little research proving that AMU in companion animals contributes to problems with AMR in animals.		0.692	
There is little research proving that AMU in companion animals contributes to problems with AMR in humans.		0.742	
My veterinary colleague(s) and I support each other to show restraint in prescribing AMs.	0.481		
I think twice before I prescribe AMs.	0.534		
For every single patient, I deliberately choose which type of AM to prescribe.	0.572		
In the case of a non-cooperative animal, I am more inclined to prescribe long-acting injectable AMs.	-0.44		
When prescribing AMs, it is important to use (results of) bacterial cultures and susceptibility tests.	0.446		
It is easy to translate culture and susceptibility results into practical applications.	0.56		
It takes too long before I receive my results of further diagnostics (other than culture and susceptibility tests).	-0.543		

Table 3 continued

When prescribing AMs, it is important to use further diagnostics (other than culture and susceptibility tests, e.g., diagnostic imaging or urine analysis).	0.471		
Further diagnostics (other than culture and susceptibility tests) help me in choosing a specific type of AM.			0.475
In my clinic, we have sufficient possibilities to send in samples to a laboratory for culture and susceptibility tests.	0.603		
In my clinic, sufficient possibilities to perform further diagnostics (other than culture and susceptibility tests) are available.	0.618		
It is important to have a clear diagnosis before prescribing AMs.	0.549		
I regularly have practical problems in taking samples for culture and susceptibility tests.	-0.593		
When choosing a specific type of AM, I take into account whether it is a bactericidal or -static AM.	0.429		
When choosing a specific type of AM, I take my knowledge about pharmacokinetics into account.	0.442		
When choosing a specific type of AM, I consider which pathogens might be involved.	0.555		
My choice for a specific type of AM is regardless of my perception of what an owner wants.	0.578		
I find it difficult NOT to prescribe AMs when an owner wants me to prescribe AMs.	-0.445		
My choice for a specific type of AM has nothing to do with what an owner wants.	0.555		
I think it is important that the AM I prescribe is authorised for the specific indication and animal species concerned.	0.481		
Even when a shift is busy, I take enough time to apply alternative treatment options (i.e. non-AM treatment options).	0.573		
Practically performing further diagnostics is too time-consuming (including culture and sensitivity tests).	-0.536		
Total (Eigenvalue)	7.692	3.881	2.727
Cronbach's Alpha	0.894	0.763	0.651
VAF%	20.80%	10.50%	7.40%

*AM=antimicrobial

3.3.1. Regression analysis of demographics on CATPCA Dimensions

The results of the univariate and multivariate analysis assessing the association between demographics with the above-defined three dimensions are shown in Tables 4 and 5.

Results from the multivariate regression analysis show that dimension 1 ("social responsibility") is positively associated with veterinarians working in clinics entirely dedicated to companion animals, with veterinarians working in a referral clinic, and with more experienced veterinarians (i.e. working more years in practice). Dimension 2 ("scepticism") is positively associated with being a male veterinarian and with more experienced veterinarians. Dimension 3 ("risk avoidance") is negatively associated with veterinarians working in clinics in urban areas and with veterinarians working part-time.

Table 4: Results of univariate linear regression analysis, testing demographics for their association with the three different dimensions resulting from the CATPCA (representing estimate values and 95% confidence intervals (CI)). Dimension 1 is related to "social responsibility", dimension 2 to "scepticism" and dimension 3 to fear of the possible consequences of not prescribing AMs.

	Dimension 1	**Dimension 2**	**Dimension 3**
Univariate	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Percentage of working hours spend on companion animals (>75% versus 50-75%)	0.49 (-0.01 to 1.00)		-0.43 (-0.93 to 0.07)
Gender (male versus female)	0.23 (0.02 to 0.45)*	0.62 (0.41 to 0.82)*	
Type of clinic (1) (companion animals only versus mixed-animals)	0.35 (0.12 to 0.58)*		-0.22 (-0.46 to 0.01)
Type of clinic (2) (urban versus rural)	0.22 (0.01 to 0.44)*		-0.23 (-0.44 to -0.02)*
Work situation (1) (working on payroll versus clinic owner)	-0.35 (-0.57 to -0.13)*	-0.40 (-0.61 to -0.18)*	
Work situation (1) (other versus clinic owner)	-0.09 (-0.56 to 0.38)	-0.26 (-0.73 to 0.21)	
Work situation (2) (part-time versus full-time)	-0.26 (-0.47 to -0.05)*	-0.42 (-0.62 to -0.21)*	-0.25 (-0.46 to -0.04)*
Work situation (3) (referral versus first opinion)	1.20 (0.68 to 1.72)*		0.53 (-0.00 to 1.07)
Work situation (3) (faculty versus first opinion)	-0.02 (-1.37 to 1.33)		-0.75 (-2.14 to 0.64)
Work situation (3) (other versus first opinion)	0.80 (0.33 to 1.28)*		0.48 (-0.01 to 0.97)
Year of birth**	-0.01 (-0.02 to 0.00)	-0.02 (-0.03 to -0.01)*	
Year of graduation**	-0.01 (-0.02 to 0.00)*	-0.02 (-0.03 to -0.01)*	
Work experience (per year)**	0.01 (0.00 to 0.02)*	0.03 (0.02 to 0.04)*	
Number of veterinarians per clinic only treating companion animals	0.04 (0.01 to 0.07)*		
Number of veterinarians per clinic also treating other species	-0.04 (-0.08 to 0.01)		

*p-value <0.05
**years as continuous variable

Table 5: Results of multivariate linear regression analysis, testing demographics for their association with the three different dimensions resulting from the CATPCA (representing estimate values and 95% confidence intervals (CI)). Dimension 1 is related to "social responsibility", dimension 2 to "scepticism" and dimension 3 to fear of the possible consequences of not prescribing AMs.

	Dimension 1	**Dimension 2**	**Dimension 3**
Multivariate	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Gender (male versus female)		0.50 (0.28 to 0.72)*	
Type of clinic (1) (companion animals only versus mixed-animals)	0.28 (0.06 to 0.51)*		
Type of clinic (2) (urban versus rural)			-0.22 (-0.43 to -0.01)*
Work situation (2) (part-time versus full-time)			-0.24 (-0.45 to -0.03)*
Work situation (3) (referral versus first opinion)	1.14 (0.63 to 1.66)*		
Work situation (3) (faculty versus first opinion)	-0.15 (-1.47 to 1.17)		
Work situation (3) (other versus first opinion)	0.75 (0.28 to 1.21)*		
Work experience (per year)**	0.01 (0.00 to 0.02)*	0.02 (0.01 to 0.03)*	

*p-value <0.05
**years as continuous variable

3.4. Possible options to support responsible AMU

The 14 questions in part 3 of the questionnaire on possible options to support responsible AMU were scored on a 6-point Likert scale by 350 veterinarians (3/353 veterinarians did not complete part 3 of the questionnaire). These questions and their mean scores are shown in Figure 1, which gives a general impression on how these possible options to support responsible AMU are perceived.

Promising options to support responsible AMU (Figure 1) seem to be the encouragement of supportive treatment options not containing antimicrobials. More education on responsible AMU for veterinarians and education of companion animal owners on AMR and responsible AMU also scored relatively high. Decoupling of prescribing and selling antimicrobials by veterinarians scored lowest.

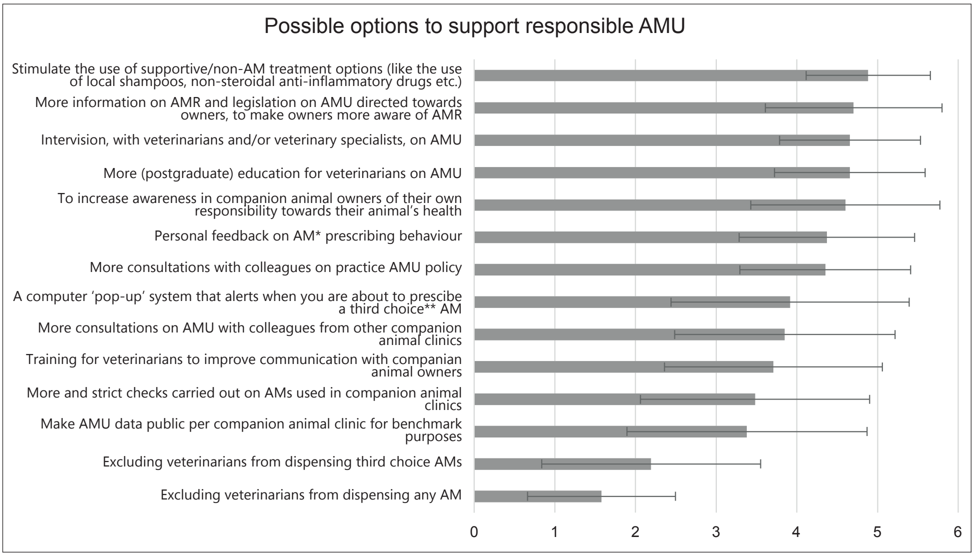

Figure 1: Questions on possible options to support responsible AMU. Questions were scored on a 6-point Likert scale (1=completely disagree; 6=completely agree) and are displayed here in order of highest to lowest mean score. *AM=antimicrobial, **third choice antimicrobials according to Dutch policy on veterinary AMU (i.e. fluoroquinolones and 3rd and 4th generation cephalosporins).

4. Discussion

This study showed different attitudes and perceptions of Dutch companion animal veterinarians towards AMU and AMR and revealed associations with demographic characteristics.

Whereas financial pressure or the tendency to meet client's expectations have been identified as possible drivers of inappropriate AMU in other studies [10, 14-16], veterinarians in our survey reported that their antimicrobial prescribing behaviour was hardly influenced by economic drivers nor by owners' demands. This indicates an autonomous working routine, although this might be biased by the fact that in our study it concerns self-reported behaviour, based upon own opinions and views. Therefore, it is possible that veterinarians did not want to openly admit that owners or economic drivers might influence their antimicrobial prescribing behaviour. On the other hand, campaigns on AMR aimed at the general public might have resulted in increased awareness among companion animal owners and with that decreased pressure to prescribe antimicrobials. Furthermore, the implementation of guidelines and legislation on veterinary AMU in recent years might act as a supportive tool for veterinarians to convince companion animal owners and to withstand their strong demands [16].

Respondents reported to have sufficient possibilities in their clinics to perform further diagnostics and to send in samples for susceptibility testing. However, unwillingness of an owner and financial constraints are indicated as possible barriers to perform further diagnostics. Other studies support these findings [11, 14, 18, 19]. Development of cheaper and faster diagnostics will increase the use of diagnostic testing and support responsible antimicrobial prescribing [11, 20].

In the assessment of the possible options to support responsible AMU (Figure 1), options regarding "decoupling" of antimicrobial sales and prescribing scored lowest. This finding is supported by other studies on antimicrobial prescribing in food-producing animals [10, 12]. A possible explanation of why this option was less favourable could be fear to lose profit. On the other hand, veterinarians reported their antimicrobial prescribing behaviour to be independent of economic drivers. The fear to lose the right to sell antimicrobials might also originate from a fear of losing autonomy, additional administrative procedures, time delays between prescribing and actual administration of antimicrobials, and practical disadvantages for companion animal owners.

The CATPCA revealed three main attitudinal profiles, and differences in these profiles were associated with several demographic characteristics. Attitudes, such as "social responsibility" and acting self-confident and independently (the first dimension), were positively associated with more experienced veterinarians and veterinarians dedicated to treating companion animals. Several studies showed that younger veterinarians might experience more difficulties in acting independently from (perceived) demands of animal owners [10, 11], implying that younger veterinarians might be less self-confident. The positive association with veterinarians dedicated to treating companion animals only could be the result of better knowledge or awareness of new treatment options and specific guidelines.

Scepticism about the possible risks of AMU in companion animals as related to AMR emergence in companion animals and general healthcare was positively associated with males and more experienced veterinarians. The study of Speksnijder et al. [10] supports this finding stating that increased experience is associated with being less concerned about a possible veterinary contribution to AMR. When optimising AMU in all Dutch companion animal clinics, these differences in knowledge and attitudes on responsible AMU and the importance of AMR between less and more experienced veterinarians should be taken into account. This could be done, for example, by offering educational training on the latest insights on AMR to more experienced veterinarians or training on communication skills to less experienced veterinarians.

Working in rural areas and working full-time were positively associated with risk avoidance, especially regarding surgical procedures. Hardefeldt et al. [21] did not find a difference between rural and metropolitan clinics when comparing compliance with AIDAP (Australian Infectious

Disease Advisory Panel) and BSAVA (British Small Animal Veterinary Association) guidelines on AMU for surgical prophylaxis. However, they found that the odds of compliance was 1.4 (95% CI, 1.1-1.9) times greater for companion animal veterinarians compared to mixed species veterinarians. In another study, Hardefeldt et al. [22] found that animals from urban areas had 35% higher odds of having an insurance claim submitted and a 6.3% higher odds of having AMs prescribed compared to animals from rural areas, which seems to be contrary to the findings of our present study. The difference could be the result of differences in attitudes of companion animal owners in urban versus rural areas, e.g., with regard to when they seek for veterinary care. The difference might also be explained by the lack of a clear definition of urban and rural. In both studies, the distinction was based upon the opinion of responding veterinarians and not on a clear definition or postal code. A possible explanation why full-time working veterinarians in rural areas were positively associated with this behavioural profile of “risk avoidance” (e.g., unnecessary surgical prophylaxis) could be differences in clinic policies, facilities and equipment, and different client expectations in comparison with urban clinics. In the past, rural clinics mainly focused on food-producing animals, but now they are focussing more on companion animals too. The facilities, equipment and clinic policies might be somehow different from typical urban clinics, in which the focus has always been on companion animals. Besides, companion animal owners in rural areas might have other (financial) expectations than companion animal owners in cities. To increase adherence to current guidelines and to decrease unnecessary AMU, more attention should be paid to education on hygiene measures and AM prophylaxis around surgery (e.g., no standard AMU as prophylaxis for routine surgery), and veterinarians’ fears to omit AMU should be further explored, especially in rural clinics.

This study has some strengths and limitations that need to be addressed. The relatively low response rate of 32% (22% based on complete questionnaires), although comparable with other studies [10, 18, 21], might have caused participation bias. Regarding mean age and mean age at graduation of the respondents, as well as the proportion of female and male respondents and their provinces of employment, the demographics were comparable to those of the Dutch population of veterinarians [10, 23, 24].

Due to the study design, socially desirable answers to the questionnaire might have been received. However, respondents had the opportunity to return the questionnaire anonymously (approximately 40% of the completed questionnaires), minimising this potential bias. Moreover, answers in the survey differed considerably between respondents, and all scores (totally disagree to totally agree) were chosen. This indicates that these data support a diversity of opinions and attitudes regarding AMU and AMR among Dutch companion animal veterinarians.

In conclusion, self-reported antimicrobial prescribing behaviour among companion animal veterinarians in the Netherlands appears to be well considered and not influenced by economic drivers. Unwillingness of owners and financial constraints were perceived as important barriers for performing further diagnostics. Changing prescribing behaviour is complex and we recommend that measures or strategies to improve AMU are diverse, multimodal and attuned to the specific situation [15, 16, 25, 26]. Results of the present study will be used in the development of an antimicrobial stewardship programme (ASP) in Dutch companion animal clinics. A multifaceted and dynamic approach will be applied to safeguard the clinical efficacy of antimicrobials by optimising AMU while minimising the emergence of AMR and other possible adverse effects [27, 28]. This multifaceted approach, taking differences between companion animal veterinarians (e.g., in experience and gender) and differences in work situation (e.g., urban versus rural clinics) into account, should not only be directed at companion animal veterinarians but also companion animal owners. Educational training and peer-to-peer consultation on AMU, AMR, the implementation and use of current guidelines and legislation should be included in this ASP. Other stakeholders, such as veterinary nurses, guideline developers, pharmaceutical industry and providers of diagnostics, should be involved as well to stimulate their input in a joint and comprehensive effort to optimise AMU in companion animals. This could be done, for example, by informing them on the outcomes of present study and by organising a stakeholders meeting.

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Submission declaration

This research study has not been published elsewhere previously.

Conflicts of interest

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Chapter 4

Quantifying antimicrobial use in Dutch companion animals

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Abstract

Antimicrobial resistance is an increasing threat, both in human and in veterinary medicine. To reduce the selection and spread of antimicrobial resistance, antimicrobial use should be optimized, also in companion animals. To be able to optimize antimicrobial use, a feasible method to quantify antimicrobial use and information on current antimicrobial use are needed. Therefore, a method to quantify antimicrobial use was developed, using the number of Defined Daily Doses Animal (DDDA). This method was used to explore applied antimicrobial classes and to identify differences in prescribing patterns in time and between veterinary clinics.

Antimicrobial procurement data of the years 2012-2014 were collected retrospectively from 100 Dutch veterinary clinics providing care for companion animals. The mean number of DDDAs per clinic per year decreased significantly from 2012 to 2014. A shift in used classes of antimicrobials was seen as well, with a significant decrease in use of third choice antimicrobials (i.e. fluoroquinolones and third generation cephalosporins). Large differences in total antimicrobial use were seen between clinics ranging from 64-fold in 2012 to 20-fold in 2014.

Despite the relative low and decreasing antimicrobial use in Dutch companion animal clinics during the study, the substantial differences in antimicrobial prescribing practices between clinics suggest that there is still room for quantitative and qualitative optimization of AMU.

1. Introduction

Antimicrobial resistance (AMR) is an increasing threat, both in human and in veterinary medicine. Many antimicrobials (AMs) used in veterinary medicine are used in human medicine as well. Due to the close contact between people and their companion animals, the importance of companion animals as potential reservoirs of (multi)-resistant pathogens for humans has received increasing attention [1-5]. Besides the potential public health threat, AMR also has a direct impact on animal health and welfare, because of treatment failure. To prevent selection and spread of resistant bacteria and to keep antimicrobials valuable for the future, antimicrobial use (AMU) should be optimized.

From 2008 onwards, AMU in Dutch food-producing animals received increasing attention, actions were taken at different levels and AMU was reduced considerably [6-9]. Most actions addressed food-producing animals, but classification of AMs in 1st, 2nd and 3rd choice AMs [10] and legislation on mandatory susceptibility testing for the use of 3rd choice AMs [11] also hold for companion animals.

Risk management of AMR needs to be based on valid and most updated information. Therefore, it is crucial to monitor the amount and types of AMs used in animals. Amounts and types of AMs used in animals have been investigated in several countries, particularly in food-producing animals [12-17]. Only a few studies describe AMU and prescribing patterns in companion animals [18-22]. The majority of studies regarding AMU in companion animals uses total sales or prescription data expressed in kilograms of AMs [19], the mass of active AM substances (by AM class or subclass) in relation to a specified population to express AMU or the number of prescriptions [15, 21-23]. These different measurement units make it hard to compare data between these studies. The European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption group (EMA ESVAC) has introduced the veterinary Defined Daily Dose for Animals (DDD_{VET}) to objectify the numerator [24, 25]. DDD_{VET} is defined as a "technical unit of measurement similar to the Defined Daily Dose (DDD), usually based on recommendations from the Summary of Product Characteristics (SPC) and in some cases based on scientific literature, intended for the purpose of drug consumption studies. DDD_{VET} is assigned per kilogram animal per species per day" [24, 25]. According to ESVAC, objective AMU data collection should also be organized for companion animals, rabbit production and aquaculture [26].

The aim of present study was to quantify systemic AMU in Dutch companion animal clinics (2012-2014) using Defined Daily Dose Animal (DDDA) established according to the Dutch authorization of the veterinary medicinal products, to explore applied antimicrobial classes and to identify differences in prescribing patterns in time and between veterinary clinics.

2. Materials and methods

2.1. Study design and data collection

A retrospective survey was performed. The Royal Dutch Veterinary Association (KNMvD) provided contact details of all 1,149 veterinary clinics in the Netherlands which treated companion animals. All these clinics were invited by mail to participate, followed by a reminder after two weeks by e-mail. Requested data were clinic population data and antimicrobial veterinary medicinal product (AVMP) procurement data for the subsequent years 2012, 2013 and 2014. Mixed-animal clinics with combined, unspecified procurement data for companion animals and non-companion animals were excluded from the study, because products with a multi-species (companion and food-producing animal) registration could not be allocated to specific animal species.

2.2. Calculation of DDDAs

In the Netherlands, AMs for veterinary use are on prescription only and sold to companion animal owners (or farmers) by veterinarians exclusively. Therefore, antimicrobial procurement data are supposed to reflect the total amount of AMs used in animals. These procurement data were used to calculate the number of Defined Daily Doses Animal (DDDAs) per clinic per year ($DDDA_{CLINIC}$). For each year and clinic, the number of ordered packages of AVMPs for systemic use was provided, identified by their unique European Article Number (EAN)-code. To calculate the number of DDDAs per clinic, two variables are needed [17]. First, the total animal mass in kilogram that can be treated for one day with the amount of AMs prescribed; for every individual AVMP this can be derived from the “DG-standaard” by EAN-code. The DG-standaard is an online Dutch database containing all packages of AVMPs once authorized in the Netherlands, managed by the Netherlands Veterinary Medicines Institute. For every single AVMP package, per species the total animal mass in kilogram that can be treated is defined, preferably based on authorized doses, for cascade use based on comparable AVMPs or literature [27]. This database was initially developed and applied for the monitoring of antimicrobial consumption in the major food-producing animal sectors, enabling e.g., benchmarking of farms within sectors. Second, the total weight (in kg) of the clinic animal population at risk to be treated with the AVMP. The latter was estimated based on the clinic animal population represented by the number of dogs, cats and rabbits attending the clinic at least once in a specified 3-year period. The total weight was calculated by multiplying the number of dogs, cats and rabbits with previously established average body weights for dogs (19.1 kg) and cats (4.1 kg) [28], for rabbits the average weight was based upon expert opinion (2.5 kg). For every AVMP, the denominator was determined separately depending on the animal species the AVMP was authorized for. By dividing the two variables for all individual AVMPs and consequently adding up the outcomes, the total number of DDDAs is obtained. This sum of all AVMPs is suitable for comparison between clinics and between consecutive years ($DDDA_{CLINIC}$).

This calculation results in the indicator $DDDA_{CLINIC}$/year that represents the theoretical number of days per year an average animal (dog, cat or rabbit) was treated with AVMPs in the clinic concerned. For example, a $DDDA_{CLINIC}$ in 2014 of 2 implies that the average dog, cat and rabbit in care of this veterinary clinic has received 2 days of AM-treatment in 2014.

2.3. Classification of AMU

Classification of AMU in present study (Table 1) is according to the Dutch policy on veterinary AMU [10].

Table 1: Classification of veterinary antimicrobials (AMs) in 1^{st}, 2^{nd} and 3^{rd} choice AMs, according to Dutch policy on veterinary AMU.

Classification	Reasoning	Main classes of AMs
1^{st} choice	Empirical therapy; Do not select for (to current knowledge), nor are specifically meant for treatment of ESBL-producing micro-organisms.	Tetracyclines, nitroimidazoles, narrow-spectrum penicillins, trimethoprim, sulfonamides and phenicols.
2^{nd} choice	All AMs not classified as 1^{st} or 3^{rd} choice AMs; Use of these AMs might select for ESBL-producing bacteria or is specifically indicated in case of an ESBL-infection.	Aminopenicillins (with/without beta-lactamase inhibitors), 1^{st} generation cephalosporins, aminoglycosides and colistin.
3^{rd} choice	Highest Priority Critically Important AMs for human medicine according to WHO; By Dutch law restricted to use only in individual animals and after culture and susceptibility testing.	Fluoroquinolones, 3^{rd} and 4^{th} generation cephalosporins.

2.4. Statistical analysis

$DDDA_{CLINIC}$ data were used to determine the proportion of 1^{st}, 2^{nd} and 3^{rd} choice AMs, to identify trends in AMU during the study period and to identify differences between clinics. Mixed models were used to explore the variation in AMU over time, both within and between clinics. Models for AMU (total, 1^{st}, 2^{nd} and 3^{rd} choice) were fitted using PROC GLIMMIX (SAS 9.4, SAS Institute, Inc., Cary, NC, USA) assuming a log-normal distribution and allowed for changes in residual variance over time. Within clinic correlations were modelled using an autoregressive (ARH(1)) model and a random intercept. The year of prescription was included as a categorical covariate and statistical significance was tested for using likelihood ratio-testing, comparing model fit to that of a model that not included this covariate (both fitted using maximum likelihood). P-values of <0.05 were considered statistically significant.

3. Results

3.1. Inclusion of clinics

In total, 155 veterinary clinics responded and were willing to provide specified antimicrobial procurement data (13.5% of the total number of invited clinics). Because of missing data or Practice Management System (PMS) incapability to properly report the animal population data, 44 clinics were excluded. Procurement data from 111 veterinary clinics (period 2012-2014) were included and analyzed. Data from 11/111 veterinary clinics turned out to be inconsistent or unrealistic, i.e. reporting an unexpectedly high or low number of dogs or cats (about 10-times higher or lower than the average clinic) or antimicrobial veterinary medicinal products (AVMPs) for food-producing animals appeared to be incorrectly ascribed to companion animals. Therefore, results are based on data of 100 participating clinics.

3.2. Antimicrobial use: changes over time and differences between clinics

The mean number of DDDAs per clinic per year ($DDDA_{CLINIC}$) decreased from 2.33 (± 1.46) in 2012 to 1.88 (± 1.20) in 2014 (Figure 1). Use of 2nd choice AMs also decreased during the study period (0.97 (± 0.77) in 2012 to 0.81 (± 0.63) in 2014) as was the case for 3rd choice AMs (0.55 (± 0.38) in 2012 to 0.14 (± 0.15) in 2014) (Figure 2). First choice AMU increased from 0.81 (± 0.93) in 2012 to 0.93 (± 0.71) in 2014. Mixed model analyses of AMU (log-transformed data) indicated that all differences between 2012 and 2014 were statistically significant.

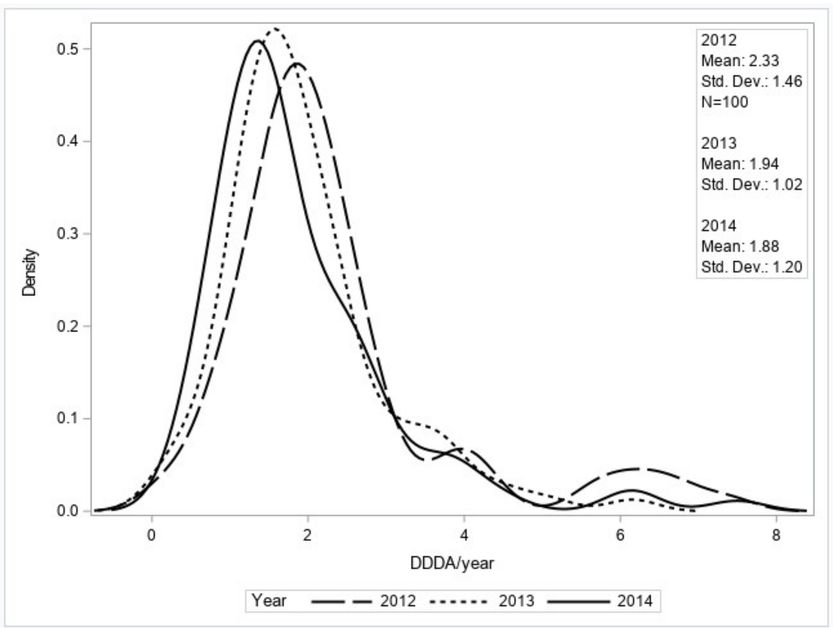

Figure 1: Density function of $DDDA_{CLINIC}$/year for total AMU based upon procurement data of 100 clinics for 2012, 2013 & 2014.

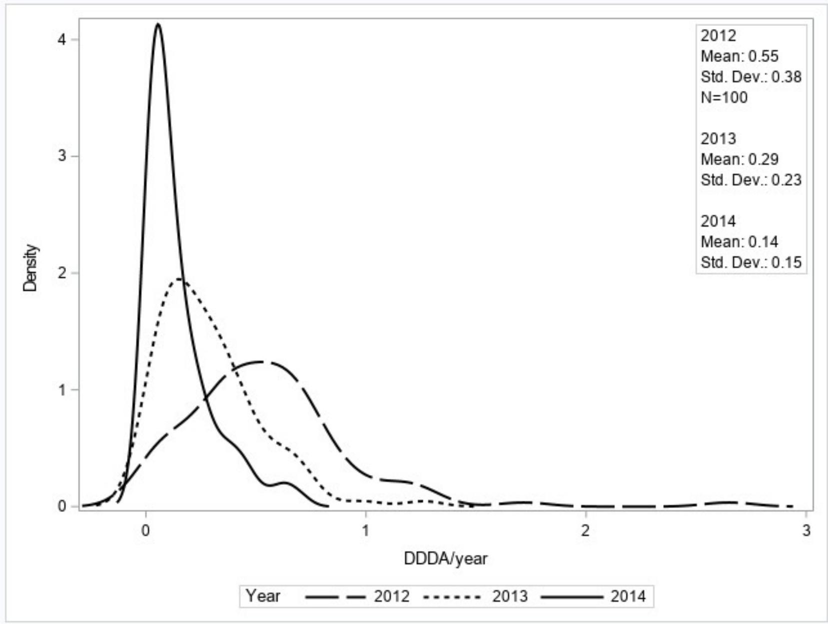

Figure 2: Density function of $DDDA_{CLINIC}$/year for third choice AMU based upon procurement data of 100 clinics for 2012, 2013 & 2014.

In 2012 and 2013, 2nd choice AMs were the most frequently used compounds (42% and 46% of total AMU), whereas in 2014, 1st choice antimicrobials were most frequently used (50% of total AMU). With regard to the groups of AMs used, aminopenicillins (with or without clavulanic acid) defined as 2nd choice AMs, represented the largest group in all three consecutive years (2012: 31%, 2013: 36% and 2014: 36% of total AMU). In 2012, the second largest group of AMs consisted of 3rd generation cephalosporins (i.e. cefovecin) (14% of total AMU), in 2013 and 2014 the second largest group consisted of trimethoprim/sulfonamides (11% and 13% of total AMU, respectively) which are 1st choice AMs. The use of fluoroquinolones and 3rd generation cephalosporins (both 3rd choice AMs) decreased from a mean $DDDA_{CLINIC}$/year number of 0.22 and 0.33 (2012) to 0.08 and 0.07 (2014), respectively.

The majority of systemically used AMs were orally administered (2012 66%; 2013 73%; 2014 77%, respectively). However, major part of 3rd choice AMs were applied parenterally (2012 67%; 2013 63%; 2014 55%, respectively), although this distribution is shifting towards more oral use as well.

The $DDDA_{CLINIC}$ numbers varied from year to year and per clinic (Figure 3 & 4). From 2012 to 2014, overall $DDDA_{CLINIC}$ numbers from individual clinics ranged from 0.11 (minimum $DDDA_{CLINIC}$, 2013) to 7.5 (maximum $DDDA_{CLINIC}$, 2014). In 2012, the between clinic difference in total AMU was almost 64-fold (Figure 3). In 2014, the between clinic difference was smallest and amounted a 20-fold difference between the minimum and maximum $DDDA_{CLINIC}$ (0.37 – 7.50) (Figure 4). An interesting detail in this observation is that a higher minimum $DDDA_{CLINIC}$ caused the drop in the between clinic difference, not a lower maximum $DDDA_{CLINIC}$. Spearman correlations between repeated measures of total AMU for different pairs of years ranged between 0.7 and 0.8. Regarding the use of 3rd choice AMs, the between clinic difference was larger. Five clinics reported no 3rd choice AMU in 2014. The lowest use that was reported accounted for a $DDDA_{CLINIC}$ of 0.001 while the maximum use was 0.70 in the same year, accounting for a 500-fold difference in 3rd choice AMU between clinics in 2014.

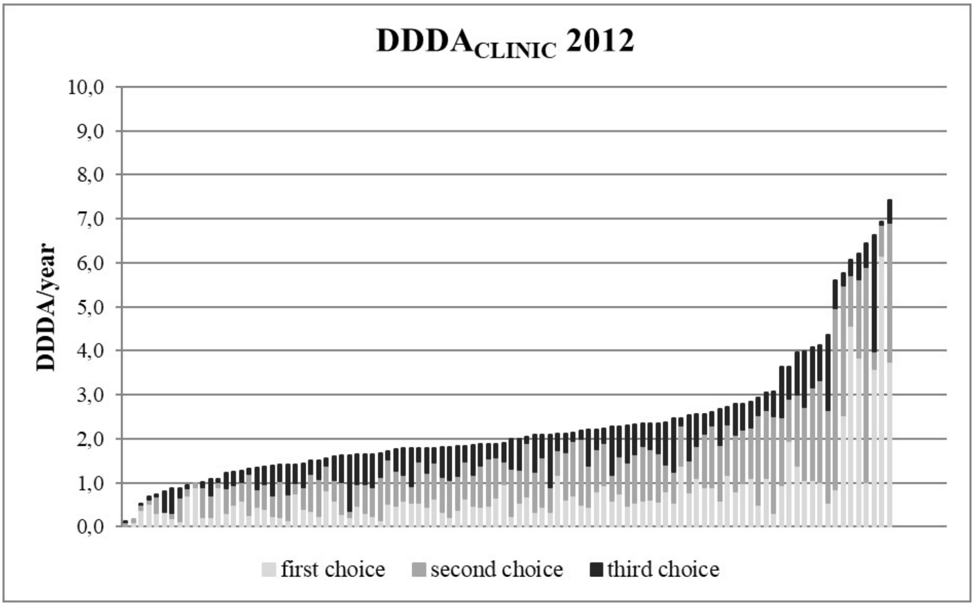

Figure 3: $DDDA_{CLINIC}$ figures for all 100 clinics in 2012, specified for first, second and third choice antimicrobials, showing the differences in AMU between clinics (based upon procurement data of these 100 clinics).

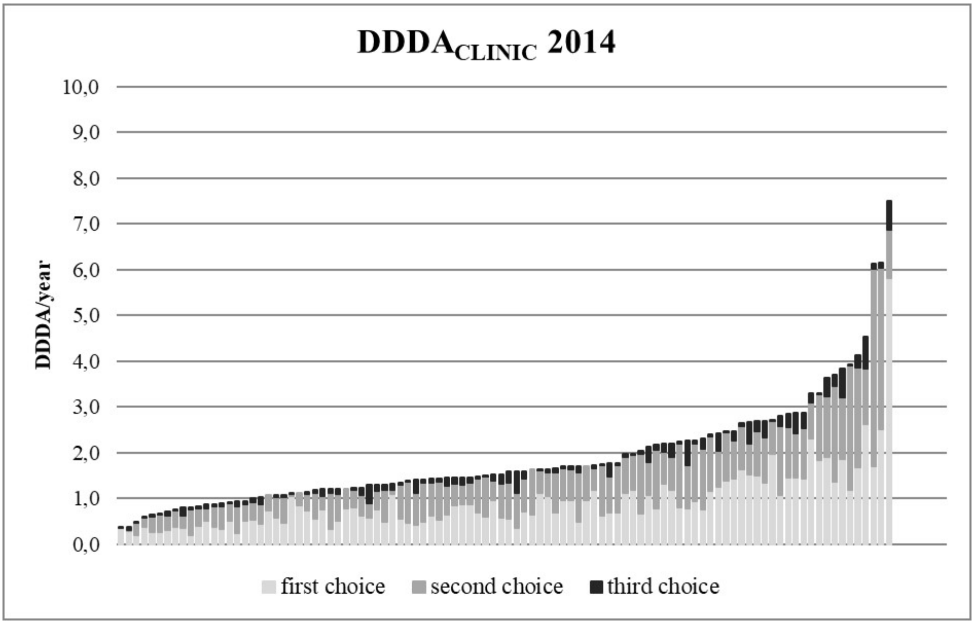

Figure 4: DDDA$_{CLINIC}$ figures for all 100 clinics in 2014, specified for first, second and third choice antimicrobials, showing the differences in AMU between clinics (based upon procurement data of these 100 clinics).

Statistical modelling established the observed differences in AMU between clinics by the mixed model analyses of AMU (log-transformed data) with a heterogeneous AR(1) model, a random 'clinic' effect and year of prescription as a covariate. For total AMU the residual variances decreased by 26% from 2012 to 2014. However, for 3rd choice AMU the residual variances increased by 102%, indicating that differences between clinics for the use of these AMs became more prominent over time. The estimated correlation between residuals of repeated measures of total AMU for a single clinic for different pairs of years ranged from 0.62 and 0.77 (using log-transformed data), indicating that clear systematic differences exist between practices in AMU.

4. Discussion

The present study used the number of DDDAs per clinic to express AMU in companion animals. By applying DDDAs dosing differences between AMs due to e.g., the relative potency and differences in pharmacokinetics, are taken into account, as well as dosing differences between species. This measure enables objectified comparison over time and between clinics, even internationally. This measure is adopted in monitoring AMU in food-producing animals and endorsed by EMA ESVAC [25]. Despite the advantages of a more harmonized way of presenting AMU, there are some disadvantages as well. Disadvantages of using DDDAs are linked to the way DDDAs are calculated. Two variables are needed for this calculation [17] (1) a numerator expressing the total treated animal weight and (2) a denominator expressing the total weight of the clinic animal population. Both variables might be biased. For the numerator this might be the case when an AVMP is authorized for use in more than one animal species. The majority of AVMPs in this study is authorized for more than one of the companion animal species concerned and due to lacking prescription information, it could not be specified whether these AVMPs were prescribed to dogs, cats and/or rabbits. When it is unknown whether the product has been administered to dogs, cats or rabbits, the resulting $DDDA_{CLINIC}$ cannot be stratified to specific animal species. At the same time, to be able to determine the total treated animal weight in case of an AVMP that is authorized for more than one companion animal species, the numerator was calculated using the average number of kilograms treated of the species the AVMP was registered for. As an example, if an AVMP was authorized for both dogs, cats and rabbits, the average number of treated kilograms of dogs, cats and rabbits was calculated as the numerator. In food-producing animals, prescription data are collected on farm level making it easier to allocate the AVMPs to specified animal species. Only prescription data (identifying the animal the AVMP was prescribed for) can mitigate this problem of AVMPs authorized for more than one companion animal species. For the denominator, bias might be caused by the total weight of the different animal species and the clinic animal population represented by the number of dogs, cats and rabbits attending the clinic at least once in a specified 3-year period. In our study, the total clinic animal population of all 100 participating clinics consisted of 228,000 dogs, 228,000 cats and 25,000 rabbits. These 100 clinics represented 8.7% of 1,149 veterinary clinics treating companion animals in the Netherlands. When these numbers are extrapolated and compared to official estimates on the number of dogs, cats and rabbits in the Netherlands [29], the total number of dogs in the Netherlands is overestimated (correction factor 0.57), the number of cats seems to be estimated correctly (correction factor 0.99) and the number of rabbits is underestimated (correction factor 4.13). The discrepancies between the number of dogs and rabbits registered in veterinary clinics versus official estimates in the Netherlands (based upon a survey among 7500 Dutch households) might be explained by the fact that rabbit owners consult a veterinarian less often and dog owners might visit more different clinics (e.g., for a second opinion). The relatively high number of dogs compared to rabbits, might also be explained by the fact that rabbit owners mainly visit a veterinarian in case a rabbit is ill, while dog and cat owners might also seek preventive veterinary medicine (e.g., yearly check-ups, vaccinations etc.).

Additional calculations taking above mentioned correction factors into account, result in a mean overall AMU of 2.8 DDDA/year in 2012 (versus 2.33 without correction factors), 2.34 DDDA/year in 2013 (versus 1.94 without correction factors) and 2.27 DDDA/year in 2014 (versus 1.88 without correction factors). Third choice AMU accounted for a mean DDDA/year of 0.69 in 2012 (versus 0.55), 0.36 in 2013 (versus 0.29) and 0.19 in 2014 (versus 0.14), respectively. Although absolute $DDDA_{CLINIC}$ numbers are higher using the correction factors, observed trends and patterns in AMU and differences between clinics remain the same. Regarding the applied denominator per clinic, the absolute $DDDA_{CLINIC}$ values should be interpreted with caution. DDDA is a powerful and objective measure. For comparisons over time and between studies, the denominator should be well defined.

This study shows a significant decrease of AMU from a mean $DDDA_{CLINIC}$ of 2.33 DDDA/year in 2012 to 1.88 in 2014. This decrease was combined with a clear shift in classes of AMs used. Increased attention for AMU in general and national action plans to establish reduction of AMU in food-producing animal sectors, appeared to have affected AMU in Dutch companion animals as well. Not only in the Netherlands, but also in other countries a recent decrease in AM prescriptions in companion animals was reported [21, 22]. However, in the present study considerable differences in AMU between clinics were seen, suggesting possibilities for optimization of AMU. Given the observation that repeated measures of total AMU from one specific clinic were clearly correlated and substantial between-clinic differences were observed, it would be worth focusing on those clinics with less favorable figures first, although differences between clinics reduced with decreasing use as well. Because 3^{rd} choice AMU was already relatively low, yearly use tended to fluctuate more. Therefore, repeated measures of 3^{rd} choice AMU from one specific clinic appeared less correlated.

Despite a significant reduction in total AMU and especially in 3^{rd} choice AMs (CIAs of highest priority for human medicine according to WHO [30]), the use of these AMs still accounted for 7.7% of total AMU in 2014. However hard to compare due to using different measurements of AMU, other countries report similar or slightly higher use of highest priority CIAs: in the UK, CIAs of highest priority accounted for just over 6% of AMs used in dogs and 34% in cats (calculated as number of events) [19] and in Australia 8% of the AM courses prescribed belonged to CIAs of highest priority, in which cats were 4.8-times more likely than dogs to receive 3^{rd} generation cephalosporins [22].

Second choice AMs (mainly aminopenicillins and 1st generation cephalosporins) represented the AMs most frequently used in studied Dutch companion animal clinics in 2012 and 2013. Aminopenicillins are categorized as CIAs with a high priority for human medicine [30]. These findings are in line with studies in other countries [19, 22].

Total AMU in companion animals is decreasing and relatively low compared to livestock (e.g., in 2014 $DDDA_{NAT}$ for cattle was 2.44, 21.15 for veal calves and 9.52 for pigs, respectively [31]) and AMU in humans (total AMU in the primary care sector of 10.58 DDD/1000 inhabitant days in 2014, corresponding to 3.86 DDD/inhabitant year [32]). However, regarding the potential selection of ESBL-producing bacteria and regarding the use of 3rd choice AMs, there seems to be room for improvement in the classes and subclasses of AMs used in companion animals. Focus should be on further reduction of 2nd and 3rd choice AMU.

Since January 2013, use of 3rd choice AMs as well as AMs authorized for human use is discouraged by legislation (susceptibility testing is mandatory). Therefore, the amount of AMs authorized for human use used in veterinary medicine is expected to be low. Based on the present study with veterinary wholesalers' procurement data, the exact amount of AMs authorized for human use (e.g., nitrofurantoin, some clindamycin and trimethoprim/sulfonamide products) could not be calculated, because data from human pharmacies was not included.

Remarkable differences in AMU between clinics were observed. Overall AMU differed 20-fold in 2014, while for 3rd choice AMs this difference was 500-fold. The residual variance for 3rd choice AMU increased, indicating that differences between clinics with regard to 3rd choice AMU became more prominent. In human primary care the difference in number of antimicrobial courses between Dutch practices was only 5-fold [33]. Observed differences in present study might partially be attributed to differences in animal population between clinics. E.g., when clinics treat mainly small or very large breeds, the standardized average animal species weights used for DDDA calculations might not be correct and might cause under- or overestimation of the $DDDA_{CLINIC}$. Also differences in first opinion clinics versus referral (i.e. secondary or tertiary) clinics, or clinics mainly treating emergency patients might account for observed differences between clinics. However and probably more important, AMU will be determined by prescribing policy and habits within companion animal clinics (e.g., the introduction and implementation of current guidelines regarding AMU) and veterinarian related prescribing habits, e.g., personal preferences in used dosages, frequency of dosing and course lengths, as was shown in previous qualitative studies on AMU in companion animal clinics [34-36]. The observation of clear and systematic differences between clinics in AMU highlights a potential for further optimization of AMU, eventually leading to smaller differences in AMU between clinics. Therefore, it is of interest to explore underlying factors which may explain differences in AMU between clinics in future studies more in-depth.

Only 8.7% of the 1,149 veterinary clinics treating companion animals were enrolled in present study. The representativeness of these clinics for all Dutch companion animal clinics might be questioned. Participating clinics might have had special interest in AMU and therefore display a more responsible attitude in their AMU compared to non-participating clinics. On the other hand, large differences in AMU between clinics could be observed, indicating that not only clinics with a low AMU were participating. Furthermore, participating clinics were distributed over the whole country. Therefore, the authors believe that the patterns of antimicrobial prescribing are likely to reflect those of the greater population and absolute DDDA numbers can be assumed to provide a reliable lower estimate of AMU across the remainder of the Dutch population of companion animal veterinary clinics.

In conclusion, systemic AMU in Dutch companion animal clinics is decreasing, in particular the use of 3rd choice AMs. However, substantial differences in AMU between clinics could be observed, both in (sub)classes as well as in total amount of AMs used, showing room for improvement.

Conflicts of interest

This study has been conducted under contract with the SDa (The Netherlands Veterinary Medicines Institute) and was commissioned by the Ministry of Economic Affairs (Funding number 115704-1300019854 Survey antibioticumgebruik gezelschapsdieren).

Author Contributions Statement

DH, JW, MD and IG contributed to the concept and design of the study; MD and IG collected the data; NH and IG performed the data analysis; all authors contributed to the writing and revising process of the manuscript.

Datasets are available on request

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

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Chapter 5

Time trends, seasonal differences and determinants of systemic antimicrobial use in companion animal clinics 2012-2015

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Abstract

Any antimicrobial use (AMU) in humans and animals selects for antimicrobial resistance (AMR) and responsible AMU should therefore be promoted both in human and veterinary medicine. Insight into current AMU in companion animal clinics is necessary to be able to optimise antimicrobial (AM) prescribing behaviour. The objective of this study was to describe systemic AMU in 44 Dutch companion animal clinics over a 3-year time period (2012-2015), using retrospectively collected data. The number of Defined Daily Doses for Animals (DDDAs) per month and per clinic were calculated from prescription data for total, 1st, 2nd and 3rd choice AMU (classification according to Dutch policy on veterinary AMU). Time trends, seasonality and the influence of potential determinants (e.g., the number of dogs, cats and rabbits per clinic and other clinic characteristics) were explored using statistical modelling.

Overall, the findings show that total AMU decreased over time and a shift in used classes of antimicrobials towards more 1st choice AMs was visible. Mean total AMU decreased from 1.82 DDDA/year in 2012-2013 to 1.56 DDDA/year in 2014-2015. Aminopenicillins, with and without clavulanic acid, accounted for the largest group of antimicrobials used; 38.7% (2012-2013), 40.2% (2013-2014) and 39.3% (2014-2015) of total AMU, respectively.

Strong seasonal differences in AMU were found, with highest AMU in July-August and lowest in February-March. The distribution of different animal species per clinic appeared to affect AMU as well. In clinics with a larger proportion of dogs, 2nd choice AMU was significantly higher, whereas in clinics with a larger proportion of rabbits, 2nd choice AMU was significantly lower. Despite the decrease of AMU during the study period, there is still room for improvement, especially with regard to the antimicrobial classes prescribed. According to Dutch classification of veterinary AMU, 1st choice AMs should be used as empirical therapy. A decrease in 2nd (might select for ESBL-producing bacteria) and 3rd choice AMU (i.e. fluoroquinolones and 3rd generation cephalosporins) should be aimed for.

1. Introduction

Antimicrobial use (AMU) in humans and animals promotes the selection and dissemination of antimicrobial resistance (AMR), as well as the emergence of new resistant bacteria [1-3]. The increase of AMR has been recognised as a global concern and risk for public health. Responsible AMU is therefore needed and should be promoted both in human and veterinary medicine [4-6].

In human medicine, guidelines and antimicrobial stewardship programmes (ASPs) are developed and implemented to promote responsible AMU [7-11]. In veterinary medicine, just recently (inter)national guidelines to promote responsible AMU in companion animals have been developed [12-16].

From 2008 onwards, AMU in Dutch food-producing animals received increasing attention; action plans and regulations to reduce AMU were implemented, resulting in a decrease in AMU of almost 68% between 2007 and 2017 [17, 18]. One of the keys to success of the Dutch reduction policy was to get complete and reliable data on AMU in food-producing animals [19]. This transparency in AMU enabled the possibility to set reduction targets and to monitor attainment of these targets. Benchmarking of farmers was established as well, which contributed to social pressure and an increased awareness among farmers. Antimicrobial use in companion animals is not continuously monitored so far, and although AMU in companion animals is expected to be low compared to food-producing animals, the antimicrobial (AM) classes used in companion animals appear to be less preferable. A survey on prescription data of 68 companion animal clinics in the Netherlands during 2009-2011, showed that use of 3rd generation cephalosporins and fluoroquinolones (i.e. highest priority critically important antimicrobials for human medicine according to the World Health Organisation (WHO)) accounted for 18% of total AMU, based upon the number of Defined Daily Doses for Animals (DDDAs) [20, 21]. Insight into current AM prescribing behaviour and AMU patterns in Dutch companion animal clinics is pivotal to enable development, implementation and evaluation of an antimicrobial stewardship programme (ASP) to optimise AMU. The aim of this study was to describe systemic AMU in 44 Dutch companion animal clinics over a 3-year time period (from July 2012 to June 2015) and to explore time trends, seasonality and influencing determinants. Systemic AMU was evaluated in a standardised way using the number of DDDAs.

2. Materials and Methods

2.1. Study design

A retrospective survey was performed in Dutch companion animal clinics, in which AMU was evaluated using AM prescription data from 2012-2015. These clinics were part of a larger (intervention) study on AMU in Dutch companion animal clinics. Information collected from each of the participating clinics included general clinic characteristics, data on the clinic population and antimicrobial veterinary medicinal product (AVMP) prescription data on a monthly basis.

2.2. Selection of participating clinics

Companion animal clinics were approached for participation using the database of the Royal Dutch Veterinary Association (KNMvD). The total number of clinics treating companion animals was estimated to be 1204 in 2014 [22]. Convenience sampling was used to select clinics based on previous shown interest to participate in a study on AMU in companion animal clinics and on geographic location. In 2016, clinics were invited to participate by e-mail, followed by a phone call to answer questions and to arrange a visit to collect requested data. Clinic visits were planned within a month after first contact with the clinic. Clinics were eligible for inclusion if the Practice Management System (PMS) was able to provide information on monthly antimicrobial prescription data specified for companion animals. Both clinics treating companion animals only and so-called "mixed" clinics able to specify prescription data for companion and non-companion animals were included in the study. Before enrolment in the study, all clinics received written and oral information on the purpose of the study. Each clinic signed an informed consent granting permission to use their patient data for research purposes after anonymisation.

2.3. Data collection and management

Each clinic filled out a short questionnaire on clinic characteristics and demographics at the beginning of the study. Information on the number of dogs, cats and rabbits attending the clinic at least once in a specified 3-year period, were retrieved from the PMS. AMU data were retrieved retrospectively by extracting AM prescription data per month from July 2012-June 2015.

2.4. Calculation of AMU

The European Surveillance of Veterinary Antimicrobial Consumption group (ESVAC) has defined the Defined Daily Dose for animals (DDD_{VET}) as "the assumed average dose per kg animal per species per day" [23, 24]. The method used in present study to calculate the number of Defined Daily Doses for Animals (DDDAs) per clinic is explained and discussed in detail in a previous study [25]. In summary, to calculate the number of DDDAs per clinic, two variables are needed [26]. First, the total animal mass in kilogram that can be treated for one day with the amount of AMs prescribed. Second, the total weight (in kg) of the clinic animal population at risk to be treated with the AVMPs. By dividing the two variables for all individual AVMPs prescribed and consequently adding up the outcomes, the total number of DDDAs was obtained. This sum of all prescribed AVMPs per month describes the mean AMU of all dogs, cats and rabbits of the concerning clinic ($DDDA_{CLINIC}$) which enables comparison of AMU between clinics and over time. A $DDDA_{CLINIC}$ of 0.5 per month implies that the average animal (dog, cat and rabbit) in the clinic was exposed to antimicrobials for half a day per month.

For each clinic, total $DDDA_{CLINIC}$ was calculated per month from 1 July 2012 till 30 June 2015 and specified per antimicrobial class, according to Dutch policy on veterinary AMU (Table 1) [27].

In the present study, only systemic (i.e. oral or parenteral) AMU was described, antimicrobials applied topically were excluded from further analyses.

Table 1: Classification of veterinary AMU according to Dutch policy on veterinary AMU.

Classification	Reasoning	Main classes of AMs
1^{st} choice	Empirical therapy; Do not select for (to current knowledge), nor are specifically meant for treatment of ESBL-producing micro-organisms.	Tetracyclines, nitroimidazoles, narrow-spectrum penicillins, trimethoprim, sulfonamides and phenicols.
2^{nd} choice	All AMs not classified as 1^{st} or 3^{rd} choice AMs; Use of these AMs might select for ESBL-producing bacteria or is specifically indicated in case of an ESBL-infection.	Aminopenicillins (with/without beta-lactamase inhibitors), 1^{st} generation cephalosporins, aminoglycosides and colistin.
3^{rd} choice	Highest Priority Critically Important AMs for human medicine according to WHO; By Dutch law restricted to use only in individual animals and after culture and susceptibility testing.	Fluoroquinolones, 3^{rd} and 4^{th} generation cephalosporins.

2.5. Data analysis

Potential determinants of AMU (all the clinic characteristics retrieved from the questionnaire and the number of dogs, cats and rabbits per clinic, as shown in Table 2) were evaluated in a multivariable regression model with log-transformed AMU data (either total, 1^{st}, 2^{nd} or 3^{rd} choice AMU) as the outcome variable. All determinants were entered in the model to explore the possible influence of determinants of AMU in their context. To reduce collinearity between variables, the number of veterinarians (highly correlated with the total number of dogs, cats and rabbits treated, Pearson's r = 0.75) and the proportion of cats (highly correlated with the proportion of dogs, Pearson's r = 0.75) were excluded from further analyses. P-values$\leq$0.05 were considered as statistically significant and P-values between 0.05 and 0.10 were considered borderline statistically significant and represent a trend or tendency. General time trends were modelled using natural regression splines with a single interior knot placed at the median time point (January 2014), while seasonal effects were modelled using a combination of four (two pairs of) harmonic (sine/cosine) functions. To allow for between-clinic heterogeneity in time and seasonal trends and to account for the autocorrelation of observations within a clinic over time, the statistical model included clinic-specific intercepts and trend coefficients as random effects and an auto-regressive (AR1) correlation structure for the residuals. The natural spline bases were centred at the interior knot location to allow interpretation of the fixed effects as the ratio of geometric means (GMR) of estimated AMU at this timepoint. Model fit for simpler models (e.g., models that did not include an auto-regressive structure) proved inferior to that of the selected model. Despite small numerical differences, results were qualitatively similar. A model allowing for clinic-specific residual variances failed to converge when used with the full determinant model, but point estimates and standard errors compared well with the selected model for smaller submodels.

SAS (SAS 9.4, SAS Institute, Inc. Cary, NC, USA) was used to organise the data and R (version 3.5) was used to perform the statistical analyses, using the nlme package (version 3.1) to fit the mixed effects models and to graphically present the data.

3. Results

3.1. Participating clinics

In total, 54 clinics were contacted to participate. Six clinics were not willing to participate and four clinics did not have a suitable PMS to provide monthly prescription data. Finally, 44 clinics were included in the study. Table 2 shows characteristics of the participating clinics. Eight clinics were not able to provide prescription data from July 2012 onwards (e.g., because the clinic had just opened or switched to another PMS), for these clinics data were provided from the earliest moment possible.

Table 2: Characteristics of 44 participating Dutch companion animal clinics.

Characteristic (number of clinics = 44)	Mean (range)
Number of dogs	2151 (14 - 5353)
Number of cats	1910 (350 - 5113)
Number of rabbits	271 (0 - 797)
Total number of veterinarians	3 (1 - 10)
Number of veterinarians treating companion animals	2.7 (1 - 8)
Number of affiliated practices	1.25 (1 - 3)
Mean number of years experience per clinic	16.2 (5.8 - 34)
Characteristic (number of clinics = 44)	**Distribution (% of total)**
Companion animals only versus mixed-animal clinics	40 (90.9%) / 4 (9.1%)
Urban, rural or urban-rural	29 (65.9%) / 14 (31.8%) / 1 (2.3%)
Conventional medicine only versus also offering non-conventional medicine options	39 (88.6%) / 5 (11.4%)
Veterinarians only graduated in the Netherlands versus other countries of graduation	31 (70.5%) / 13 (29.5%)
Only female, only male or mixed gender clinic	19 (43.2%) / 6 (13.6%) / 19 (43.2%)
Serving shelters or kennels versus not serving shelters or kennels	11 (25%) / 33 (75%)
Serving breeders versus not serving any breeders	29 (65.9%) / 15 (34.1%)
PMS* type used 1 / 2 / 3 / 4	26 (59.1%) / 6 (13.6%) / 5 (11.4%) / 7 (15.9%)

* PMS type 1, 2 and 3 represent three different Practice Management Systems, PMS type 4 represents a group of 'other' systems, all only used in a few clinics.

3.2. Defined Daily Doses for Animals

3.2.1. Mean AMU per year

Mean total AMU decreased from 1.82 to 1.56 DDDA/year in the participating clinics (Table 3). Aminopenicillins (amoxicillin with and without clavulanic acid) accounted for the largest group of used AMs in the three consecutive periods, 38.7%, 40.2% and 39.3% of total AMU, respectively. Tetracyclines accounted for 8%, 11.2% and 12.6% of total AMU in these three years. Cefovecin (3rd generation cephalosporin) was the second most used substance in 2012/2013 (9.5%). However, the use of cefovecin decreased 3-fold when comparing the first year with the last year (from 0.17 DDDA/year to 0.05 DDDA/year). Likewise, the use of fluoroquinolones showed a decrease from 2012 to 2015 (0.15 DDDA/year to 0.07 DDDA/year).

Table 3: Mean AMU in numbers of DDDA/year (total, 1st, 2nd and 3rd choice antimicrobials) in the participating clinics in the 3 consecutive years (July 2012-June 2013, July 2013-June 2014 and July 2014-June 2015).

Classification of antimicrobials	2012/2013	2013/2014	2014/2015
First choice (% of total)	0.62 (33.8%)	0.67 (40.3%)	0.7 (44.6%)
Second choice (% of total)	0.88 (48.5%)	0.81 (48.9%)	0.74 (47.2%)
Third choice (% of total)	0.32 (17.7%)	0.18 (10.8%)	0.13 (8.1%)
Total DDDA per year (SD)	1.82 (1.0)	1.65 (0.98)	1.56 (1.0)

3.2.2. Time trends and seasonality

Results from our statistical model indicated that total, 1st, 2nd and 3rd choice AMU changed significantly over time ($P<0.001$), in which total, 2nd and 3rd choice AMU decreased, whereas 1st choice AMU increased. AMU showed a strong seasonal pattern with a peak in July-August and a lowest value in February-March (see Figure 1 for total AMU). This seasonal pattern was statistically significant ($P<0.001$) for total, 1st and 2nd choice AMU.

3.2.3. Determinants of AMU

Results of the multivariable regression analysis are shown in Table 4. Total AMU tended to be higher in clinics with a larger proportion of dogs (GMR 1.22, 95% CI 0.99-1.50 per 10% increase in the proportion of dogs), which was significant for 2nd choice AMU (GMR 1st choice AMU 1.24, 95% CI 0.94-1.65, GMR 2nd choice AMU 1.26, 95% CI 1.06-1.51, GMR 3rd choice AMU 1.01, 95% 0.66-1.54, respectively, per 10% increase in the proportion of dogs). A negative association was found between total AMU and the proportion of rabbits, which was significant for 2nd choice AMU (GMR for total AMU 0.00, 95% CI 0.00-17.79, GMR for 2nd choice AMU 0.00, 95% CI 0.00-0.04, respectively, per 1% increase in the proportion of rabbits). Total AMU in mixed-animal clinics appeared lower compared to companion animal only clinics, but this was only significant for 2nd choice AMU (GMR for total AMU 0.60, 95% CI 0.31-1.16, GMR for 2nd choice AMU 0.54, 95% CI 0.31-0.95). All other determinants showed no or only borderline associations with AMU (Table 4).

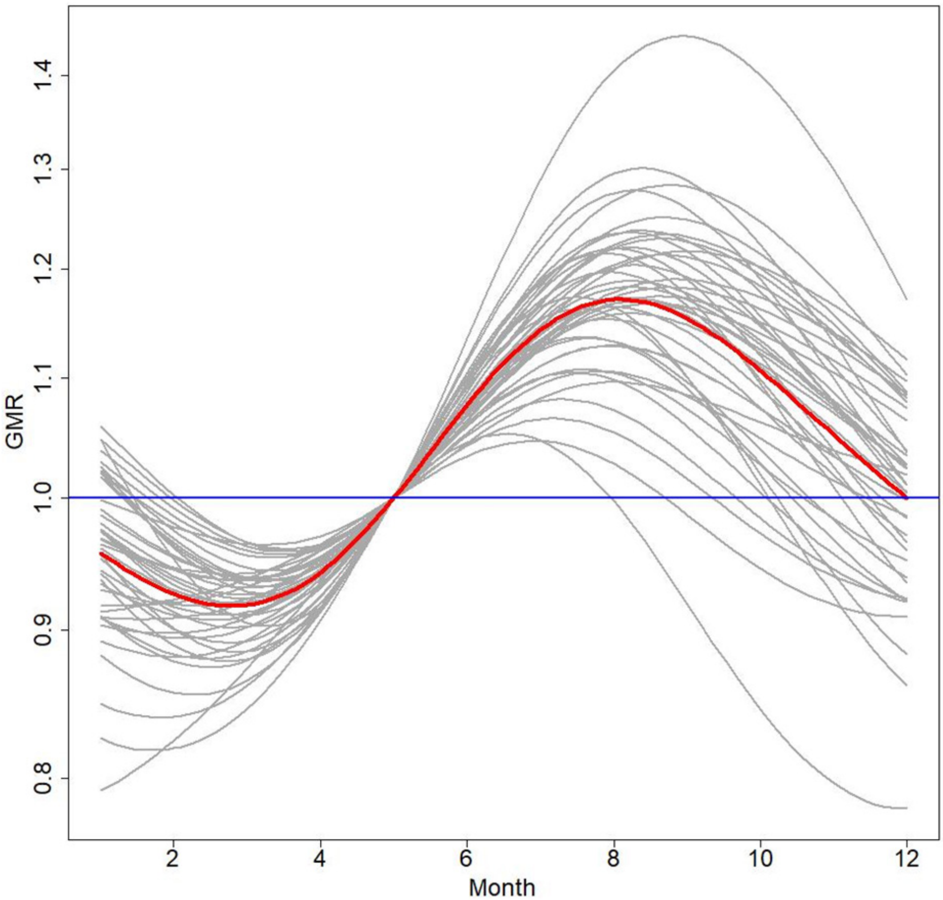

Figure 1: Seasonality in total AMU in participating companion animal clinics during July 2012-June 2015. Seasonal effects are expressed as Geometric Mean Ratios (GMRs), comparing the geometric mean AMU in each month to that of the average across the year. Seasonal effects were modelled using harmonic functions and estimated using a mixed effect model that allowed for between-clinic heterogeneity. The mean of the random effects distribution ("average" seasonal effect) is shown in red, clinic specific (empirical bayes) estimates are shown in grey. On the horizontal axis, numbers 1-12 are used for January-December.

Table 4: Effect estimates for potential determinants of AMU from a multivariable regression model, for total, 1st, 2nd and 3rd choice AMU (log-transformed data). Time trends were modelled using natural regression splines, seasonal effects were modelled using a combination of four harmonic functions. The statistical model included clinic-specific intercepts and trend coefficients as random effects and an auto-regressive (AR1) correlation structure for the residuals.

	Total AMU		First choice[1]		Second choice[1]		Third choice[1]	
Clinic characteristic	**GMR**	**95% CI**	**GMR**	**95% CI**	**GMR**	**95% CI**	**GMR**	**95% CI**
Proportion of dogs (per 10% increase)	1.22	**0.99-1.50****	1.24	0.94-1.65	1.26	**1.06-1.51***	1.01	0.66-1.54
Proportion of rabbits (per 1% increase)	0.00	0.00-17.79	0.91	$0.00\text{-}62.9\times10^{3}$	0.00	**0.00-0.04***	0.64	$0.00 - 10.4\times10^{6}$
Total number of animals	0.98	0.88-1.10	0.93	0.80-1.08	1.09	**0.99-1.20****	0.94	0.75-1.18
Number of affiliated practices	1.09	0.78-1.52	0.96	0.61-1.51	1.05	0.79-1.39	1.18	0.60-2.34
Mean experience per clinic (number of years)	0.91	0.67-1.24	0.95	0.63-1.43	1.04	0.80-1.34	0.79	0.43-1.47
Mixed-animal clinics versus companion animals only	0.60	0.31-1.16	0.73	0.30-1.78	0.54	**0.31-0.95***	0.57	0.15-2.16
Urban versus rural or urban-rural	1.28	0.82-2.00	1.09	0.60-2.01	1.15	0.79-1.68	1.88	0.76-4.64
Conventional medicine only versus also offering non-conventional medicine options	0.79	0.45-1.41	0.62	0.29-1.35	0.85	0.52-1.37	0.66	0.20-2.12
Veterinarians only graduated in the Netherlands versus other countries of graduation	0.96	0.64-1.45	0.90	0.52-1.58	1.08	0.76-1.52	1.79	0.77-4.17
Only female (versus only male or mixed gender clinic)	1.14	0.70-1.86	0.98	0.51-1.91	1.46	**0.97-2.19****	0.99	0.37-2.66
Not serving shelters or kennels versus serving shelters or kennels	0.89	0.61-1.31	1.07	0.64-1.81	0.89	0.64-1.24	0.75	0.34-1.65
Not serving any breeders versus serving breeders	1.04	0.64-1.69	0.60	0.31-1.16	1.20	0.79-1.82	0.85	0.32-2.31
PMS 2 versus PMS 1, 3 or 4	0.82	0.50-1.33	0.86	0.45-1.66	0.66	**0.44-0.99****	0.83	0.31-2.24

[1] according to Dutch policy on veterinary AMU (Table 1), * P-value≤0.05, ** 0.05<P-value≤0.10.

4. Discussion

This study describes systemic AMU in companion animals over the period 2012-2015 in Dutch companion animal clinics, based upon monthly prescription data and using the number of Defined Daily Doses for Animals (DDDAs) as a measure to quantify systemic AMU. Overall, the findings show that AMU-patterns are changing over time with a decrease in total AMU and a shift in the used classes of antimicrobials towards more 1^{st} choice AMs. Strong seasonal differences in AMU were found and the distribution of different animal species appeared to affect AMU.

Only a limited number of studies describe AMU in companion animals and all studies use different measurements to quantify AMU. Incautious comparison of AMU in different studies might lead to wrong conclusions. We chose to use the number of DDDAs as a measure to quantify AMU. This measure is already established for Dutch food-producing animals and takes dosing differences between AMs and between animal species into account. Using the number of DDDAs and DDDA$_{CLINIC}$, and its strengths and limitations, are discussed in detail in a previous study [25].

Whether the participating 44 clinics are representative for the whole country is difficult to assess. The number of clinics is limited and estimated to be approximately 4% of the total number of companion animal clinics in the Netherlands. Participation was based on voluntariness and interest to participate in a larger study on AMU in companion animals. Large differences in AMU between clinics indicate that participating clinics seem to be diverse. Moreover, the decreasing trend shown in the current study resembles findings of another Dutch study on yearly procurement data of 100 companion animal clinics [25].

The observed decrease in the use of cefovecin and fluoroquinolones (i.e. 3^{rd} choice AMs) in present study can most probably be attributed to a combination of increased awareness on AMR and implementation of policies to reduce AMU in the Netherlands, e.g., the mandatory susceptibility testing for veterinary use of these 3^{rd} choice AMs [28]. In other countries, e.g., Denmark and Sweden, similar policies have been implemented, which resulted in comparable decreasing trends in the use of critical AMs like fluoroquinolones and 3^{rd} and 4^{th} generation cephalosporins [29, 30].

The reduction in total, 2^{nd} and 3^{rd} choice AMU is a promising development, however, the use of aminopenicillins, that might select for ESBL-producing bacteria, is still relatively high and 3^{rd} choice AMU (i.e. AMs considered as highest priority critically important AMs for human medicine by WHO [21]) still accounts for 8% of total AMU. In other countries similar data are shown for the use of these antimicrobial classes [31-34]. This warrants the need for guidelines or actions to further restrict the use of these AMs in animals. A possible explanation for the relatively high use of aminopenicillins could be the fact that aminopenicillins have a wide range of indications, dogs and cats tolerate them quite well, many authorised formulations are available for both dogs and cats in the Netherlands and, probably likewise important, companion animal veterinarians are used to these AMs, as was shown in a previous qualitative study [35].

In the present study, seasonal differences in AMU were found with the highest total use in July-August and the lowest use in February-March. A similar seasonal pattern was described for AMU in dogs and cats in Australia [34]. In dogs AMU was higher in spring and summer compared to AMU in winter months, and was discussed on as attributable to peaks in seasonal diseases, such as allergic dermatitis, seen in warmer months [34]. In human medicine, seasonality was also shown for AMU, with higher systemic AMU in winter months [36-39]. Higher use of AMs in humans in winter coincides with the occurrence of flu epidemics. In companion animals, the higher use of 2nd choice AMs (mainly aminopenicillins and 1st generation cephalosporins) in summer months might be explained by more (bite)wounds and dermatological problems during warmer months. Cephalosporins (1st generation) are often used for dermatologic problems in dogs [40]. Aminopenicillins have a wide range of indications, an important indication for the use of these AMs in cats could be wound infections, which might be more prevalent during summer when cats are roaming outside and fight more than in winter. Singleton et al. [33] confirm that the main complaints resulting in AM prescribing are pruritus in dogs and trauma in cats, which could fit with the seasonal increase of 2nd choice AMU. The peak in 1st choice AMU is partially caused by a peak in tetracyclines of which the most common one is doxycycline. Doxycycline is mainly indicated for respiratory infections [41], suggesting that respiratory problems might be more present in late summer/autumn period. This may be caused by the holiday season when pets are housed in kennels more often, increasing the risk for respiratory infections, like kennel cough. An increased risk on vector borne diseases, like borreliosis and anaplasmosis, most often treated with doxycycline, might be another explanation for this peak in 1st choice AMs. However, more detailed studies are needed to explore these suggestions.

The distribution of different animal species per clinic appeared to affect AMU. Clinics with a higher proportion of rabbits appeared to be associated with lower AMU, especially of 2nd choice AMs. This could be explained by the fact that 2nd choice AMs are mainly aminopenicillins and 1st generation cephalosporins. Oral treatment with these AMs is generally considered contra-indicated in rabbits because it may result in dysbiosis and enterotoxaemia [42]. In the Netherlands, there are only a few 2nd choice AMs authorised for use in rabbits.

Second choice AMU was significantly higher in clinics with a higher proportion of dogs. There are several studies indicating that dogs receive more AMs compared to cats and thus supporting current findings [32, 34]. Second choice AMs appear to be used more often in dogs, whereas especially 3rd generation cephalosporins (which are defined as 3rd choice AMs) are used more frequently in cats [32-34]. Six participating clinics in the present study were able to produce individual animal-specified prescription data (data not shown). These animal-specified data, also based upon actual animal weights according to the PMS (average dog weight of 21.2 kg, average cat weight of 4.3 kg), demonstrated that dogs receive in general slightly more AMs than cats (approximately 14% more over the whole 3-year period). Differences are more prominent in the choices of AMs used, with dogs receiving more 1st and 2nd choice AMs than cats (approximately 1.3 and 1.6 times, respectively) and cats receiving explicitly more 3rd choice AMs than dogs (approximately 4 times more). To be able to optimise AMU in the future, more information is needed on the differences in AMU between dogs, cats and rabbits and on which specific indications account for the highest AMU.

Most clinics and practice management systems are not equipped to extract data on individual prescription information linked to specific indications in an automatic, uniform and feasible way. However, this detailed information is needed to optimise AMU further within companion animal clinics. Therefore, companies developing practice management systems are requested to enable this within their systems.

Slight differences in AMU appeared to be present between companion animal only and mixed-animal clinics. However, only four clinics were mixed-animal clinics, therefore this could be a coincidence. On the other hand, AMU in food-producing animals already received attention since 2008 onwards and actions were taken at different levels [19, 43]. This might have resulted in an early, increased awareness in companion animal veterinarians in mixed-animal clinics as well.

Although systemic AMU decreased and used AM classes changed during the study period, there still is room for improvement left. According to the Netherlands Veterinary Medicines Institute (SDa), continuous monitoring of AMU in companion animals is not needed so far, only once every three years [44]. However, the Dutch formulary on AMU in companion animals [16] advises proper diagnostics and, if necessary, prefers the use of 1st choice AMs over the use of 2nd and 3rd choice AMs. Therefore, present study and used calculation method could be used as a starting point for a follow-up study on the development, implementation and evaluation of an antimicrobial stewardship programme in Dutch companion animal clinics to optimise AMU.

In conclusion, this study showed a decrease and a change in systemic AMU towards more preferable AMs in 44 Dutch companion animal clinics (2012-2015). The influence of season and the distribution of different animal species per clinic were demonstrated using the number of DDDAs and $DDDA_{CLINIC}$ to quantify veterinary AMU.

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Submission declaration

This research study has not been previously published elsewhere. Preliminary data were presented at the ICOHAR congress (16-18 April 2019, poster presentation) and at the BSAVA congress (4-7 April 2019, oral presentation).

Ethical approval

Not required.

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Chapter 6

Implementation and evaluation of an Antimicrobial Stewardship Programme in companion animal clinics: a stepped-wedge design intervention study

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Abstract

To curb increasing resistance rates, responsible antimicrobial use (AMU) is needed, both in human and veterinary medicine. In human healthcare, antimicrobial stewardship programmes (ASPs) have been implemented worldwide to improve appropriate AMU. No ASPs have been developed for and implemented in companion animal clinics yet. The objective of the present study was to perform and evaluate the effectiveness of an ASP in 44 Dutch companion animal clinics.

The study was designed as a prospective, stepped-wedge, intervention study. The multifaceted intervention was developed using previous qualitative and quantitative research on current prescribing behaviour in Dutch companion animal clinics. Objectives of the ASP were to increase awareness on AMU, to decrease total AMU whenever possible and to shift AMU towards 1st choice antimicrobials, according to Dutch guidelines on veterinary AMU. The number of Defined Daily Doses for Animal (DDDAs) per clinic (total, 1st, 2nd and 3rd choice AMU) was used to quantify systemic AMU. Monthly AMU data were described using a mixed effect time series model with auto-regression. The effect of the ASP was modelled using a step function and a change in the (linear) time trend.

A statistically significant decrease of 15% (7%-22%) in total AMU, 15% (5%-24%) in 1st choice AMU and 26% (17%-34%) in 2nd choice AMU could be attributed to participation in the ASP, on top of the already ongoing time trends. Use of 3rd choice AMs did not significantly decrease by participation in the ASP. The change in total AMU became more prominent over time, with a 16% (4%-26%) decrease in (linear) time trend per year.

This study shows that, although AMU in Dutch companion animal clinics was already decreasing and changing, AMU could be further optimised by participation in an antimicrobial stewardship programme.

1. Introduction

The increase of antimicrobial resistance (AMR) is recognised as a threat for modern medicine and public health [1]. To help control AMR, responsible use of antimicrobials (AMs) is warranted and a decrease in inappropriate use of AMs is necessary, both in human and veterinary medicine [1-3].

In human medicine, the term antimicrobial stewardship programme (ASP) generally refers to specific programmes or series of interventions to monitor and direct antimicrobial use (AMU) at the hospital or primary care level [4-7]. In veterinary medicine, it usually encompasses numerous elements of improved AMU and it is often associated with country-wide surveillance of AMU and development of (inter)national guidelines on AMU [8].

In Dutch food-producing animals between 2008 and 2017, a combination of compulsory and voluntary actions resulted in a 64% reduction in AMU, a decrease in resistance rates was observed as well [9-12]. Only since the end of 2011 onwards, more attention is being paid to AMU in companion animals. Legislation (2013) on mandatory susceptibility testing for veterinary use of 3rd choice AMs, also holds for companion animals [13]. The Royal Dutch Veterinary Association pays more attention to the use of guidelines on AMU as well.

A survey on prescription data of 68 companion animal clinics in the Netherlands during 2009-2011, showed that the use of 3rd generation cephalosporins and fluoroquinolones (i.e. highest priority critically important antimicrobials for human medicine according to the World Health Organisation (WHO)) accounted for 18% of total AMU, based upon the number of Defined Daily Doses for Animals [14, 15]. During the past years, AMU in Dutch companion animal clinics has been decreasing (-19% when comparing 2012-2014) [16]. However, especially with regard to the (sub)classes of AMs used, there is still room left for improvement. According to Dutch classification of veterinary AMU, 2nd choice AMs (i.e. mainly aminopenicillins and 1st and 2nd generation cephalosporins) still accounted for 43% of total AMU and 3rd choice AMs (i.e. 3rd generation cephalosporins and fluoroquinolones) for 8% of total AMU in 2014.

Antimicrobial prescribing behaviour can only be improved if interventions are attuned to the specific situation and the target group, and factors influencing antimicrobial prescribing are taken into account [17, 18]. Qualitative research in Dutch companion animal clinics indicated that antimicrobial prescribing behaviour is influenced by four main categories of factors: veterinarian-related factors, patient-related factors, treatment-related factors and contextual factors [19]. These categories of factors were taken into account when the intervention elements of present study were developed. The aim of this study was to perform and evaluate the effectiveness of such a customised ASP, aiming to improve antimicrobial prescribing, in 44 Dutch companion animal clinics.

2. Material and methods

2.1. Study design

The Antimicrobial Stewardship and Pets-study (ASAP) was designed as a prospective, stepped-wedge intervention study aiming to optimise antimicrobial prescribing in Dutch companion animal clinics by implementing an antimicrobial stewardship programme. The intervention study was performed from March 2016 until March 2018.

2.1.1. Time schedule

Clinics, divided into four clusters, were offered all separate intervention elements of the ASP. The period considered as the actual "intervention period" comprised 12 months: from start of implementation of the ASP (i.e. filling in patient evaluation forms) up to 4-5 months after the feedback meeting (i.e. when clinics started filling in patient evaluation forms for the second time). Time schedule of the applied stepped-wedge design is shown in Figure 1. First clinics were contacted in December 2015, their intervention period started in March 2016. The intervention period of the last cluster started in January 2017. Clinics were grouped into four clusters based on their geographic location.

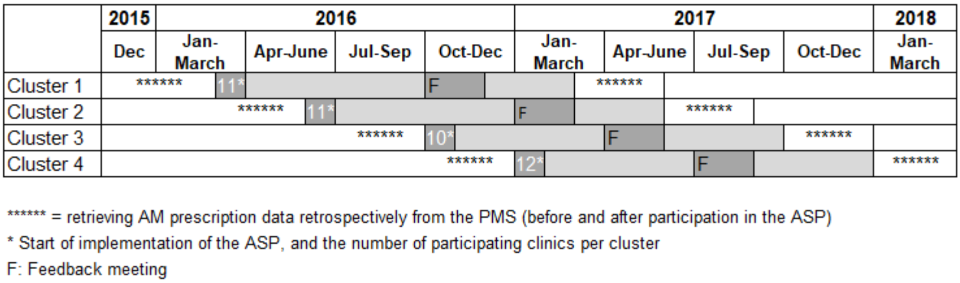

Figure 1: Time schedule of the applied stepped-wedge design, indicating the start and the duration of the period considered as the "intervention period" for the four separate clusters of participating clinics.

2.2. Participating clinics

2.2.1. Sample size

The study aimed at including at least 40 clinics. This number was based on a power calculation which indicated that with 40 clinics a minimal change of 8% in mean total AMU could be detected with a power of 0.80 (=beta) and a significance of 0.05 (=alpha) over a one-year period. Calculations were based on AMU data at clinic level from an earlier conducted study [15].

2.2.2. Clinic selection

Companion animal clinics were approached for participation using the database of the Royal Dutch Veterinary Association (KNMvD) containing all Dutch veterinary clinics. Clinics were sampled based upon previous shown interest to participate in a study on optimisation of AMU in companion animal clinics and on geographic location.

Clinics were invited by e-mail, followed a week later by a phone call to answer questions and to arrange a visit. Ultimately, clinics were only included when the Practice Management System (PMS) appeared to be able to provide information on antimicrobial prescription data specified for companion animals on a monthly basis. Clinics treating companion animals only and so-called 'mixed clinics' (i.e. clinics treating companion animals and non-companion animals, but with separated companion and non-companion animal prescription data) were included.

Clinics were offered a financial compensation, which was based upon estimated time investment per clinic and a standard hourly tariff for veterinarians. Educational training included in the ASP was accredited as professional continuing education for participating veterinarians.

The study was exempt from ethical approval as no animal experiments were involved. Participating veterinarians remained fully autonomous in their daily practice. Before enrolment, all clinics received written and oral information on the purpose of the study. Every clinic signed an informed consent to confirm their commitment to participate and to give permission for the use of their patient data for research purposes after anonymisation.

2.3. Applied intervention approach

A stewardship programme to optimise AMU was developed based upon previous qualitative research [19] and field experiences from co-authors involved in human medicine. Objectives of the ASP were to increase awareness on AMU, to decrease total AMU whenever possible and to shift AMU towards 1st choice agents, which is according to current guidelines on AMU. Cues from the RESET Model to change human behaviour were used; Rules & regulations, Education & information, Social pressure, Economics, and Tools [20, 21]. A so-called Support-Team (S-Team) was assembled, in the analogy of the human Antibiotic Stewardship-Teams (A-team) [22, 23]. The S-team included a veterinary microbiologist, a veterinary specialist in internal medicine of companion animals, a veterinary pharmacologist, a hospital pharmacist and the project leader. The S-Team members were involved in the different elements of the ASP (Table 1). Dutch classification of veterinary AMU (Table 2), current Dutch guidelines (on otitis externa, urinary tract infections and skin infections) and formulary on veterinary AMU, and legislation on mandatory susceptibility testing for veterinary use of 3rd choice AMs were used as treatment standards during the ASP [13, 24-26].

Table 1: Separate intervention elements as offered during the ASP, including when they were offered, who were involved and the estimated time investment for participants.

Intervention element	When	Who are involved	Estimated time investment
1) Filling in (preferably) 100 patient evaluation forms per clinic; to reflect on own AM prescribing behaviour	At the start of the intervention period & at the end	Veterinarians	2-5 minutes per evaluation form
2) Post educational training 1; on AMR, international and national regulations, and guidelines on responsible AMU	Month 1	Veterinarians and 2 S-Team members	2.5 hours
3) Exercise to write down own AM prescribing behaviour; to compare it with current guidelines and to discuss it with colleagues	Between post educational training 1 & 2	Veterinarians within the same clinic	2 hours
4) Post educational training 2; on behavioural change and communication skills towards companion animal owners	Month 4	Veterinarians, veterinary nurses, 2 S-Team members and 1 communication trainer	2.5 hours
5) Commitment form; to sign within the clinic, committing to use AMs responsibly	After post educational training 2	Veterinarians and veterinary nurses	0.5 hour
6) Benchmarking of quantitative AMU data	During post educational training 1 and the feedback meeting	Veterinarians and S-Team members	
7) Information leaflet for companion animal owners on responsible AMU and AMR	During participation in the intervention programme	Veterinarians and veterinary nurses	
8) Asking questions to the S-team members, on AMU and AMR, via email or phone call	During participation in the intervention programme	Veterinarians and S-Team members	
9) Feedback meeting; every clinic was visited once, clinic based feedback was given on all gathered data on AMU (1, 3 and 6). Clinic specific AMU objectives were defined, questions were answered and topics on AMU and AMR were discussed	Month 8	Veterinarians and 2 S-Team members	2-3 hours

2.4. Data collection and management

Participating clinics supplied clinic population data and monthly antimicrobial veterinary medicinal product (AVMP) prescription data. Information on the composition of the clinic's animal population (represented by the number of dogs, cats and rabbits attending the clinic at least once in a specified 3-year period) and monthly AM prescription data were retrieved retrospectively from the PMS, once before participation in the ASP and once after participation in the ASP.

2.5. Outcome measures

The primary outcome measure was total AMU. AMU was further classified into 1^{st}, 2^{nd} and 3^{rd} choice AMU (Table 2) [26].

Systemic AMU was quantified as described and discussed in detail in previous study [16] and is comparable with the Defined Daily Dose Animal ($DDDA_{VET}$), a measure suggested by the European Surveillance of Veterinary Antimicrobial Consumption group (ESVAC) [27, 28]. In summary, a $DDDA_{CLINIC}$ of 0.25 per month means that the average dog, cat and rabbit in the clinic was treated with antimicrobials for a 0.25 day per month. Per clinic, total $DDDA_{CLINIC}$ was calculated per month and specified with 1^{st}, 2^{nd} and 3^{rd} choice AMU.

Mean absolute AMU numbers are presented for 24-12 months and 12-0 months prior to start of the intervention period and for a period of 12 months considered as the actual intervention period, taking one month transition time into account.

In the present study, only systemic (i.e. oral or parenteral) AMU was described. AMs applied topically were excluded from analyses.

Table 2: Classification of veterinary AMU according to Dutch policy on veterinary AMU [26].

Classification	Reasoning	Main classes of AMs
1^{st} choice	Empirical therapy; Do not select for (to current knowledge), nor are specifically meant for treatment of ESBL-producing micro-organisms.	Tetracyclines, nitroimidazoles, narrow-spectrum penicillins, trimethoprim, sulfonamides, lincosamides and phenicols.
2^{nd} choice	All AMs not classified as 1^{st} or 3^{rd} choice AMs; Use of these AMs might select for ESBL-producing bacteria or is specifically indicated in case of an ESBL-infection.	Aminopenicillins (with/without beta-lactamase inhibitors), 1^{st} and 2^{nd} generation cephalosporins, aminoglycosides and colistin.
3^{rd} choice	A selection of Highest Priority Critically Important AMs for human medicine according to WHO; By Dutch law restricted to use only in individual animals and after culture and susceptibility testing.	Fluoroquinolones, 3^{rd} and 4^{th} generation cephalosporins.

2.6. Statistical analysis

A mixed effect time series model was used to describe monthly AMU from 12 months before until 12 months after the introduction of the ASP, that allowed for a linear trend over time, while seasonal patterns were modelled using Fourier (sine- and cosine-) terms. AMU appeared to follow an approximate log-normal distribution and therefore log-transformed AMU-data were used as the dependent variable. As a result, presented models estimate geometric mean (GM) AMU. Geometric mean ratios (GMRs; the ratio of two GMs) are used to quantify effects (e.g., the ratio of the GM during the intervention period to that before the intervention period).

The effect of the intervention was modelled using a step function and by modelling a change in the (linear) time trend. For each clinic, a dummy variable was included to indicate the month the ASP was introduced, because AMU in that month could not be unambiguously assigned to either the pre- or post-intervention period (transition period).

Heterogeneity in baseline AMU, time trends, seasonal patterns, and intervention effects across different clinics were modeled using (correlated) random effects. Short-term time series dynamics were accounted for by an auto-regressive (AR1) structure and the residual variance was allowed to be different for each clinic.

The estimated average intervention effects (i.e. the stepwise change and change in time trend) across clinics are reported. The model was used to evaluate the overall effect of the ASP for total, 1^{st}, 2^{nd} and 3^{rd} choice AMU separately. Effects are expressed as GMRs and (alternatively) as proportional decreases in use. P_{WALD} values are used to indicate whether the separate coefficients are significantly different from 0, P_F values are used to indicate the significance of the overall intervention effect.

SAS (SAS 9.4, SAS Institute, Inc. Cary, NC, USA) was used to organise the data and the nlme package (version 3.1) in R (version 3.5) was used to perform the statistical analyses.

3. Results

3.1. Participating clinics

In total, 54 clinics were contacted to participate. Six of these clinics were not willing to participate and four clinics were excluded, because their PMS appeared not suitable to provide monthly prescription data. Finally, 44 clinics were included in the study.

Table 3 provides a summary of characteristics of participating clinics. All clinics could provide AMU data prior to the introduction of the stewardship programme for a minimum of 25 months, with the exception of one clinic, which could only provide data for 13 months prior to the introduction of the ASP.

Data of 41 clinics were included in the data analysis. Three clinics were excluded from data analysis, because one clinic was lost to follow-up (unspecified reason) and two clinics had substantial changes in their clinic's animal composition (i.e. one clinic closed and one clinic opened an extra location with the same PMS making AMU calculations unreliable).

Table 3: Mean (range) or distribution of characteristics of 44 clinics participating in the ASP.

Characteristic (number of clinics = 44)	Mean (range)
Number of dogs	2151 (14 - 5353)
Number of cats	1910 (350 - 5113)
Number of rabbits	271 (0 - 797)
Number of veterinarians treating companion animals	2.7 (1 - 8)
Mean work experience per clinic (years)	16.2 (5.8 - 34)
Characteristic (number of clinics = 44)	**Distribution**
Companion animals only versus mixed-animal clinics	40 / 4
Urban, rural or urban-rural	29 / 14 / 1

3.2. Outcomes

3.2.1. Mean, absolute AMU (total, 1^{st}, 2^{nd} and 3^{rd} choice AMU)

Mean total AMU was 0.134 and 0.132 DDDA/month, respectively, in the two years prior to implementation of the ASP and decreased to 0.114 DDDA/month during the period considered as the intervention period (Table 4). Similar decreasing trends were seen for 3^{rd} choice AMU (i.e. fluoroquinolones and 3^{rd} generation cephalosporins) and 2^{nd} choice AMU (i.e. mainly aminopenicillins, with and without clavulanic acid). AMU shifted towards more 1^{st} choice AMU.

Table 4: Mean absolute AMU in numbers of DDDA/month (and percentage of total AMU) of total, 1^{st}, 2^{nd} and 3^{rd} choice antimicrobials in participating clinics before and during participation in the ASP.

Classification of antimicrobials[1]	Pre-ASP period (24-12 months)	Pre-ASP period (12-0 months)	During participation in the ASP (2-13 months)
First choice (% of total)	0.059 (44.1%)	0.060 (45.5%)	0.066 (57.8%)
Second choice (% of total)	0.064 (47.6%)	0.063 (48.0%)	0.045 (39.2%)
Third choice (% of total)	0.011 (8.3%)	0.009 (6.5%)	0.003 (3.0%)
Total DDDA per month (SD)	0.134	0.132	0.114

[1] according to Dutch policy on veterinary AMU (Table 2)

3.2.2. Intervention effect

As a result of participation in the ASP a stepwise decrease was estimated for total, 1st and 2nd choice AMU of 15% (95%CI: 7%-22%; p<0.01), 15% (95% CI: 5%-24%; p<0.01) and 26% (95% CI: 17%-34%; p<0.01) respectively. No statistically significant effect was estimated for 3rd choice AMU. The change in (linear) time trend was statistically significant for total AMU only with an additional 16% decrease over the year (95% CI: 4%-26%, p=0.01) (Table 5).

As absolute figures for 1st choice AMU were increasing (not visible from Figure 2, because the trend before the ASP was set at 100%), the net effect of the stepwise decrease in 1st choice AMU is a smaller increase in use than was expected based upon the pre-intervention time trend for 1st choice AMU.
Although AMU decreased in the majority of clinics, there were considerable differences in estimated intervention effects between clinics (Figure 2).

Table 5: Stepwise change and change in (linear) trend of total, 1st, 2nd and 3rd choice AMU. Reported effects are averaged estimates of 41 participating clinics, from a random effects model that includes a (linear) time trend and seasonal effects, and allows for heterogeneity of effects between clinics and residual auto-correlation. Effects are expressed as GMRs and (alternatively) as proportional decreases in use.

Classification of antimicrobials[1]		GMR (95% CI)	% Decrease	P_{WALD}	P_F
First choice	Stepwise change in use	0.85 (0.76-0.95)	15% (5% to 24%)	<0.01	<0.01
	Change in (linear) trend (/year)	0.92 (0.74-1.13)	8% (-13% to 26%)	0.41	
Second choice	Stepwise change in use	0.74 (0.66-0.83)	26% (17% to 34%)	<0.01	0.01
	Change in (linear) trend (/year)	0.85 (0.69-1.04)	15% (-4% to 31%)	0.12	
Third choice	Stepwise change in use	0.94 (0.72-1.23)	6% (-23% to 28%)	0.66	0.62
	Change in (linear) trend (/year)	0.78 (0.46-1.32)	22% (-32% to 54%)	0.35	
Total	Stepwise change in use	0.85 (0.78-0.93)	15% (7% to 22%)	<0.01	<0.01
	Change in (linear) trend (/year)	0.84 (0.74-0.96)	16% (4% to 26%)	0.01	

[1] according to Dutch policy on veterinary AMU (Table 2)

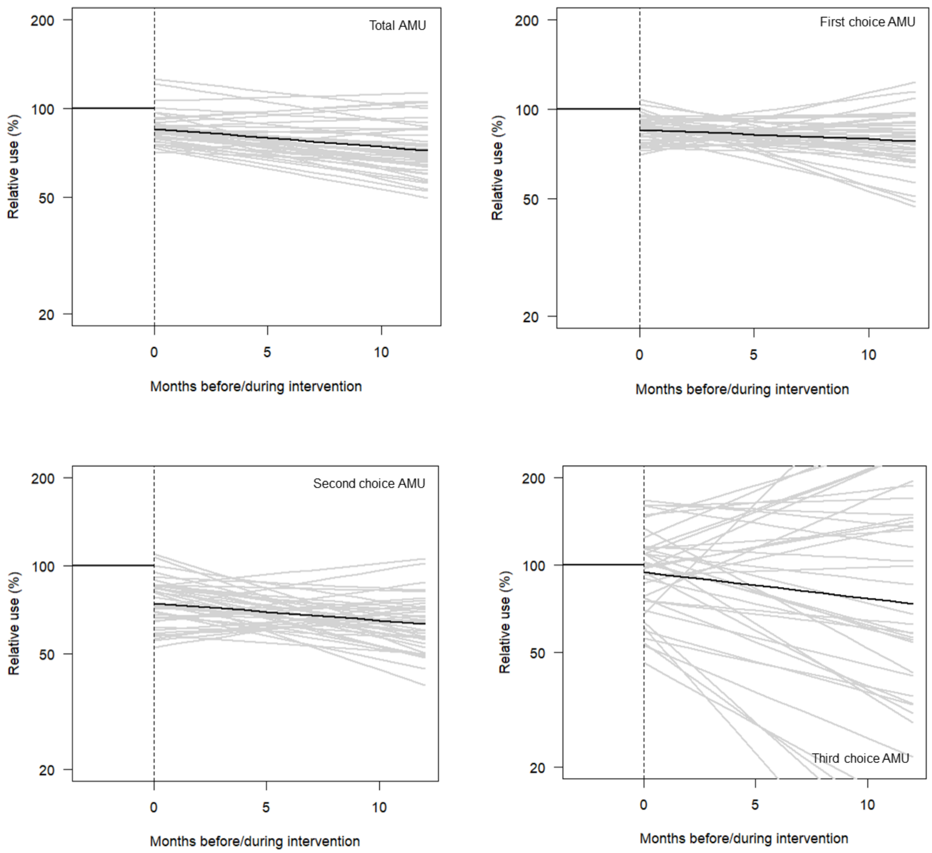

Figure 2: Average and clinic-specific effects of the ASP on total, 1st, 2nd and 3rd choice AMU. Combined effect of participation in the ASP (stepwise change & change in time trend) is shown for the average effect (black) and for each individual clinic (grey) after standardisation to the estimated AMU before the intervention period (as 100%).

4. Discussion

A strong and statistically significant decrease in total, 1st and 2nd choice AMU was observed in a sample of Dutch companion animal clinics, with a shift towards use of 1st choice antimicrobials, that could be attributed to participation in an antimicrobial stewardship programme (ASP). The change in total AMU became more prominent over time after introduction of the ASP.

The results of the statistical model indicate that 1st choice AMU decreased. However, absolute 1st choice AMU increased during the intervention period. Therefore, after introduction of the ASP, the nett effect is a less pronounced increase in use of 1st choice

AMs than was expected. The statistical model used to estimate the intervention effect, assumed a linear, random time trend per clinic and a stepwise reduction in AMU after adjustment for seasonal effects. The stepwise effect was observed in the majority of clinics. No statistical significant effect on 3rd choice AMU could be attributed to participation in the ASP. This is likely explained by the fact that 3rd choice AMU was already significantly reduced in the years preceding the ASP [29], and because 3rd choice AMU was already rather low, a further decrease as result of the ASP is difficult to demonstrate due to lack of statistical power.

Goal of the ASP was to increase awareness on AMU, to decrease total AMU whenever possible and to shift AMU towards 1st choice AMs, according to Dutch guidelines on veterinary AMU [24, 26]. The observed changes as result of the ASP are in line with these objectives and therefore considered relevant.

A strength of the design of the present study is that repeated monthly measurements per clinic were involved, which allowed to control intervention effects for baseline levels and ongoing time trends. By starting the ASP at different timepoints for the four different clusters of clinics, the probability that the overall effect was influenced by external events was minimised (e.g., increased attention on responsible AMU in general) [6].

As a possible limitation of present study, it could be argued that overall AMU is a non-specific measure without information on appropriateness of AM therapy, as is the case for looking at 1st, 2nd and 3rd choice AMU [6, 30, 31]. Moreover and more important, an increase in quality of AMU can be reached without a reduction in AMU (or even with an increase in AMU), e.g., by using more 1st choice AMs instead of 2nd or 3rd choice AMs, or by using better dosing [6, 32, 33]. On the other hand, as any use of AMs selects for AMR, any reduction of AMU that can be achieved by improving adherence to current guidelines (by definition appropriate AMU) is an advantage, as is the case for using 1st instead of 2nd or 3rd choice AMs. The persistence of the effect during the follow-up period of 12 months (especially of total AMU with a significant change in linear time trend) suggests sustainability of the changes in AMU. However, repeated AMU-measurements in the nearby future are needed to evaluate the sustainability over a longer period of time.

A second limitation is the fact that participating clinics were contacted approximately 2-3 months before actual start of the ASP. This could have led to a change in AM prescribing behaviour already, because clinics knew their AM prescribing behaviour would be monitored. These 2-3 months are part of the "baseline measurement period". As a result, the intervention/ASP effect could have been slightly diminished [6, 34]. Another potential weakness of the stepped-wedge design is contamination of the interventions [6].

Information, insights or effects from clinics already having started the ASP could have influenced clinics still in the baseline period. Because participating clinics were clustered based on their geographic location, this effect was expected to be minimal, but could not be excluded.

The representativeness of the participating clinics for the whole country might be questioned. These 44 clinics were not randomly selected but selection was based upon willingness to participate. It is possible that participating clinics already had a more responsible attitude towards AMU and had more motivation to change their AM prescribing behaviour compared to other, not-participating clinics. On the other hand, results of the present study might also be regarded as a proof of principle. If even in clinics that already had an interest in responsible AMU, optimisation of AMU could be attained, clinics with less interest in responsible AMU might be able to change even more. However, and irrefutable, it will be harder to change behaviour of veterinarians who do not believe that responsible AMU is a desirable or necessary behaviour [19, 20, 35].

AM prescribing behaviour is influenced by many factors. Multifaced interventions, attuned to the specific setting and influencing factors of AMU are advised to optimise AM prescribing behaviour [7, 8, 18, 19, 36-38]. The present ASP was based upon a previous qualitative study and the RESET model, containing the most important cues to change human behaviour [19, 20]. Only 'Economics', covering profits and costs, bonuses and penalties, as factor influencing prescribing behaviour was not addressed directly in the ASP. However, the importance of economics was discussed (e.g., the difference between earning money because of prescribing AMs versus performing further diagnostics). Besides, clinics were aware of possible inspections by the Dutch Food and Consumer Product Safety Authority (NVWA) of the Dutch Government, possibly leading to financial penalties in case of prescribing 3rd choice AMs without culture and susceptibility testing.

The present study showed that the set of interventions worked. An important question to answer is which intervention might work best in a chosen setting, which in general depends on the local barriers [39]. Identifying which elements of the ASP worked best and were experienced as most useful, should be done based upon evaluation of the ASP by participants and in consultation with other stakeholders [40].

The present ASP tried to address many different persons involved in AMU [8]. However, important stakeholders, e.g., pharmaceutical companies, were missing. These companies could support veterinarians by developing more convenient 1st choice AMs and alternative treatment options (without AMs), which was confirmed by participants and was shown in previous research [19].

Conclusion

Participation in a multifaceted antimicrobial stewardship programme to optimise AMU in companion clinics, showed a positive effect on AMU in Dutch companion animal clinics. For future and feasible, large scale implementation, the most effective and efficient parts of the ASP need to be selected.

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Declaration of interest

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Submission declaration

This research study has not been previously published elsewhere. An oral presentation was held during the BSAVA-congress and the European Veterinary Conference Voorjaarsdagen (both in April 2019).

Author contributions

NH, MH, DH, TV, JW, JP, TB, LS, IvG and EB contributed to the concept of the study. NH was responsible for execution of the project and data collection. TB, LS, IvG and EB were involved in project activities as well. LP, DH and NH performed the data analysis. All authors contributed to the writing and revising process of the manuscript.

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Chapter 7

General discussion

The overall objective of this thesis was to develop, to implement and to evaluate the effectiveness of an “antimicrobial stewardship programme” (ASP) to optimise antimicrobial use in companion animals, to protect both animal and human health.

To facilitate development of the ASP, factors influencing antimicrobial prescribing behaviour, and attitudes towards and perceptions on antimicrobial use and antimicrobial resistance were, both qualitatively and quantitatively studied. A method to quantify antimicrobial use was introduced to enable comparison of clinics over time and with each other (benchmarking). Results from these studies, together with recent literature and input from experts in the human field, were used to develop, implement and evaluate the effectiveness of the ASP in 44 Dutch companion animal clinics.

Main findings of this thesis

In Chapter 2, a conceptual model on factors influencing antimicrobial prescribing behaviour indicated four major categories of influencing factors; veterinarian related factors, patient-related (i.e. owner- and pet-related) factors, treatment-related factors (i.e. alternative treatment options and antimicrobial related factors) and contextual factors (i.e. professional interactions, further diagnostics and environmental factors). Opinions on the importance of antimicrobial resistance (AMR) and responsible antimicrobial use (AMU) in companion animals appeared to differ considerably between interviewed veterinarians.

Chapter 3 describes a Categorical Principal Component Analysis (CATPCA) to identify associations between attitudes and perceptions on AMU and AMR. The CATPCA revealed three “attitudinal profiles” (dimensions): “social responsibility”, “scepticism” and “risk avoidance”, which were associated with several, different demographic characteristics.

Chapter 4 describes AMU using yearly procurement data from 100 Dutch veterinary clinics, expressed as the number of Defined Daily Doses for Animals (DDDAs). Results showed a significant decrease in total AMU from 2012 to 2014. A shift in used classes of AMs was seen as well, with a statistically significant decrease in 2nd and 3rd choice AMU and an increase in 1st choice AMU, when comparing 2012 and 2014. Although AMU was relatively low and decreased during the study, large differences in AMU between clinics and used AM classes were present.

In Chapter 5, baseline information is shown for companion animal clinics selected for participation in the ASP. The monthly prescription data from the 44 included Dutch companion animal clinics (July 2012-June 2015) showed time-trends comparable with findings in Chapter 4 (based on a larger sample of clinics). Statistical modelling indicated that total, 2nd and 3rd

choice AMU decreased over time, whereas 1st choice AMU increased. Strong seasonal differences in AMU were found, with highest AMU in July-August and lowest in February-March. The distribution of different animal species per clinic appeared to affect AMU as well.

In Chapter 6, the effect of participation in an ASP was evaluated in the 44 clinics from Chapter 5. A clear and statistically significant decrease in total, 1st and 2nd choice AMU was observed, attributable to participation in the ASP.

Why is Antimicrobial Stewardship important in companion animals?

Absolute amounts of antimicrobials (AMs) used in companion animals are considerably lower than in food-producing animals [1, 2]. Based upon sales data, AMU in Dutch companion animals and horses combined was estimated at 4,163 kg in 2018, compared to 157,211 kg (registered) AMU in all food-producing animals combined (i.e. in the Dutch veal, broiler, turkey, cattle, pig and rabbit farming sectors). This comparison, based upon kilograms of AMs, does not take dosing differences between AMs into account and should therefore be made with caution. The observed difference in kilograms can partially be explained by the relatively low number of companion animals compared to the number of food-producing animals in the Netherlands [3-5]. However, when using the number of Defined Daily Doses for Animals (and therefore taking potency of AMs into account (Chapter 4)), similar conclusions can be drawn. In 2014, the estimated AMU in 100 Dutch companion animal clinics (Chapter 4; 1.88 DDDA/year) was considerably lower compared to the calculated AMU in most food-producing animal species (cattle 2.44 DDDA_{NAT}/year, pigs 9.52 DDDA_{NAT}/year, veal calves 21.15 DDDA_{NAT}/year and broilers 15.76 DDDA_{NAT}/year) [6, 7]. Although based upon the same method to quantify AMU, cross species comparisons should be interpreted with caution.

Since absolute and relative AMU in companion animals is relatively low, it raises the question: why is antimicrobial stewardship important in companion animals?

1) Treatment failure in the individual companion animal

"I have seen too many dogs suffering from MRSP after multiple AM courses in which euthanasia was the only treatment option left….." (quote from a participating veterinarian in the ASAP-project)

It should be considered that AMR in animal pathogens may lead to treatment failure with a direct effect on animal health and welfare. Over the last decade, there has been an increase in resistance rates in pathogens isolated from companion animals [8-11].

Infections with resistant bacteria, e.g., methicillin resistant *Staphylococcus pseudintermedius* (MRSP), might be more difficult to treat. They might lead to treatment failure, additional diagnostic work-ups, more expensive treatments, more visits to a veterinarian, use of highest priority Critically Important AMs (CIAs) or use of AMs not registered for veterinary use, resulting in more adverse effects [12-15]. Additionally, the veterinarian could be facing an ethical dilemma: "should AMs that are (highly) critical for treatment of infections with multi-resistant bacteria in human medicine [16], be used in companion animals at all?" AMR might lead to situations in which euthanasia is the only alternative [15]. Therefore, AMR and resulting treatment failure might have negative social consequences, both for the companion animal owner and for the veterinarian.

2) Occupational risk and risk for companion animal owners

Companion animals can act both as source and reservoir of resistant bacteria. This might pose an occupational risk to veterinarians and veterinary technicians. E.g., in case of methicillin resistant *Staphylococcus aureus* (MRSA) or MRSP, veterinary staff and owners of infected companion animals have an increased risk of MRSA and MRSP carriage [14, 17-19]. "Outbreaks" of resistant bacteria might also lead to stricter infection control measures, requiring more attention and logistic adjustments, they could have financial consequences and result in turmoil [20]. In food-producing animals a reduction in AMU was followed by a reduction in resistance among indicator bacteria [21-23]. Based on these data it could be expected that responsible AMU in companion animals would be associated with reduced selection for resistant organisms as well. Subsequently, exposure of veterinarians, veterinary technicians and owners to resistant bacteria would decrease.

Precautionary principle

Any AMU might select for resistance in the bacterial strain causing infection, as well as in the patient's commensal microbiota [21, 24-26]. There are no major known outbreaks of AM resistant bacteria in humans, resulting from companion animals yet, but that does not exclude possible outbreaks in the future. Therefore, precautionary measures to reduce misuse and overuse of AMs are recommended, even when present scientific evidence proving transmission from resistant bacteria from companion animals to their owners is limited. This line of reasoning is based upon the so-called "precautionary principle", which has been politically accepted as a risk management strategy involving the protection of the environment and human, animal and plant health and safety [27]. It was one of the key drivers of the AM reduction policies in food-producing animals in the Netherlands [28].

In conclusion, care for the individual patient and people owning and/or exposed to companion animals should be the main reasons to use antimicrobials responsibly, also in companion animal clinics.

Quantifying AMU in companion animals

To be able to evaluate effects of measures to reduce and optimise AMU, like implementing an ASP (Chapter 6), transparency and quantification of AMU is an essential prerequisite.

Both in human and veterinary medicine, different methods, indicators and datasets are currently applied to measure AMU, which might result in substantial variation in outcomes [23, 29, 30]. To enable comparison of AMU at an (inter)national level, one of the recommended metrics for AMU, the Defined Daily Dose (DDD), was introduced in human medicine [23, 30-32]. In food-producing animals, the Defined Daily Dose Animal (DDDA) as measure to quantify AMU was introduced in monitoring AMU in the Netherlands [33-35]. Prescription data used to calculate the number of DDDAs are derived from databases of the various quality systems involved in the different food-producing animal sectors. Data on the number of animals present at the farm are linked to these prescription data as well. As these prescription data are provided on farm level, it is feasible to allocate the prescribed antimicrobial veterinary medicinal products (AVMP) to specified animal species. A central way of registering AM prescription data is currently only in use for food-producing animals. For companion animals, data on AMU are much harder to retrieve, because this sector is organised in a different way than the food-producing animal sectors and without central registration of data. In Chapter 4, a method to quantify AMU in companion animals, based on the number of DDDAs, is introduced, which was used in Chapter 5 & 6 as well. Data extraction and processing from different practice management systems, with different ways of data management, appeared to be a complex, time-consuming and tedious process. By using a central registration of prescription data, this process might become automated resulting in more uniform data formats. If new EU legislation on collecting AMU data at companion animal level comes into effect in 2029 [36], a more standardised way of organising and collecting AMU is required. Establishing this will be a mission for the companion animal clinics the upcoming years.

Besides quantifying AMU in a transparent way, measuring quality or appropriateness of AMU is important as well. To be able to optimise AMU and to evaluate the effect of implementation of antimicrobial stewardship, the ability to measure quality of AMU is necessary [37]. Several sets of guidelines, quality indicators and checklist are in use to measure appropriateness of AMU, mainly in hospitalised patients [37-43]. Some examples of indicators of appropriate AMU are: use of AMs to which the pathogen is sensitive and which are recommended in the treatment guidelines, taking blood cultures and cultures from the site of infection (prior to start of systemic AM therapy), documentation of an AM plan (which includes indication, name, dose, route and interval of administration) and discontinuation of AM-therapy if infection is not confirmed.

In the Netherlands, only three treatment guidelines for companion animals are available to date (on the diagnostic work-up and treatment of urinary tract infections, skin infections and otitis externa (available since 2014-2015)). A formulary on AMU in companion animals indicating if AMs are needed, and if so, which AMs are recommended as 1st, 2nd or even 3rd choice options, is available as well [44-46]. Finally, the specific product characteristics (SPC) are guiding dosage and course length of the used AVMP. No other checklists or quality indicators currently exist for companion animals. As a result, total, 1st, 2nd and 3rd choice AMU and their proportions as used in companion animal clinics, compared with the formulary and advises in the guidelines, are the only distinct and feasible criteria available to estimate the appropriateness of AMU.

When using the (total) number of DDDAs as an indicator of appropriateness of AMU, an increase in quality of AMU could potentially be reached without a reduction in the number of DDDAs or even with an increase (e.g., because of better dosing according to the SPC). Additionally, the classification of AMs into 1st, 2nd and 3rd choice AMs, is not based upon effectiveness of AMs, but on the possibility to select for ESBLs. The CIA-list of WHO was taken into consideration as well [16]. More importantly, the number of DDDAs as single outcome variable does not indicate whether an individual patient (i.e. dog, cat or rabbit) received the most optimal treatment.

Possible parameters to assess individual patients outcomes in companion animals, based upon parameters used in human medicine, could be: the number of re-consultations, the number of cases in which treatment prolongation or adjustment was necessary and mortality rates [47-51]. Therefore, detailed information on the individual patient and follow-up is needed. However, data on therapy evaluation is not standardly collected and registered.
During implementation of the ASP in 44 Dutch companion animal clinics, veterinarians were asked to fill in patient evaluation forms as an exercise to reflect on their own AMU (Chapter 6). Last question in this form was on therapy evaluation. Large differences between clinics were observed in if, and how, therapy evaluation is performed. In some clinics a phone call with the owner or a re-consultation at the end of an initiated therapy was regarded as 'standard', whereas in other clinics no active therapy evaluation occurred. Likewise, differences in attitudes of companion animal owners were observed. Some owners preferred to have a check-up at the end of a therapy, while others did not. Here, a disadvantage in companion animal clinics might be the fact that companion animal owners are free to visit any companion animal

clinic, contrary to the situation in food-producing animals in the Netherlands. In Chapter 4, e.g., discrepancies between the number of dogs registered in veterinary clinics versus official estimates in the Netherlands, might have resulted from the same phenomenon, i.e. dog owners visiting more companion animal clinics. As a result, unsatisfied owners (no matter what the exact reason) might decide to go to another companion animal veterinarian, making therapy evaluation even more difficult. To be able to evaluate the appropriateness of AMU and to assess individual patient outcomes, a better patient follow-up is needed. This will involve efforts from companion animal veterinarians, veterinary technicians and companion animal owners.

Quantification of topically used AMs

For systemically used AMs it is known that they might select for AMR in the intestinal tract and on the skin, which is one of the main reasons they are monitored. Evidence shows that exposure to topical AMs could lead to selection of AMR as well [52, 53], albeit mainly on the location where they are applied. At this moment topical AMs are not included in the quantification of AMU in companion animals [1, 2]. These topical treatments may represent only a minority of total AMU [54], but exact data are lacking. Monitoring of topical treatments is of interest, because of the local selection of AMR and the possible direct skin exposure for the owner when applying these treatments. Topically applied AMs, e.g., in ears, could reach higher concentrations, and therefore be effective, even when susceptibility results indicate resistance [55]. Therefore, although topically used AMs are not monitored so far, it will be of great interest for future research to study: "which and how many topical AMs are currently used in companion animal clinics and how should topically applied AMs be quantified in an objective way?". This research question might be the topic of a follow-up research on a dataset from the 44 companion animal clinics participating in the ASP. This is of particular interest as the majority of topically applied AMs are used to treat otitis externa or cases of skin infections. Specifically for these indications, guidelines are available and therefore treatment appropriateness according to guidelines can be assessed.

Evaluation of participation in the Antimicrobial Stewardship Programme

To evaluate participation in the ASP introduced during the ASAP-project, an internet-based questionnaire was developed, based upon Hulscher et al. (2013) [56] and Kreuwel et al. (2013) [57]. The objective was to explore experiences and opinions of participants (i.e. both veterinarians and veterinary nurses), of which a summary of the results are presented here. During the ASP, separate intervention elements were offered to all participating clinics, consisting of:

1) two post educational trainings, 2) clinic specified, context based feedback on AM prescribing behaviour, 3) a “commitment” form, as public declaration committing to use AMs responsibly and 4) an information leaflet for companion animal owners. A “Support-Team” (S-Team) was assembled by analogy with the human Antibiotic Stewardship-Teams [31, 41]. Members of the S-Team were involved in all separate intervention elements.

Sixty-five veterinarians and nurses completed the questionnaire; the majority (completely) agreed to use AMs more responsibly after participation in the ASP. Financial compensation for participation was only regarded by a minority (18%) as an important argument to participate and majority of the participants would still participate in the stewardship programme in case there would be no financial compensation for the clinic. Filling in patient evaluation forms was experienced as useful, although it was explicitly mentioned as time-consuming by several participants.

The majority of the participants could mention at least three changes in AMU after participation in the ASP, a very limited selection of the numerous changes that were mentioned:

“*We use less AMs in general, because of the use of more diagnostics and alternative treatment options without AMs*” (veterinarian);

“*Use of shorter AM-courses, combined with therapy evaluation*” (veterinarian);

“*Well considered use of ear ointments in case of an otitis externa. Most of the times, these ears appear to be a consequence of an atopic dermatitis or it involves a yeast infection, so AMs are not indicated!*” (veterinarian);

“*Everyone is more aware of AMU. We now have ways to explain AMU and chosen treatment options more clearly towards clients*” (veterinary nurse);

“*Awareness that selection in the intestinal tract is an important consequence of oral AMU*” (veterinarian).

At the end of the questionnaire, several participating veterinarians stated that “*Reflecting on own AM prescribing behaviour, learning from colleagues and discussing on responsible AMU and AMR can be fun!*”.

Intervention elements 1 (post educational trainings) and 2 (feedback meeting) were considered most useful and helpful in improving awareness on AMU and optimising AM prescribing behaviour. Elements 3 (the commitment form) and 4 (information leaflet for companion animal owners) scored lowest.

It is important to mention that evaluation of the ASP was based upon individual opinions, whereas AMU outcomes (total, 1^{st}, 2^{nd} and 3^{rd} choice AMU, as described in Chapter 5 & 6) were clinic based. Therefore, possible associations between personal opinions and experiences on one hand, and AMU outcomes on the other hand, could not be studied.

Recommendations for the future

Although a decrease in AMU and a shift towards 1^{st} choice AMs was observed before participation in the ASP and even more thereafter, clear differences in AMU between clinics were present, both in quantitative and qualitative AMU. As an example, in 2014, the difference in total AMU was 20-fold when comparing minimum and maximum AMU, based upon procurement data of 100 clinics (Chapter 4). With regard to 3^{rd} choice AMs this difference was even larger. Five clinics reported no 3^{rd} choice AMU, whereas the maximum use was 0.70 $DDDA_{CLINIC}$. More importantly, we only included 44 companion animal clinics in the intervention study (estimated to be approximately 4% of the total number of companion animal clinics in the Netherlands [5]). Therefore, a large number of companion animal clinics was not reached yet. These clinics are possibly less aware of or might not agree with the importance of responsible AMU in companion animals. Therefore, more companion animal veterinarians as well as other key players in the field should be motivated to optimise AMU in companion animal clinics.

Based upon the evaluation of the ASAP-project as described earlier, an e-learning module will be developed to be offered on a broader scale to more companion animal veterinarians. This e-learning module will be based upon theory on AMU, AMR, Dutch formulary and guidelines on AMU. Other subjects incorporated in the e-learning module should be communication towards owners, an exercise reflecting on own, current AM prescribing behaviour and reflection on clinic specific AMU policies. This e-learning module could be part of (obligatory) training on responsible AMU as well.

Involving other stakeholders

Results of this thesis should be shared and discussed with other stakeholders as well.

First, companion animal owners need to be involved in responsible AMU. The government could increase awareness on AMU and AMR, e.g., by awareness campaigns like: www.daarwordtiedereenbetervan.nl or www.antibioticguardian.com. Veterinarians can involve companion animal owners as well, by communicating on AMU and AMR and by clearly addressing the actual concern, worries or questions of an owner and explaining the proposed treatment plan [50].

Second, input of pharmaceutical industry is needed. Simple practical tools, e.g., labels to distinguish 1st, 2nd and 3rd choice AMs from each other and tasteful oral 1st choice AMs for cats, could help veterinarians considerably in daily practice to adhere to current guidelines on AMU. Furthermore, pharmaceutical companies should pay more attention to development of feasible, supportive treatment options without AMs. Alternative treatment options should be user friendly, non-inferior compared to AMs and treatment costs should not exceed a treatment with AMs. Development of evidence based and practical alternative treatment options (e.g., skin products with only corticosteroids, but without AMs) might be expensive. Therefore, promotion of other, already available treatment options without AMs is encouraged as well.

Third, diagnostic agencies (laboratories or providers of diagnostic assays) should be involved [59]. Diagnostic agencies could help in providing timely and accurate species identification and AM susceptibility testing. Development of accurate and reliable on-site diagnostics is important as well, e.g., for use in case of cystitis or otitis externa, and diagnostic laboratories could provide support to veterinarians in interpreting lab results [15].

Fourth, to be able to monitor and measure AMU in companion animals in an objective way, administration and reporting of AMU data has to be standardised and improved. Therefore, software providers are urgently requested to support companion animal clinics to harmonise administration of AMU in the future and to make data collection more straightforward. In the most optimal situation, algorithms behind the generation of data output should be publicly available.

Fifth, veterinary students should be educated on AMU and AMR. This topic is already addressed during the master of veterinary medicine at Utrecht University, but results of present thesis and tools to improve communication with clients should be addressed in educational trainings. Veterinary students are the veterinarians of the future, therefore their involvement is essential.

Guidelines

To optimise AMU in Dutch companion animals, clear communication should be directed at all Dutch companion animal veterinarians to make and keep them aware of current regulations and guidelines on veterinary AMU. Guidelines are important to optimise AMU and are, by definition, based upon appropriate AMU [37]. Veterinary practice guidelines are generally negatively affected by numerous knowledge gaps [15, 60]. Optimal duration of treatment was one of the topics participating veterinarians showed the most uncertainty on, which is reflected in literature often stating "optimal duration of treatment unknown". More evidence-based research of high-level quality is warranted to fill these knowledge gaps. For example, properly designed clinical trials to evaluate different AMs and different treatment regimens [61-63]. These knowledge gaps will be hard to fill, because of limited financial resources for research on AMU in companion animals [15]. In the meantime, (inter)national guidelines should be based upon already existing veterinary literature, recommendations from veterinary experts, recommendations in the SPC, and if needed, recommendations from research in human medicine, although this should be done with caution [61]. Implementation of current and future guidelines is another important step, and should be based upon context based drivers and barriers to follow treatment guidelines and guideline implementation studies [64-67]. From the interviews performed in Chapter 2, it became clear that distribution of guidelines should be clearly communicated, guidelines need to be easy to find and user-friendly.

Obligatory measures....?

Most proposed measures and options are based upon voluntariness. Access to effective AMs should be considered as a privilege. Mandatory monitoring of AMU, preferably using a central and uniform registration system, should involve all Dutch veterinarians prescribing AMs. To improve awareness, this should be followed by feedback or benchmarking of AMU, as is applied in Dutch food-producing animals [2, 15, 68]. In this context, veterinarians should be educated on the importance of accurate and clear registration of used veterinary medicinal products [44].

In the Netherlands, no mandatory post educational training for companion animal veterinarians exists. In human medicine, some health insurance companies oblige general practitioners to attend "Farmaco therapeutic Reflection"-meetings (FTO), and even support in organising these meetings, in which AMU is discussed as well [69]. Education on infection prevention, AMR and responsible AMU could become mandatory for every companion animal veterinarian as well, e.g., one meeting or course per year. This could be enforced by the Dutch Government, together with the veterinary associations. The faculty of veterinary medicine might encourage these courses as well, e.g., by supporting the development and organisation, and by making these courses obligatory for clinics responsible for external education of veterinary students.

There is no "one size fits all"-strategy to optimise AMU. Everyone who is, in one way or another, involved in AM prescribing in companion animals should be kept involved to stimulate a joint and comprehensive effort to make sustainable optimisation of AMU in Dutch companion animal clinics possible.

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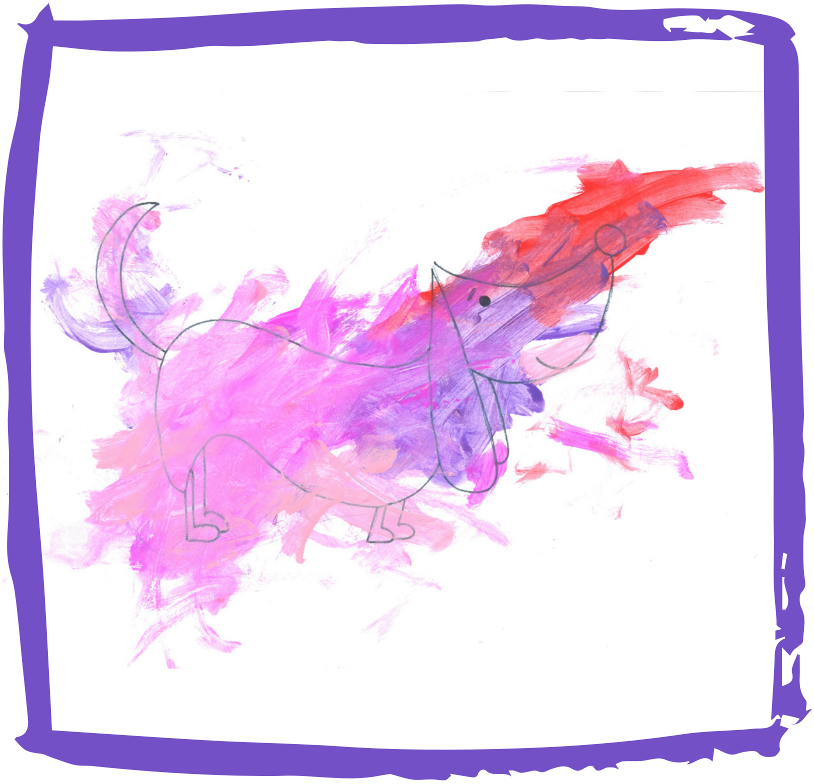

English summary

The discovery of antimicrobials in the previous century, is one of the most important advancements in human and veterinary medicine. Without effective antimicrobials, the core of modern medicine and treatment of bacterial diseases are threatened. Animal health and welfare rely on access to effective antimicrobials as well.

The increase of antimicrobial resistance (AMR) is recognised as a threat for modern medicine and public health. To help control AMR, responsible use of antimicrobials (AMs) is warranted and a decrease in inappropriate use of AMs is necessary, both in human and veterinary medicine. In general, three main strategies are proposed to preserve AMs as resources for future generations; 1) infection control and prevention strategies to prevent the spread of (resistant) bacteria, since every infection prevented is one that needs no treatment; 2) stimulate research and development of new (classes of) AMs and other treatment options effective against resistant strains; 3) secure the efficacy of the existing antimicrobial treatment options.

In human medicine, many initiatives at international, national and local level have been launched to fight AMR and many antimicrobial stewardship programmes (ASPs) were developed and implemented to promote responsible AMU. In the Netherlands, from 2008 onwards, antimicrobial use (AMU) in food-producing animals received increasing attention. Actions were taken at different levels and AMU was reduced considerably (with 64% between 2009 and 2018). Most actions addressed food-producing animals, because the majority of AMs were and are used in these sectors and they represent a significant higher number of animals compared to companion animals. However, in 2011, the advisory report of the Health Council of the Netherlands on "the use of AMs in food animal production and resistant bacteria in humans" also mentioned the presence of highly resistant microorganisms (HRMO) in companion animals as a real concern. As a result of this advisory report, the classification of AMs for veterinary use was revised. This (revised) classification of AMs in 1st, 2nd and 3rd choice AMs, and legislation on mandatory susceptibility testing for use of 3rd choice AMs (since January 2013), also hold for companion animals. During development of the Dutch policy on veterinary AMU, the advisory report of the Health Council of the Netherlands and the so-called Critically Important Antimicrobials-list of the World Health Organisation were taken into consideration.

In the context of all actions against the emergence of AMR, a more responsible and restricted use of antimicrobials in companion animals can not be disregarded. Everyone involved in using AMs has a responsibility to use them judiciously, including companion animal veterinarians.

Data on AMU in companion animals are scarce, however, available data show that there is room for improvement of AMU. The relevance of responsible and rational AMU in companion animals is also demonstrated by increasing resistance rates in bacteria isolated from companion animals and their owners.

Since 2014, there are three guidelines published for companion animals by the Royal Dutch Veterinary Association (KNMvD) on the diagnostic work-up and treatment of urinary tract infections, skin infections and otitis externa. The formulary indicates which AM to use. It is unlikely that the development and publication of guidelines and a formulary alone will be sufficient to optimise AMU in companion animals. Therefore, in 2014, the research project described in this thesis was started with the overall aim to develop, implement and evaluate the effectiveness of an antimicrobial stewardship programme to optimise AMU in companion animals, to protect both human and animal health. This project received the acronym "ASAP-project"; Antibiotic Stewardship and Pets.

To facilitate development of the antimicrobial stewardship programme (ASP), factors influencing antimicrobial prescribing behaviour, and attitudes towards and perceptions on AMU and AMR were studied, both qualitatively and quantitatively in Chapter 2 and 3.

In Chapter 2, factors influencing antimicrobial prescribing behaviour of companion animal veterinarians in the Netherlands were explored qualitatively, using face-to-face, semi-structured interviews with 18 Dutch companion animal veterinarians. The conceptual model developed during this study shows four major categories of factors that influence the antimicrobial prescribing behaviour: veterinarian-related factors, patient-related factors (i.e. owner- and pet-related), treatment-related factors (i.e. alternative treatment options and antimicrobial-related factors) and contextual factors (i.e. professional interactions, further diagnostics and environmental factors). Opinions on the importance of AMR and responsible AMU in companion animals appeared to differ considerably between interviewed veterinarians. However, as factors were studied qualitatively, it was not possible to quantify the (relative) importance of the different potential influencing factors.

Therefore, in Chapter 3, a questionnaire was developed based upon this qualitative interview study, and 1608 potential participants (i.e. Dutch practising companion animal veterinarians) were invited. Aim of the study was to quantitatively investigate attitudes and perceptions of companion animal veterinarians towards AMU and AMR, and to identify associations with demographic characteristics as possible explanatory variables. When considering complete questionnaires, the response rate was 22%. A Categorical Principal Component Analysis (CATPCA) was conducted on 76 questions. This resulted in a final model with 37 questions explaining 38.7% of the variance of the question scores, with three underlying dimensions ("attitudinal profiles"). Additionally, general descriptives were added to the CATPCA as possible explanatory variables. The first dimension, related to "social responsibility", was positively associated with veterinarians working in clinics dedicated to companion animals, with veterinarians working in a referral clinic, and with more experienced veterinarians. The second dimension was related to "scepticism", which was positively associated with being a male veterinarian and with more experienced veterinarians. The third dimension was related to "risk avoidance", especially regarding surgical procedures, and was negatively associated with veterinarians working in clinics in urban areas and with veterinarians working part-time. Antimicrobial prescribing behaviour was self-reported to be well considered, and respondents did not see economic drivers as important influencing factors. The unwillingness of owners and financial constraints were perceived as important barriers for performing further diagnostics. To optimise AMU, a multifaceted approach, taking differences between companion animal veterinarians and differences in work situation into account, should be directed at companion animal veterinarians and owners. Moreover, a joint and comprehensive effort of several stakeholders, like veterinary nurses, guideline developers, pharmaceutical industry, and providers of diagnostics, is needed to optimise AMU in companion animals.

To be able to optimise AMU, a feasible method to quantify AMU is needed as well to enable comparison of clinics over time and with each other (benchmarking). Therefore, in Chapter 4, a method to quantify systemic AMU was introduced, using the number of Defined Daily Doses for Animals (DDDAs). Antimicrobial procurement data of the years 2012-2014 were collected retrospectively from 100 Dutch companion animal clinics. The mean number of DDDAs per clinic per year decreased significantly from 2012 to 2014. A shift in used classes of AMs was seen as well, with a significant decrease in 2nd and 3rd choice AMU and an increase in 1st choice AMU, when comparing 2012 and 2014. Large differences in total AMU were seen between clinics ranging from 64-fold in 2012 to 20-fold in 2014. Despite the relatively low and decreasing AMU, the substantial differences in antimicrobial prescribing practices between clinics suggest that there is still room for quantitative and qualitative optimisation of AMU.

In Chapter 5 and 6, results from previous studies, together with recent literature and input from experts in the human field, are used to develop an ASP and to implement and evaluate the effectiveness of the ASP in 44 Dutch companion animal clinics.

In Chapter 5, baseline information is shown for companion animal clinics selected for participation in the ASP. Systemic AMU in these 44 Dutch companion animal clinics is described over a 3-year time period (2012-2015), using retrospectively collected monthly prescription data. Overall, findings show that total AMU decreased over time and a shift in used classes of AMs towards more 1st choice AMs was visible. Mean total AMU decreased from 1.82 DDDA/year in 2012-2013 to 1.56 DDDA/year in 2014-2015. Aminopenicillins, with and without clavulanic acid, accounted for the largest group of antimicrobials used; 38.7% (2012-2013), 40.2% (2013-2014) and 39.3% (2014-2015) of total AMU, respectively. Strong seasonal differences in AMU were found, with highest AMU in July-August and lowest in February-March. The distribution of different animal species per clinic appeared to affect

AMU as well. Despite the decrease of total AMU during the study period, there is still room for improvement left, especially with regard to the antimicrobial classes prescribed.

In Chapter 6, the effect of participation in an ASP was evaluated in these 44 Dutch companion animal clinics. The study was designed as a prospective, stepped-wedge design, intervention study. Objectives of the ASP were to increase awareness on AMU, to decrease total AMU whenever possible and to shift AMU towards 1st choice AMs, according to Dutch guidelines on veterinary AMU. A statistically significant decrease of 15% (7%-22%) in total AMU, 15% (5%-24%) in 1st choice AMU and 26% (17%-34%) in 2nd choice AMU could be attributed to participation in the ASP, on top of the already ongoing time trends. Use of 3rd choice AMs did not significantly decrease by participation in the ASP. The change in total AMU became more prominent over time, with a 16% (4%-26%) decrease in (linear) time trend per year. This study shows that, although AMU in Dutch companion animal clinics was already decreasing and changing, AMU could be further optimised by participation in the ASP.

In Chapter 7, the main findings of this thesis are summarised and a number of key issues related to AMU in companion animal clinics is discussed and followed by recommendations for the future. Absolute and relative AMU in companion animals is relatively low, which raises the question why antimicrobial stewardship is important in companion animals. First, it should be considered that AMR in companion animal pathogens may lead to treatment failure with a direct effect on (individual) animal health and welfare. Second, companion animals can act as reservoir of resistant bacteria. This might pose a risk to veterinarians, veterinary technicians and companion animal owners. Third, any AMU might select for resistance in the bacterial strain causing infection, as well as in the patient's commensal microbiota. There are no major known outbreaks of AM resistant bacteria in humans resulting from companion animals yet, but that does not exclude possible outbreaks in the future. Therefore, precautionary measures to reduce misuse and overuse of AMs are recommended, even when present scientific evidence proving transmission from resistant bacteria from companion animals to their owners is limited.

In the ASAP-project, many Dutch companion animal clinics and veterinarians were not reached yet, as well as other key players in the field. Therefore, specific recommendations are made in Chapter 7 to involve more companion animal veterinarians, companion animal owners, pharmaceutical industry, diagnostic agencies, software providers, veterinary students, the Dutch Government, the faculty of veterinary medicine and veterinary associations to optimise AMU in companion animals. There is no "one size fits all" strategy to optimise AMU. Everyone who is, in one way or another, involved in AM prescribing in companion animals should be kept involved to stimulate a joint and comprehensive effort to make sustainable optimisation of AMU in Dutch companion animal clinics possible.

Nederlandse samenvatting

De ontdekking van antibiotica in de vorige eeuw is van onschatbare waarde gebleken voor de humane geneeskunde en de diergeneeskunde. Zonder werkzame antibiotica is de huidige, moderne vorm van geneeskunde niet mogelijk en komt de behandeling van bacteriële infecties in gevaar. Diergezondheid en dierenwelzijn zijn eveneens afhankelijk van werkzame antibiotica.

De toename in antibioticaresistentie wordt gezien als een bedreiging voor de huidige, moderne geneeskunde en de volksgezondheid. Om antibioticaresistentie en de gevolgen daarvan zoveel mogelijk te beperken, is het noodzakelijk terughoudend met antibiotica om te gaan en onjuist gebruik van antibiotica tegen te gaan, zowel in de humane geneeskunde als in de diergeneeskunde. Er zijn drie strategieën om de gevolgen van antibioticaresistentie te beperken en werkzame antibiotica te behouden: 1) infectiepreventie en infectiebestrijding om de verspreiding van (resistente) bacteriën tegen te gaan. Iedere infectie die voorkomen kan worden, hoeft immers niet behandeld te worden; 2) onderzoek naar en ontwikkeling van nieuwe (klassen) van antibiotica en andere behandelmogelijkheden, werkzaam tegen (resistente) bacteriën; 3) behouden van de werkzaamheid van de huidige, bestaande antimicrobiële middelen.

In de humane geneeskunde zijn en worden (inter)nationale en lokale initiatieven in gang gezet om antibioticaresistentie (en de gevolgen daarvan) tegen te gaan. Zogenoemde "antimicrobial stewardship programma's" (ASPs) zijn geïntroduceerd om zo goed en terughoudend mogelijk met antibiotica om te gaan.

Sinds 2008 is er in Nederland meer aandacht voor het terughoudend gebruik van antibiotica bij dieren. Op verschillende niveaus zijn stappen gemaakt en het totale antibioticagebruik is aanzienlijk gereduceerd (met 64% in 2018 t.o.v. 2009). De meeste wet- en regelgeving en actieplannen om terughoudend antibioticagebruik te stimuleren, betreffen voedselproducerende dieren. Dit, omdat de hoeveelheid antibiotica die gebruikt werden (en worden) bij deze, in groepen gehouden, diersoorten vele malen hoger lag (en ligt) dan bij individueel gehouden dieren, onder andere omdat het hier aanzienlijk meer dieren betreft en groepsbehandelingen worden ingezet. Echter, in 2011 noemt de Gezondheidsraad het voorkomen van Extended Spectrum Beta-Lactamase (ESBL)-producerende bacteriën bij gezelschapsdieren verontrustend, onder meer omdat mensen en gezelschapsdieren in nauw contact samenleven. Naar aanleiding van dit rapport van de Gezondheidsraad is de indeling van antibiotica voor veterinair gebruik (in 1^{e}, 2^{e} en 3^{e} keuze middelen) herzien. Sinds januari 2013 is het volgens de Nederlandse wet verplicht voor dierenartsen om een bacteriologisch onderzoek in combinatie met een gevoeligheidsbepaling te (laten) verrichten, voordat 3^{e} keuze antibiotica mogen worden gebruikt. Deze verplichting en de indeling van antibiotica in 1^{e}, 2^{e} en 3^{e} keuze middelen (gebaseerd op het rapport van de Gezondheidsraad en de lijst met "Critically Important Antimicrobials" van de Wereldgezondheidsorganisatie) gelden voor gebruik van antibiotica bij alle dieren en dus ook voor gebruik van antibiotica bij gezelschapsdieren.

Gezien de vele inspanningen die worden geleverd, kan extra aandacht voor antibioticagebruik in de gezelschapsdierensector niet uitblijven. Iedereen die direct of indirect betrokken is bij het gebruik van antibiotica, heeft de verantwoordelijkheid dit verantwoord te doen.

Gegevens over het gebruik van antibiotica bij gezelschapsdieren zijn schaars. De gebruiksgegevens die er zijn, laten echter zien dat er ruimte is voor verbetering. De toename van resistente bacteriën die gevonden wordt bij gezelschapsdieren en huisdiereigenaren toont aan dat verantwoord gebruik van antibiotica aandacht behoeft bij gezelschapsdieren.

Sinds 2014 zijn er in Nederland door de Koninklijke Nederlandse Maatschappij voor Diergeneeskunde (KNMvD) drie richtlijnen gepubliceerd voor de gezelschapsdierensector met betrekking tot de diagnostiek en behandeling van bacteriële urineweginfecties, bacteriële huidinfecties en otitis externa. Daarnaast geeft het formularium aan welk antibioticum voor welke indicatie gebruikt dient te worden. Het is echter onwaarschijnlijk dat enkel en alleen de ontwikkeling en publicatie van richtlijnen en een formularium voldoende zullen zijn om het antibioticagebruik bij gezelschapsdieren te verbeteren. Daarom is eind 2014 het onderzoeksproject gestart dat beschreven wordt in dit proefschrift, met als hoofddoel de ontwikkeling, introductie en effectiviteitsevaluatie van een "antimicrobial stewardship programma" (ASP). Doel van dit programma is het antibioticagebruik bij gezelschapsdieren te optimaliseren, ter bescherming van de humane gezondheid en diergezondheid. Dit project heeft als acroniem "ASAP-project"; Antibiotic Stewardship and Pets.

Om een ASP te kunnen ontwikkelen, is het van belang om te weten welke factoren van invloed zijn op het voorschrijfgedrag van gezelschapsdierenartsen en opvattingen over antibioticagebruik en antibioticaresistentie in beeld te brengen (omdat deze opvattingen het voorschrijfgedrag eveneens kunnen beïnvloeden). Deze factoren en opvattingen zijn zowel kwalitatief als kwantitatief onderzocht in Hoofdstuk 2 en 3 van dit proefschrift.

In Hoofdstuk 2 zijn factoren die van invloed zijn op het voorschrijfgedrag van gezelschapsdierenartsen kwalitatief onderzocht, gebruikmakend van semigestructureerde, face-to-face interviews met 18 Nederlandse gezelschapsdierenartsen. Het conceptuele model dat tijdens deze studie werd ontwikkeld, laat vier grote groepen van beïnvloedende factoren zien: dierenarts gerelateerde factoren, patiënt gerelateerde factoren (te weten huisdier- en huisdiereigenaar gerelateerde factoren), behandeling gerelateerde factoren (zijnde “alternatieve” behandelmogelijkheden en antibiotica gerelateerde factoren) en contextuele factoren (zijnde professionele interacties, verdere diagnostiek en omgevings gerelateerde factoren). De opvattingen over het belang van antibioticaresistentie en het verantwoord gebruik van antibiotica bij gezelschapsdieren bleken uiteen te lopen tussen de geïnterviewde dierenartsen. Omdat de beïnvloedende factoren kwalitatief zijn onderzocht, was het echter niet mogelijk het belang van de verschillende factoren te kwantificeren.

Daarom is in Hoofdstuk 3 een enquête ontwikkeld op basis van dit kwalitatieve onderzoek. Voor deelname werden 1608 potentiële deelnemers (zijnde praktiserend gezelschapsdierenartsen) uitgenodigd. Het doel van deze enquête was opvattingen over antibioticagebruik en resistentie kwantitatief te onderzoeken en associaties met demografische kenmerken als mogelijke, verklarende variabelen te bepalen. Deze enquête werd door 22% van de potentiële deelnemers volledig ingevuld. Vervolgens werd een “Categoriale, Principale Componenten Analyse” (CATPCA) uitgevoerd op 76 vragen. Dit leverde een model op waarin 37 vragen 38,7% van de variantie verklaarden, met drie onderliggende dimensies (“attitudinal profiles”). De eerste dimensie, gerelateerd aan “sociale verantwoordelijkheid”, was positief geassocieerd met dierenartsen werkzaam in een kliniek waar uitsluitend gezelschapsdieren worden behandeld, met dierenartsen werkzaam in een verwijskliniek en met meer ervaren dierenartsen. De tweede dimensie, gerelateerd aan “scepsis”, was positief geassocieerd met mannelijke dierenartsen en met meer ervaren dierenartsen. De derde dimensie, gerelateerd aan “risicovermijding”, in het bijzonder in het kader van chirurgische ingrepen, was negatief geassocieerd met dierenartsen werkzaam in stedelijke praktijken en dierenartsen die parttime werken. Dierenartsen omschreven hun voorschrijfgedrag als weloverwogen en financiële prikkels werden niet gezien als belangrijke beïnvloedende factoren. Onwil van eigenaren en financiële bezwaren werden ervaren als belangrijke barrières voor het uitvoeren van aanvullend onderzoek.

Om het antibioticagebruik te kunnen verbeteren, is een veelzijdige aanpak nodig, waarin rekening wordt gehouden met de verschillen tussen gezelschapsdierenartsen en de verschillen in werkomgeving, en waarbij zowel dierenartsen als huisdiereigenaren worden betrokken. Bovendien is een gezamenlijke input van andere stakeholders, zoals paraveterinairen, richtlijnontwikkelaars, de farmaceutische industrie, laboratoria en andere leveranciers van diagnostica nodig om het antibioticagebruik te optimaliseren.

Tevens is een praktische methode nodig om het antibioticagebruik te kunnen kwantificeren, zodat praktijken in de tijd en met elkaar vergeleken kunnen worden (benchmarking). Daarom wordt in Hoofdstuk 4 een methode geïntroduceerd om systemisch antibioticagebruik bij gezelschapsdieren te kwantificeren, waarbij gebruik wordt gemaakt van het aantal Dierdagdoseringen (DDDAs). Inkoopdata van antibiotica van 100 Nederlandse gezelschapsdierenpraktijken werden verzameld over de jaren 2012-2014. Tussen 2012 en 2014 nam het gemiddeld aantal DDDAs per praktijk per jaar significant af. Tevens was een verschuiving in de gebruikte keuzes van antibiotica zichtbaar, met een significante daling in het gebruik van 2^e en 3^e keuze middelen en een toename in het gebruik van 1^e keuze middelen. Grote verschillen in het totale antibioticagebruik waren zichtbaar tussen de verschillende praktijken, met een factor 64-verschil in 2012 en een factor 20-verschil in 2014. Ondanks dat het gebruik van antibiotica bij gezelschapsdieren relatief laag is en al een daling liet zien, geven de substantiële verschillen in antibioticagebruik tussen praktijken aan dat er ruimte is voor verbetering, zowel kwantitatief als kwalitatief.

In Hoofdstuk 5 en 6 worden de resultaten van de eerdere studies, recente literatuur en input van experts uit het humane veld gebruikt om een ASP te ontwikkelen, te implementeren en de effectiviteit ervan te evalueren in 44 Nederlandse gezelschapsdierenpraktijken.

In Hoofdstuk 5 worden baseline gegevens beschreven van deze 44 praktijken, die zijn geselecteerd voor deelname aan het ASP. Het systemisch antibioticagebruik in deze praktijken wordt beschreven over een periode van drie jaar (2012-2015), gebruik makend van retrospectief verkregen, maandelijkse voorschrijfdata. In het algemeen liet het totale antibioticagebruik een daling zien en er was een verschuiving zichtbaar richting meer gebruik van 1^e keuze middelen. Het gemiddelde, totale antibioticagebruik nam af van 1,82 DDDA/jaar in 2012-2013 naar 1,56 DDDA/jaar in 2014-2015. De groep van antibiotica die het meeste gebruikt werd, was de groep van de aminopenicillinen (met en zonder clavulaanzuur); 38,7% (2012-2013), 40,2% (2013-2014) en 39,3% (2014-2015) van het totale antibioticagebruik. Er bleek tevens sprake te zijn van een duidelijk verschil in antibioticagebruik tussen de verschillende seizoenen, met het hoogste antibioticagebruik in de maanden juli-augustus en het laagste gebruik in februari-maart. De verdeling van de verschillende diersoorten (hond, kat en konijn) binnen een praktijk bleek eveneens van invloed te zijn. Ondanks de afname van het totale antibioticagebruik, bleef er ruimte voor verbetering, met name in de keuzes van voorgeschreven antibiotica.

In Hoofdstuk 6 wordt het effect van deelname aan een ASP geëvalueerd. Deze studie is opgezet als een prospectieve interventiestudie. De interventies zijn per cluster van dierenartsenpraktijken ingevoerd (volgens het stepped-wedge design). Het doel van het ASP was de bewustwording rond antibioticagebruik te vergroten, het antibioticagebruik waar nodig te verminderen en het gebruik van 1^e keuze middelen (in plaats van 2^e of zelfs 3^e keuze middelen) te stimuleren, volgens de Nederlandse richtlijnen en het formularium. Een statistisch significante daling van 15% (7%-22%) in totaal antibioticagebruik, 15% (5%-24%) in 1^e keuze gebruik en 26% (17%-34%) in 2^e keuze gebruik kon worden toegeschreven aan deelname aan het ASP, bovenop de veranderingen in antibioticagebruik die al gaande waren. Het gebruik van 3^{e} keuze antibiotica werd niet significant beïnvloed door deelname aan het ASP. De verandering in het totale antibioticagebruik werd na verloop van tijd duidelijker, met een afname van 16% (4%-26%) per jaar in de (lineaire) tijdstrend. Deze studie laat zien dat, hoewel het antibioticagebruik in Nederlandse gezelschapsdierenpraktijken al daalde en veranderingen liet zien, dit nog verder verbeterd kan worden door deelname aan het ASP.

In Hoofdstuk 7 worden de belangrijkste conclusies van dit proefschrift samengevat, een aantal onderwerpen met betrekking tot antibioticagebruik bij gezelschapsdieren wordt bediscussieerd en tot slot wordt een aantal aanbevelingen voor de toekomst gegeven.

Absoluut en relatief antibioticagebruik bij gezelschapsdieren is relatief laag, waardoor de vraag opkomt waarom antimicrobial stewardship belangrijk is bij gezelschapsdieren. Ten eerste is het belangrijk dat men zich realiseert dat antibioticaresistentie binnen pathogenen voor gezelschapsdieren kan leiden tot therapiefalen met een direct effect op (de individuele) diergezondheid en dierenwelzijn. Ten tweede kunnen gezelschapsdieren als reservoir van resistente bacteriën fungeren. Dit kan een mogelijk risico zijn voor dierenartsen, paraveterinairen en gezelschapsdiereneigenaren. Ten derde kan elk gebruik van antibiotica selecteren op resistentie in bacteriën die voor infectie zorgen, maar óók in de commensale microbiota van een patiënt. Tot op heden zijn er geen grote uitbraken van resistente bacteriën bij mensen bekend, die terug te voeren zijn naar gezelschapsdieren. Dit wil echter niet zeggen dat dit in de toekomst niet mogelijk is. Daarom worden maatregelen geadviseerd om onjuist en "over"-gebruik van antibiotica te verminderen, ondanks dat wetenschappelijke literatuur, die overdracht van resistente bacteriën van gezelschapsdieren naar hun eigenaren aantoont, beperkt is.

Aan het ASAP-project heeft maar een klein aantal Nederlandse gezelschapsdierenpraktijken deelgenomen. Tevens zijn andere belangrijke stakeholders nog niet bereikt. Daarom worden in Hoofdstuk 7 specifieke aanbevelingen gedaan om meer gezelschapsdierenartsen, eigenaren van gezelschapsdieren, farmaceutische industrie, laboratoria en andere leveranciers van diagnostica, softwareproviders, studenten diergeneeskunde, de Nederlandse politiek, de faculteit diergeneeskunde en veterinaire belangenverenigingen te betrekken om het antibioticagebruik bij gezelschapsdieren te verbeteren. Er bestaat geen "one size fits all" strategie. Daarom zou iedereen, die op de één of andere manier te maken heeft met het gebruik van antibiotica bij gezelschapsdieren, betrokken moeten worden om er gezamenlijk voor te zorgen dat het gebruik van antibiotica op een duurzame manier verbeterd wordt.

List of publications

Related to this thesis

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NCOH-AMR symposium, 12 October 2018, Nijmegen, the Netherlands: "Guiding prudent use of antimicrobials in companion animal practice to protect animal and human health".

ESCMID Postgraduate Education Course, Challenges in Veterinary Hospital Infection Control and Antimicrobial Stewardship, 4 April 2018, Birmingham, United Kingdom: "Guiding prudent use of antimicrobials in companion animal practice to protect animal and human health".

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About the author

Nonke Hopman was born in Nijmegen, the Netherlands, on December 2nd 1985. In 2004, she completed her Gymnasium education at Dominicus College, Nijmegen (cum laude), after which she went to study Animal Sciences at Wageningen University. After one year, she realised she wanted to become a veterinarian. Therefore, she started studying Veterinary Medicine at Utrecht University, which she did from 2005 until 2012. During summer months from 2005-2009, she worked in a veterinary clinic to support the veterinary technicians and veterinarians. From 2009-2010, she did an additional research internship (honours programme) on *Clostridium difficile* in pigs (Institute for Risk Assessment Sciences, Veterinary Public Health Division, Faculty of Veterinary Medicine, Utrecht University). This research project gave her enthusiasm, inspired her for public health and science and resulted in a first publication. In 2012, she received her degree in Veterinary Medicine (with honour), after which she started as companion animal veterinarian and worked in several companion animal clinics in the Netherlands. In November 2014, she started her PhD at the Department of Infectious Diseases and Immunology – Clinical Infectiology, Faculty of Veterinary Medicine, Utrecht University, as researcher on the "Antimicrobial Stewardship and Pets"-project. This research project was performed under supervision of dr. Els M. Broens, dr. Ingeborg M. van Geijlswijk, professor dr. Jaap A. Wagenaar and professor dr. Dick J.J. Heederik. As part of this PhD, she started (September 2015) a Postgraduate master in Epidemiology at the Faculty of Medicine, Utrecht University, which she passed in June 2019.