IMPROVING THE ANTIMICROBIAL STEWARDSHIP PROGRAM AT THE DEPARTMENT OF CLINICAL SCIENCES OF COMPANION ANIMALS AT UTRECHT UNIVERSITY

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Abstract

Antimicrobial Stewardship is of great importance to decrease antimicrobial resistance patterns. This can be carried out by stimulating changes in antimicrobial usage and monitoring and evaluating resistance data. This follow-up study compares results of 2013-2017 to 2018 and 2019 to improve the current Antimicrobial Stewardship Program (ASP) at the Department of Clinical Sciences of Companion Animals (CSCA) at Utrecht University. Antimicrobial usage was quantified by calculating the defined daily doses per animal (DDDA). The DDDA was 3.77 in 2018 and 3.08 in 2019. Compared to 2013-2017, the DDDA had decreased significantly. In both 2018 and 2019, the majority of prescribed antimicrobials were classified as second-line drugs. Penicillins were the antimicrobial group most prescribed and the most prescribed active substance in both 2018 and 2019 was amoxicillin/clavulanic acid. Out of all sub-departments at the CSCA, antimicrobials were used most at the Intensive Care Unit. In 2018, 509 out of 1206 bacterial culture samples submitted for antimicrobial susceptibility testing, tested as multi-drug-resistant (MDR). In 2019 this number was 422 out of 1082. The General Surgery division submitted the most samples in 2018 and 2019. To improve the ASP at the CSCA, antimicrobial usage and antimicrobial resistance data should be monitored and evaluated on a regular basis. Employees should be reminded of the importance of Antimicrobial Stewardship and prescribe antimicrobials carefully. In addition, more bacterial culture samples should be submitted to test antimicrobial resistance.

Introduction

In December 2018, a report covering 2013-2017 was initiated by the Antimicrobial-Team (A-team) at the Department of Clinical Sciences of Companion Animals (CSCA) at Utrecht University. The aim of this report was to define the situation regarding antimicrobial prescribing and resistance patterns and factors affecting the antimicrobial prescribing behaviour and infection control methods. The conclusion of the study stated that both the local antimicrobial prescribing and resistance patterns and the accumulated feedback provided by staff members emphasized the importance of further developing an Antimicrobial Stewardship Program (ASP) at the CSCA (van Bree, F. P. J., Broens et al. 2018).

In this follow up project, the antimicrobial drug consumption and testing data of retrospective bacterial culture and antimicrobial susceptibility at the CSCA in 2018 and 2019, will be analysed and evaluated. The aim of this research is to evaluate and improve the current ASP at the CSCA at Utrecht University to prevent the increase of antimicrobial resistance. This report focuses on what changes occurred in prescribing behaviour and resistance patterns to detect what needs to be amended to keep the program up to date. This research will be carried out by analysing the data between January 2018 and December 2019. These results will be compared to the outcome of the aforementioned research by van Bree, F. P. J., Broens et al. 2018. The research will also be carried out by analysing the current protocol status concerning antimicrobial use and examining the number of defined daily doses per animal.

Antimicrobial Stewardship

ASPs at human hospitals are obligated in the Netherlands since 2014 (Sprong, Dofferhoff et al. 2013). Every hospital is required to have its own A-team, including at least a clinical pharmacist, a microbiologist and an infectious disease physician. As an addition to the team, an IT-specialist and an epidemiologist are of great value (Guardabassi, Prescott 2015). In veterinary hospitals no such obligations exist to date.

The goal of the A-team at the CSCA at Utrecht University, is to endorse its ASP and improve antimicrobial usage to prevent the increase of antimicrobial resistance. The term Antimicrobial Stewardship can be described in various ways. As suggested in the review ‘What is Antimicrobial Stewardship?’ by O.J. Dyar, B. Huttner, J. Schouten and C. Pulcini, it can be defined as the responsible usage of antimicrobials (Dyar, Huttner et al. 2017). This involves supporting actions that balance both the long-term societal need for continued access to effective therapy and the individual’s need for suitable treatment.
The usage of the term Antimicrobial Stewardship has rapidly increased over the last 25 years, firstly used in the article ‘Does antibiotic restriction prevent resistance?’ by J.E. McGowan Jr and D.N. Gerding in 1996 (McGowan, Gerding 1996). This article described the term Antimicrobial Stewardship as the appropriate usage of antimicrobials and thereby avoiding unnecessary usage. The importance of implementing Antimicrobial Stewardship is related to the global health emergency of antimicrobial resistance (Hardefeldt, Gilkerson et al. 2018). Since the discovery of the first antimicrobial over 90 years ago, the antimicrobial drug usage

in human and animal medicine has been largely taken for granted, causing an increase in the threat of antimicrobial resistance. Therefore it is of great importance to implement Antimicrobial Stewardship to preserve the efficacy of antimicrobials, protect patients from harms caused by unnecessary use of antibiotics, combat antimicrobial resistance and develop alternative approaches on treating infections without antimicrobials (Prescott, Boerlin 2016). In 2014, the 5R's approach to veterinary Antimicrobial Stewardship was first described. This approach stands for the responsibility, reduction, refinement, replacement and review of antimicrobial usage (Page, Prescott et al. 2014).

Methods and Materials

Patient Population

The patient population at the CSCA at Utrecht University was extracted from the veterinary practice management software system (ORBIS Vetware, AGFA HealthCare, Mortsel, Belgium). This data comprised the number of unique companion animals visiting the CSCA in 2018 and 2019. These patients were subdivided into: dogs, cats and other animal species, the latter including other small mammal species, bird species and reptile species. The number of yearly unique patients during the period of interest was calculated.

Antimicrobial Prescribing Patterns

An overview of antimicrobial drug administration-data from January 2018 to December 2019 was extracted from the veterinary practice management software system used at the Veterinary Pharmacy department at Utrecht University (Viva 1, Corilus Veterinary, Houten, The Netherlands). The antimicrobials in this study are defined by their ATCvet codes, classified by the WHO Collaborating Centre for Drug Statistics Methodology (Index 2017). These include drugs authorised for parenteral or oral administration, with topical applications excluded. The extracted data included: date of prescription, drug identification code, quantity dispensed and the patient or the clinical department to which the drug was dispensed as stock supply. Hence, these data included both individual prescriptions by veterinarians at the CSCA to companion animal patients treated at the CSCA and the dispensing of antimicrobials to sub-departments at the CSCA. Individual prescription data also included the patient identification number and animal species. The sub-departments at the CSCA to which antimicrobials were dispensed in 2018 and 2019 are the intensive care unit, operating room, emergency clinic, nursing wards and the division of zoological medicine.

For each type of antimicrobial, the antimicrobial group, antimicrobial classification and number of treatable weight in kilograms per species per one antimicrobial quantity (single tablet or package) per day was available. A guideline composed by the WVAB was used to sort the antimicrobial classification (Werkgroep Veterinair Antibiotica Beleid 2015). This guideline was composed to prevent selection on extended-spectrum beta lactamase (ESBL) and ampicillin class C beta-lactamase (AmpC) producing bacteria. Antimicrobials were classified as first-, second-, and third-line drugs, based on the selection pressure on resistance factors. First-line antimicrobials are defined as effective against the indication without having a specific negative resistance-inducing effect. Second-line antimicrobials are not allowed to

be prescribed unless the need is further substantiated. Third-line drugs are only allowed to be prescribed when there are no alternatives available. Performing bacteriological research beforehand, including an antibiogram, is obligated. These antimicrobials are of critical importance for human medicine. Drugs used for companion animals, but licensed for humans were classified as cascade-drugs. Cascade-drugs also include antimicrobials licensed for companion animals, but administered by a different type of application than licensed. A full overview of all antimicrobials reviewed is given in Table 1.

Drug ID code	Brand Name	Non-proprietary Name	Am Group	Am Classification	DOG tw*d	CAT tw*d	EXOTIC tw*d
AMOX3	AMOXI/CLAV 500/ 50MG INJPDR	amoxicillin/clavulanic acid	penicillins	cascade-drug	20	20	7.4
AMOX4	0AMOXI/CLAV 500/100MG INJPDR	amoxicillin/clavulanic acid	penicillins	cascade-drug	20	20	
AMOX41	0AMOXI/CLAV 1000/200MG INJPDR	amoxicillin/clavulanic acid	penicillins	cascade-drug	40	40	
AMPI3	AMPICILLINE 20% INJVLST 100ML	amoxicillin/clavulanic acid	penicillins	second-line	816	816	194.5
AZIT1	AZITHROMYCINE 40MG/ML SUSP 15ML	macrolides	macrolides	cascade-drug	80	80	40
BACT2	0BACTRIMEL 48MG/ML SUSPENSIE PER ML	trimethoprim/sulfamethoxazole	trimethoprim/sulfonamides	cascade-drug	1.6	1.6	1.6
BAYT2	BAYTRIL 2,5% SUSP ORAAL 8,5ML	enrofloxacin	fluoroquinolones	third-line	42.5	42.5	19.3
BAYT3	BAYTRIL 2,5% INJVLST 50ML	enrofloxacin	fluoroquinolones	third-line	250	250	126.6
BAYT4	BAYTRIL 5% INJVLST 100ML	enrofloxacin	fluoroquinolones	third-line	1000	1000	464.7
BAYT5	BAYTRIL 150MG TABLET	enrofloxacin	fluoroquinolones	third-line	30	30	
BAYT7	BAYTRIL 15MG TABLET	enrofloxacin	fluoroquinolones	third-line	3	3	1.4
BAYT9	BAYTRIL 50MG TABLET	enrofloxacin	fluoroquinolones	third-line	10	10	
CEFA5	CEFABACTIN 50MG TABLET	cefalexin	cefalosporins 1st gen.	second-line	1	1	
CEFA6	CEFABACTIN 250MG TABLET	cefalexin	cefalosporins 1st gen.	second-line	5	5	
CEFA7	CEFABACTIN 500MG TABLET	cefalexin	cefalosporins 1st gen.	second-line	10	10	
CEFT1	CEFTAZIDIM 500MG INJPDR	ceftazidime	cefalosporins 3rd & 4th gen.	cascade-drug	7.1	7.1	11.3
CLIN1	CLINDAMYCINE 150MG/ML INJVLST 4ML	clindamycin	lincosamides	cascade-drug	30.8	27.3	12.9
CLIN3	CLINDAMYCINE 200MG TABLET	clindamycin	lincosamides	first-line	10	10	10
CLIN5	CLINDASEPTIN 25MG/ML SUSP 22ML	clindamycin	lincosamides	first-line	33.4	49.9	15.1
COTR1	COTRIMOXAZOL 48MG/ML SUSPENSIE PER ML	thrimethoprim/sulfamethoxazol	sulfonamides	cascade-drug	1.6	1.6	1.6
DIAT1	DIATRIM 200MG/ML + 40MG/ML INJVLST 100ML	thrimethoprim/sulfamethoxazol	sulfonamides	first-line	800	800	
DOXO2	0DOXORAL 15MG TABLET	doxycycline	tetracyclines	first-line	1.5	1.5	1.5
DOXO31	0DOXORAL 150MG TABLET	doxycycline	tetracyclines	first-line	15	15	15
DOXO8	0DOXORAL 75MG TABLET	doxycycline	tetracyclines	first-line	7.5	7.5	7.5
DOXY5	DOXYLIN 50% WSP POEDER 1KG	doxycycline	tetracyclines	first-line	50000	50000	20000
DUPL1	DUPLOCILLINE L.A. 100ML	benzathine benzylpenicillin/procaine b	penicillins	first-line	3000	3000	770.1
ERAD1	ERADIA 125MG/ML SUSP 100ML	metronidazole	nitroimidazole derivatives	first-line	250		
ERAD2	ERADIA 125MG/ML SUSP 30ML	metronidazole	nitroimidazole derivatives	first-line	75		
FLAG1	FLAGYL 40MG/ML SUSP PER ML VBD	metronidazole	nitroimidazole derivatives	cascade-drug	0.8	0.8	1.2
GENT1	GENTAMYCINE 5% INJVLST 50ML	gentamicin	aminoglycosides	second-line	357	357	357
GENT6	GENTAMICINE 10MG/ML INJVLST 2ML	gentamicin	aminoglycosides	cascade-drug	3.3	3.3	3.3
KEFZ1	KEFZOL 1G INJPDR	cefazolin	cefalosporins 1st gen.	cascade-drug	16.7	16.7	
MARB1	MARBOX 100MG/ML INJVLST 100ML	marbofloxacin	fluoroquinolones	third-line	5000	5000	
MARB3	MARBOCYL P 5MG TABLET	marbofloxacin	fluoroquinolones	third-line	2.5	2.5	
MARB4	MARBOCYL P 20MG TABLET	marbofloxacin	fluoroquinolones	third-line	10	10	
MARB5	MARBOCYL P 80MG TABLET	marbofloxacin	fluoroquinolones	third-line	40	40	
METR10	METRONIDAZOL 100MG/ML DRANK 50ML	metronidazole	nitroimidazole derivatives	cascade-drug	375	375	152.8
METR2	METROBACTIN 250MG TABLET	metronidazole	nitroimidazole derivatives	first-line	5	5	7.6
METR9	METRONIDAZOL 5MG/ML INFVLST 100ML	metronidazole	nitroimidazole derivatives	cascade-drug	10	10	50
NITR1	NITROFURANTOINE 50MG CAPSULE	nitrofurantoin	nitrofuran derivatives	cascade-drug	3.2	3.6	
NITR3	NITROFURANTOINE 25MG CAPSULE	nitrofurantoin	nitrofuran derivatives	cascade-drug	1.6	1.8	
NORO1	0NORODINE TMPS 24% INJVLST 100ML	trimethoprim/sulfadiazine	trimethoprim/sulfonamides	first-line	800	800	690.7
NOVA1	NOVADOX 10MG/ML SUSPENSIE 30ML	doxycycline	tetracyclines	first-line	30	30	23.4
NOVA2	NOVADOX 10MG/ML SUSPENSIE 10ML	doxycycline	tetracyclines	first-line	10	10	7.8
NUFL1	NUFLOR 300MG/ML INJVLST 100ML	florfenicol	fenicols	first-line	500	681.8	315.8
PROC6	PROCAPEN 300MG/ML INJVLST 100ML	procaine benzylpenicillin	penicillins	first-line	1000	1000	947.8
RIFA3	RIFAMPICINE 150MG CAPSULE	rifampicin	rifamycins	cascade-drug	4.4	10	
RONA1	RONAXAN 20MG TABLET	doxycycline	tetracyclines	first-line	1.2	1.2	0.5
RONA2	RONAXAN 100MG TABLET	doxycycline	tetracyclines	first-line	6.1	6.1	2.5
RONI4	RONIDAZOL 100MG/ML PDR V DRANK 40ML	ronidazole	nitroimidazole derivatives	first-line		80	
STOM1	STOMORGYL 10 TABLET	metrodinazole/spiramycin	AM combinations	first-line	10	10	
STOM2	STOMORGYL 20 TABLET	metrodinazole/spiramycin	AM combinations	first-line	20	20	
STOM3	STOMORGYL 2 TABLET	metrodinazole/spiramycin	AM combinations	first-line	2	2	
SULF1	SULFATRIM 480MG TABLET	trimethoprim/sulfadiazine	trimethoprim/sulfonamides	first-line	16	16	
SULF2	SULFATRIM 120MG TABLET	trimethoprim/sulfadiazine	trimethoprim/sulfonamides	first-line	4	4	4
SYNU3	SYNULOX 50MG/ML PDR V SUSP 15ML	amoxicillin/clavulanic acid	penicillins	second-line	30	30	9.9
SYNU4	SYNULOX 250MG TABLET	amoxicillin/clavulanic acid	penicillins	second-line	10	10	3.4
SYNU6	SYNULOX 500MG TABLET	amoxicillin/clavulanic acid	penicillins	second-line	20	20	6.9
SYNU8	SYNULOX 50MG TABLET	amoxicillin/clavulanic acid	penicillins	second-line	2	2	0.7
TRIC1	TRICHOCURE 5MG TABLET	ronidazole	nitroimidazole derivatives	first-line			0.5
TRIC2	TRICHO PLUS 50MG/G SACHET 4G	ronidazole	nitroimidazole derivatives	first-line	4,4	4,4	16.9
TYLA1	TYLAN 200MG/ML INJVLST 100ML	tylosin	macrolides	first-line	1777.8	1777.8	1402.7
VIBR4	DOXYCYCLINE SF 20MG/ML INJVLST 5ML	doxycycline	tetracyclines	cascade-drug	6.5	10	7.9
ZODO1	ZODON 88MG TABLET	clindamycin	lincosamides	first-line	6	8	2.4
ZODO2	ZODON 264MG TABLET	clindamycin	lincosamides	first-line	18	24	7.2

TABLE 1. OVERVIEW OF ALL ANTIMICROBIALS REVIEWED IN THIS RESEARCH.

The obtained data was analysed and processed to delineate and quantify the antimicrobial usage at the CSCA in defined daily doses per animal (DDDA), separately for dogs, cats and exotic species. This number represents the average number of days per year a unique patient at this clinic is treated with antimicrobials. The DDDA is calculated by multiplying the antimicrobial quantity with the antimicrobials' treated weight*day and dividing this number with the number of unique patients per year multiplied by the average animal weight.

$$DDDA = \frac{\text{antimicrobial quantity} * \text{treated weight*day}}{\#\text{ unique patients presented at the CSCA} * \text{average animal weight}}$$

The number of DDDA's was calculated per product and presented per antimicrobial substance and per antimicrobial group. The number of DDDA's was also calculated per sub-department at the CSCA, individual prescriptions, antimicrobial classification and in total. The DDDA results of 2018 and 2019 were compared to the results of 2013 to 2017. The DDDAs of 2018 and 2019 are calculated with the same formula as for 2013 to 2017, with the different population size of each year taken into account. This formula is given above. The DDDA results cannot be compared to results of other veterinary clinics in the Netherlands because there is no fixed patient population. This is because the CSCA functions as a veterinary referral centre for other veterinary clinics in the Netherlands. More complicated disorders and diseases, emergency cases and clinical surgeries are presented and carried out at the CSCA, so a different antimicrobial usage is to be expected.

The antimicrobial quantity is given in the administration-data extracted from the veterinary practice management software system (Viva 1, Corilus Veterinary, Houten, The Netherlands). The treated weight*day per product is averaged for dogs and cats, because there is no documentation of species-numbers in the sub-department data of drug administration. Because only exotic animal species are treated at the sub-department division of zoological medicine, a separate value was used for the treated weight*day per product in the DDDA formula. The number of unique patients presented at the CSCA per year was extracted from the veterinary practice management software system (ORBIS Vetware, AGFA HealthCare, Mortsel, Belgium). The average animal weight was calculated by using the average weight of dogs and cats given by the SDa (19.1 kilogram for dogs and 4.1 kilogram for cats)(van Geijlswijk, Alsters et al. 2013). These numbers were adjusted to the percentage of unique dog and cat patients each year at the CSCA, resulting into a unique average animal weight of dogs and cats for each year. The number of exotic animal species patients was not calculated into this average weight because of the lack of proper data and because this had not been done for the data from 2013 to 2017. All data were administered and analysed using Excel (Microsoft Office 2016, Microsoft Corporation, USA).

Antimicrobial Resistance Patterns

An overview of bacterial culture and antimicrobial susceptibility testing data from samples submitted to the Veterinary Microbiological Diagnostic Centre at Utrecht University by clinicians from the CSCA from January 2018 to December 2019, were extracted from the management software system (GLIMS, MIPS Diagnostics Intelligence, Belgium). These data were analysed and processed to evaluate the percentage of multi-drug-resistant (MDR) bacteria isolated from the presented companion animals-patients at the CSCA. The collected data contained the animal species, origin of the sample, sample identification number, veterinarian submitting the sample and the isolated bacterial species. The five bacterial groups analysed were *Enterobacteriaceae*, *Staphylococcus* sp., *Pseudomonas* sp., *Enterococcus* sp. and *Acinetobacter* sp.. These bacterial groups were also analysed in the

research from 2013 to 2017, which creates the possibility to compare results (van Bree, F. P. J., Broens et al. 2018). Antimicrobial susceptibility testing was done by a broth microdilution method (Micronaut, Merlin, Germany) using a VMDC-customized panel of antimicrobials. The susceptibility of the antimicrobials was classified as resistant, intermediate or susceptible based on the outcome of the test. The antimicrobials were sorted into their antimicrobial groups.

If isolates tested intermediate or resistant to one or two antimicrobials in its antimicrobial group, the antimicrobial group was labelled as resistant. When isolates tested resistant or intermediate for at least three antimicrobial groups, they were labelled as MDR.

Enterobacteriaceae and *Staphylococcus* sp. testing data were approached differently. *Staphylococcus* sp. isolates were screened for methicillin-resistance. These isolates were tested on resistance to either oxacillin or cefoxitin. *Enterobacteriaceae* isolates were screened for ESBL-producing strains. In this case, isolates resistant to third-generation cephalosporins were labelled as ESBL-producing.

The testing data of *Enterobacteriaceae*, *Staphylococcus* sp., *Pseudomonas* sp., *Enterococcus* sp. and *Acinetobacter* sp. were managed and analysed in Excel (Microsoft Office 2016, Microsoft Corporation, USA). These data included the names of employees who submitted the samples, the species of which the sample was obtained from and a description of the patient's health problem.

Questionnaire

A questionnaire was sent out to all members of the A-team at the CSCA at Utrecht University. This questionnaire included various questions about the CSCA's ASP. These questions inquired about the current ASP, the taken measurements over the past years, its awareness amongst colleagues and further recommendations for the future.

Results

Patient Population

The patient population at the CSCA at Utrecht University comprised a total of 10,063 unique patients in 2018 and 10,849 unique patients in 2019. The percentage of dogs presented at the CSCA was 64.0% in both 2018 (6436/10,063) and 2019 (6945/10,849). The percentage of cats presented was 26.2% (2632/10,063) in 2018 and 24.4% (2650/10,849) in 2019. The percentage of exotic animal species presented was 9.9% (995/10,063) in 2018 and 11.6% (1254/10,849) in 2019. A complete overview of the patients presented at the CSCA at Utrecht University from 2013 to 2019 is shown in Table 2.

	2013	2014	2015	2016	2017	2018	2019
Dog	5829	5888	5550	5533	5441	6436	6945
Cat	1220	2229	2139	2382	2293	2632	2650
Exotic	690	787	786	789	871	995	1254
Total	**7739**	**8904**	**8475**	**8704**	**8605**	**10063**	**10849**

TABLE 2. NUMBER OF UNIQUE PATIENTS PRESENTED AT THE CSCA AT UTRECHT UNIVERSITY (BASED ON REGULAR CONSULTS OF 60 MINUTES).

Antimicrobial Prescribing Patterns

The overall usage of antimicrobials at the CSCA in 2018 and 2019 expressed in daily defined doses per animal was retrospective 3.77 and 3.08. The highest percentage of antimicrobials was classified as second-line with 46.0% (1.73/3.77) in 2018 and 48.9% (1.51/3.08) in 2019. This number was followed by first-line antimicrobials with 31.6% (1.19/3.77) in 2018 and 26.2% (0.81/3.08) in 2019, cascade-drugs with 19.3% (0.73/3.77) in 2018 and 20.5% (0.63/3.08) in 2019 and third-line drugs with 3.1% (0.12/3.77) in 2018 and 4.5% (0.14/3.08) in 2019. From 2013 to 2017, the antimicrobial classification was ranked in a different order, with second-line antimicrobials used most (54.0%; 2.40/4.44), followed by cascade-drugs (19.7%; 0.87/4.44), first-line antimicrobials (19.0%; 0.85/4.44) and third-line antimicrobials (7.3%; 0.33/4.44).

	2013	2014	2015	2016	2017	2018	2019
First-line	1.07	0.69	0.61	0.81	1.07	1.19	0.81
Second-line	1.88	2.39	2.24	2.19	2.32	1.73	1.51
Third-line	0.25	0.44	0.48	0.20	0.27	0.12	0.14
Cascade	0.81	0.89	0.94	0.92	0.80	0.73	0.63
Total	**5.01**	**4.41**	**4.27**	**4.12**	**4.46**	**3.77**	**3.08**

TABLE 3. CLASSIFICATION OF THE USAGE OF ANTIMICROBIALS AT THE CSCA EXPRESSED IN NUMBER OF DDDA'S.

The most used antimicrobial group at the CSCA in 2018 were penicillins (55.4%; 2.09/3.77), with the active substance amoxicillin/clavulanic acid as 95.7% (2.00/2.09) and procaine benzylpenicillin as 4.3% (0.09/2.09). Penicillins were followed by lincosamides (17.7%; 0.67/3.77), tetracyclines (7.0%; 0.26/3.77) and first generation cephalosporins (5.8%; 0.22/3.77). In 2019, the most used antimicrobial-groups were penicillins (60.6%; 1.86/3.08) with the active substance amoxicillin/clavulanic acid as 96.8% (1.80/1.86) and procaine benzylpenicillin as 3.2% (0.06/1.86). These were followed by lincosamides (15.3%; 0.47/3.07), first generation cephalosporins (6.0%; 0.19/3.08) and tetracyclines (3.7%; 0.11/3.08). From 2013 to 2017, penicillins were used most (64.5%; 2.86/4.44) with the active substance amoxicillin/clavulanic acid as 98.3% (2.81/2.86) and procaine benzylpenicillin as 1.7% (0.05/2.86). These were followed by lincosamides (8.6%; 0.38/4.44), fluoroquinolones (7.1%; 0.32/4.44) and first generation cephalosporins (5.7%; 0.26/4.44). A full overview of all used antimicrobial groups in 2018 and 2019 is given in Table 4.

Antimicrobial Group	2018	2019
Antimicrobial Combination	0.5%	1.0%
Aminoglycosides	1.0%	0.3%
Cefalosporins 1st gen.	5.8%	6.0%
Cefalosporins 3rd & 4th gen.	0.0%	0.0%
Fenicols	0.2%	0.0%
Fluoroquinolones	3.1%	4.5%
Lincosamides	17.7%	15.3%
Macrolides	1.1%	0.7%
Nitrofuran Derivatives	0.3%	0.2%
Nitromidazole Derivatives	4.4%	4.5%
Penicillins	55.4%	60.6%
Rifamycins	0.3%	0.1%
Sulfonamides	0.0%	1.3%
Tetracyclines	7.0%	3.7%
Trimethoprim/sulfonamides	3.1%	1.6%
Total	**100.0%**	**100.0%**

TABLE 4. USED ANTIMICROBIAL GROUPS AT THE CSCA IN 2018 AND 2019 IN PERCENTAGE PER NUMBER OF DDDA.

The active substance most used in 2018 was amoxicillin/clavulanic acid (53.1%; 2.00/3.77), followed by clindamycin (17.8%; 0.67/3.77), doxycycline (6.9%; 0.26/3.77) and metronidazole (4.2%; 0.16/3.77). The active substance most used in 2019 was amoxicillin/clavulanic acid (58.4%; 1.80/3.08), followed by clindamycin (15.3%; 0.47/3.08), metronidazole (4.5%; 0.14/3.08) and doxycycline (3.6%; 0.11/3/08). In comparison, from 2013 to 2017, the active substance used most was amoxicillin/clavulanic acid (62.6%; 2.78/4.44), followed by clindamycin (8.6%; 0.38/4.44), enrofloxacin (6.8%; 0.30/4.44) and metronidazole (4.7%; 0.21/4.44)..

From 2013 to 2017, 11.9% (5041/42,428) unique patients were individually prescribed antimicrobials. In 2018, this number was 9.0% (910/10,063). In dogs, 9.2% (594/6436) was prescribed antimicrobials, in cats 7.0% (185/2632) and in exotic species 13.2% (131/995). The percentage of unique patients individually prescribed antimicrobials in 2019 was 9.3% (1014/10,849). In dogs, 9.4% (651/6945) was prescribed antimicrobials, in cats 6.9% (184/2650) and in exotic species 14.3% (179/1254). A full overview from 2013-2019 of patients to which antimicrobials were prescribed is shown in Table 5.

	2013	2014	2015	2016	2017	2018	2019
Dog	822	775	713	670	597	594	651
Cat	162	178	158	180	157	185	184
Exotic	109	112	100	117	191	131	179
Total	**1093**	**1065**	**971**	**967**	**945**	**910**	**1014**

TABLE 5. NUMBER OF UNIQUE PATIENTS AT THE CSCA TREATED WITH ANTIMICROBIALS.

In 2018, 58.6% of the antimicrobials was individually prescribed to dogs and cats (2.21/3.77) and 6.6% was individually prescribed to exotic species (0.25/3.77). The individually prescribed antimicrobials were mostly classified as second-line drugs (49.6%; 1.22/2.46). The

most individually prescribed type of antimicrobial was amoxicillin/clavulanic acid (44.3%; 1.09/2.46). In 2019, 64.3% of the antimicrobials was individually prescribed to animal patients (1.98/3.08), of which 61.7% (1.90/3.08) to dogs and cats and 2.6% (0.08/3.08) to exotic species. Similar to 2018, the individually prescribed antimicrobials were mostly classified as second-line drugs (55.6%; 1.10/1.98). The most individually prescribed type of antimicrobial was also amoxicillin/clavulanic acid (51.0%;1.01/1.98). From 2013 to 2017, 65.2% (2.90/4.44) of the antimicrobial consumption was because of individual drug prescription to animal patients. Second-line drugs were most used (61.7%; 1.79/2.90) and the drug most prescribed was amoxicillin/clavulanic acid (54.7%; 1.58/2.90).

The remaining 34.7% (1.31/3.77) and 35.7% (1.10/3.08) of distributed antimicrobials in 2018 and 2019 were distributed to wards of the CSCA. In 2018, the sub-department at the CSCA which contributed the most to the antimicrobial usage in DDDAs, was the Intensive Care Unit (14.1%; 0.53/3.77). Drugs classified as cascade drugs were used most often at this sub-department (81.1%; 0.43/0.53). The Intensive Care Unit was followed by the Emergency Clinic (12.5%; 0.47/3.77). Compared to the Intensive Care Unit, the Emergency Clinic did not use cascade-drugs the most, but drugs classified as second-line (72.3%; 0.34/0.47). In 2019, the Intensive Care Unit was also the largest contributor to the antimicrobial usage with 16.0% (0.49/3.08), followed by the Emergency Clinic with 11.7% (0.36/3.08). Drugs classified as cascade-drugs were mostly used at the Intensive Care Unit (83.7%; 0.41/0.49) and at the Emergency Clinic, second-line drugs were used most (77.7%; 0.28/0.36). The results of the antimicrobial usage at the different sub-departments at the CSCA are given in Table 6.

Sub-department	Classification	2018	2019
Intensive Care Unit	First-line	0.02	0.01
	Second-line	0.08	0.05
	Third-line	0.01	0.01
	Cascade	0.43	0.41
	Total	**0.53**	**0.49**
Operating Room	First-line	0.00	0.00
	Second-line	0.00	0.01
	Third-line	0.00	0.00
	Cascade	0.08	0.08
	Total	**0.09**	**0.08**
Outpatient Clinic	First-line	0.00	0.00
	Second-line	0.00	0.01
	Third-line	0.00	0.00
	Cascade	0.00	0.00
	Total	**0.00**	**0.01**
Emergency Clinic	First-line	0.10	0.04
	Second-line	0.34	0.28
	Third-line	0.00	0.00
	Cascade	0.03	0.03
	Total	**0.47**	**0.36**
Nursing Wards	First-line	0.02	0.00
	Second-line	0.09	0.05
	Third-line	0.01	0.00
	Cascade	0.00	0.00
	Total	**0.11**	**0.06**
Zoological Medicine	First-line	0.09	0.07
	Second-line	0.00	0.00
	Third-line	0.01	0.01
	Cascade	0.01	0.03
	Total	**0.11**	**0.11**
Prescription	First-line	0.78	0.66
	Second-line	1.21	1.09
	Third-line	0.10	0.12
	Cascade	0.12	0.03
	Total	**2.21**	**1.90**
Prescription Exotic	First-line	0.19	0.02
	Second-line	0.01	0.01
	Third-line	0.00	0.00
	Cascade	0.05	0.05
	Total	**0.25**	**0.08**
Total	First-line	1.19	0.81
	Second-line	1.73	1.51
	Third-line	0.12	0.14
	Cascade	0.73	0.63
	Total	**3.77**	**3.08**

TABLE 6. ANTIMICROBIAL CONSUMPTION DESCRIBED IN NUMBER OF DDDA'S AT THE DIFFERENT SUB-DEPARTMENTS AT THE CSCA AT UTRECHT UNIVERSITY.

Comparing the sub-departments to each other, several differences were found. Drugs classified as cascade-drugs were the sort of drugs most used at the Intensive Care Unit and

Operating Room. Drugs classified as second-line drugs were the most used drugs at the Emergency Clinic and the Nursing Wards. Drugs classified as first-line drugs were the most used drugs at the Division of Zoological Medicine.

Antimicrobial Resistance Patterns

In 2018, a total of 1206 samples were obtained from the different divisions at the CSCA and submitted for bacterial culture and antimicrobial susceptibility testing. Most of these were samples obtained from dogs (77.4%; 934/1206), followed by cats (17.7%; 214/1206) and exotic species (4.8%; 58/1206). In 2019, a total of 1082 samples was obtained, of which again most were dogs (79.4%; 859/1082), followed by cats (16.2%; 175/1082) and exotic species (4.4%; 48/1082). A full overview of the obtained samples from 2013 to 2019 is shown in Table 7. A full overview of the percentage submitted samples per total patients per year is shown in Table 8. The highest percentage of submitted samples was reached in 2013 (14.1%; 1089/7740). The lowest percentage was reached in 2019 with 10% (1082/10,849).

	2013	2014	2015	2016	2017	2018	2019
Dog	883	852	831	906	865	934	859
Cat	168	168	127	191	168	214	175
Exotic	38	29	29	33	40	58	48
Total	**1089**	**1049**	**987**	**1130**	**1073**	**1206**	**1082**

TABLE 7. NUMBER OF SAMPLES OBTAINED FROM THE CSCA SUBMITTED FOR BACTERIAL CULTURE AND ANTIMICROBIAL SUSCEPTIBILITY TESTING.

	2013	2014	2015	2016	2017	2018	2019
Dog	15.1	14.5	15.0	16.4	15.9	14.5	12.4
Cat	13.8	7.5	5.9	8.0	7.3	8.1	6.6
Exotic	5.5	3.7	3.7	4.2	4.6	5.8	3.8
Total	**14.1**	**11.8**	**11.6**	**13.0**	**12.5**	**12.0**	**10.0**

TABLE 8. PERCENTAGE OF SUBMITTED SAMPLES PER TOTAL PATIENTS PER YEAR PRESENTED AT THE CSCA.

The most submitted material in 2018 was urine with 47.5% (573/1206), followed by skin samples with 11.3% (136/1206) and ear canal samples with 10.9% (132/1206). The most submitted material in 2019 was also urine with 44.8% (485/1082), followed by skin samples with 11.3% (122/1082) and unspecified puncture specimens with 10.7% (116/1082). A full overview of all materials submitted from 2013 to 2019 is given in Table 9.

	2013	2014	2015	2016	2017	2018	2019
Urine	453	382	340	505	473	573	485
Ear Canal	133	180	175	167	134	132	105
Skin	48	70	133	152	121	136	122
Respiratory Tract	110	87	56	57	85	87	73
Wounds and Abcesses	86	96	73	60	58	60	98
Free Fluid	50	32	32	42	25	0	0
Blood	41	21	30	23	21	0	0
Synovial Fluid	14	21	21	21	29	33	23
Genital Tract	24	20	18	16	17	0	1
Nervous System	24	20	18	13	9	0	0
Faeces	13	13	10	5	19	31	10
Unspecified Puncture Specimen	76	85	67	56	69	118	116
All Other	17	22	14	13	13	36	49
Total	**1.089**	**1.049**	**987**	**1.130**	**1.073**	**1206**	**1082**

TABLE 9. OVERVIEW OF MATERIALS SUBMITTED FOR ANTIMICROBIAL SUSCEPTIBILITY TESTING IN 2018 AND 2019 AT THE CSCA.

The division submitting the most samples in 2018 was Internal Medicine with 34.1% (411/1206), followed by General Surgery with 34.0% (410/1206) and Dermatology with 9.5% (114/1206). In 2019, the division submitting the most samples was General Surgery with 36.3% (393/1082), followed by Internal Medicine with 30.3% (328/1082) and Dermatology with 12.2% (132/1082). A full overview of the origin of all obtained samples is given in Table 10.

Division	2013	2014	2015	2016	2017	2018	2019
General Surgery	556	490	413	382	398	410	393
Internal Medicine	257	286	239	384	328	411	328
Dermatology	48	84	168	178	118	114	132
Intensive Care Unit	126	99	79	84	107	73	93
Zoological Medicine	37	29	29	31	36	57	36
Ophthalmology	18	29	19	21	35	55	40
Reproductive Medicine	19	17	19	15	18	21	24
All other	28	15	21	35	33	65	36
Total	**1089**	**1049**	**987**	**1130**	**1073**	**1206**	**1082**

TABLE 10. ORIGIN OF ALL OBTAINED SAMPLES FOR ANTIMICROBIAL SUSCEPTIBILITY TESTING AT THE CSCA FROM 2013-2019.

In 2018, 42.2% (509/1206) of the submitted samples tested positive for at least one of the bacterial species of interest. In 2019, this percentage was 39.0% (422/1082).The bacterial species isolated most frequently in 2018 were *Staphylococcus* species with a total of 247 out of 1206 samples (20.5%). These bacterial species were mostly isolated out of skin samples (47,0%; 116/247). The most positive tested samples were obtained from dogs, with 91.5% (226/247). 193 samples were identified as *S. pseudintermedius* (78.1%; 193/247), of which 16 were methicillin-resistant (8.3%; 16/193). *S. pseudintermedius* was followed by coagulase-negative *Staphylococcus* species with 10.1% (25/247), of which none were methicillin-resistant. These were followed by *S. aureus* with 6.1% (15/247), of which 6.7% methicillin-resistant (1/15). 14 samples tested positive for other *Staphylococcus* species (5.7%; 14/247). These other *Staphylococcus* species included *S. delphini*, *S. pettenkoferi* and *S. schleiferi*. None of these other *Staphylococcus* species were tested positive as methicillin-

resistant. This results in a total of 17 resistant *Staphylococcus* sp. strains in 2018 (6.9%; 17/247). Most of these were obtained from dogs (94.0%; 16/17) and were isolated out of wounds and abscesses samples (58.8%; 10/17).

In 2019, *Staphylococcus* species were isolated 199 times out of 1082 samples (18.4%). These species were mostly isolated out of skin samples (50.8%; 101/199). The most positive tested samples were again obtained from dogs (92.5%; 184/199). 154 samples tested positive for *S. pseudintermedius* (77.4%; 154/199), of which 8 were methicillin-resistant (5.2%; 8/154). *S. pseudintermedius* was followed by coagulase-negative *Staphylococcus* species (13.6%; 27/199), of which none were methicillin-resistant. These were followed by *S. aureus* with 5.0% (10/199), none of the isolates were tested as methicillin-resistant. 8 samples tested positive for other *Staphylococcus* species (4.0%; 8/199). None of these other *Staphylococcus* species were tested positive as methicillin-resistant. This results in a total of 8 MDR *Staphylococcus* sp. strains in 2019 (4.0%; 8/199). 7 out of 8 samples were obtained from dogs (87.5%) and most were isolated out of skin samples (50%; 4/8).

	2013	2014	2015	2016	2017	2018	2019
Dog	14.7	4.8	8.5	7.8	7.8	7.1	3.8
Cat	21.1	8.0	5.3	0.0	5.3	0.0	8.3
Exotic	0.0	0.0	0.0	0.0	0.0	20.0	0.0
Total	**14.8**	**5.0**	**8.2**	**7.2**	**7.5**	**6.9**	**4.0**

TABLE 11. PERCENTAGE OF METHICILLIN *STAPHYLOCOCCUS* SPECIES OUT OF ALL ISOLATED *STAPHYLOCOCCUS* SPECIES FROM 2013-2019.

After *Staphylococcus* species, *Enterobacteriaceae* were isolated the most in 2018 (12.4%; 150/1206). Most of these were obtained from dogs (79.3%; 119/150). 66.0% was isolated from urine samples (99/150). *Escherichia coli* was the most isolated sort of *Enterobacteriaceae* with 68.7% (103/150), followed by *Proteus* sp. (22.0%; 33/150). The remaining isolated *Enterobacteriaceae* were *Klebsiella* sp., *Enterobacter* sp., *Salmonella* sp., *Citrobacter* sp. and *Serratia* sp.. 10 out of the 150 isolated samples were labelled as ESBL-producing (6.7%), of which 8 out of dogs (80%; 8/10) and 2 out of cats (20%; 2/10). Most of these ESBL-producing isolates were cultured from urine samples (40%; 4/10). In 2019, 144 out of 1082 samples isolated were labelled as *Enterobacteriaceae* (13.3%), most obtained from dogs (77.1%; 111/144) and 65.3% isolated from urine samples (94/144). *Eschericha coli* was again the most isolated sort of *Enterobacteriaceae* with 77.1% (111/144). This number was followed by *Proteus* sp. with 4.9% (7/144). The remaining *Klebsiella* sp., *Enterobacte*r sp., *Salmonella* sp. and *Citrobacter* sp. accounted for 12.5% (18/144). 7 out of 144 isolated samples were labelled as ESBL-producing (4.9%), of which 5 obtained from dogs (71.4%; 5/7) and two from cats (28.6%; 2/7). Most of the ESBL-producing isolates were cultured from wounds and abscesses (42.3%; 3/7) and unspecified puncture specimens (42.3%; 3/7).

	2013	2014	2015	2016	2017	2018	2019
Dog	5.8	5.2	1.0	5.0	9.1	6.8	4.6
Cat	4.0	5.9	5.9	0.0	0.0	7.4	0.0
Exotic	0.0	0.0	0.0	0.0	0.0	0.0	16.7
Total	**5.4**	**5.0**	**1.6**	**4.0**	**7.8**	**6.8**	**4.3**

TABLE 12. PERCENTAGE OF ESBL-PRODUCING SAMPLES OUT OF ALL ISOLATED *ENTEROBACTERIACEAE* SPECIES FROM 2013-2019.

Out of the 1206 bacterial culture samples in 2018, 98 were isolated *Pseudomonas s*pecies (8.1%), all confirmed as *Pseudomonas aeruginosa*. Most of these isolates were obtained from ear canal swabs (83.7%; 82/98) and 92 isolates were obtained from dogs (93.9%; 92/98). 96 isolates were confirmed to be resistant (97.6%; 96/98), with 14 labelled as MDR (14.6%; 14/96). 13 out of 14 MDR *Pseudomonas* sp. were obtained from dog ear canals (92.9%; 13/14). 1 sample was obtained from a reptiles respiratory tract (7.1%; 1/14). Resistance to antimicrobials was highest for fluoroquinolones, with 86 isolates labelled as resistant or intermediate (87.8%; 86/98). In 2019, 60 out of 1082 bacterial culture samples were isolated *Pseudomonas* species (5.5%), all confirmed as *Pseudomonas aeruginosa* except for one confirmed as *Pseudomonas luteola*. Most isolates were obtained from ear canal swabs (65.6%; 40/61) and 55 out of 61 isolates were obtained from dogs (90.2%). 59 bacterial culture samples were confirmed to be resistant to at least one antimicrobial (98.4%; 60/61), with 7 labelled as MDR (11.7%; 7/60). 6 out of 7 MDR *Pseudomonas* species were obtained from dog ear canals (85.7%), 1 was obtained from an unspecified puncture specimen from a dog (14.3%; 1/7). Resistance to antimicrobials was highest for fluoroquinolones, with 55 isolates labelled as resistant or intermediate (91.7; 55/60).

	2013	2014	2015	2016	2017	2018	2019
Dog	15.5	6.0	3.7	15.9	11.8	2.2	3.6
Cat	0.0	0.0	0.0	0.0	50.0	0.0	0.0
Exotic	0.0	0.0	0.0	0.0	50.0	0.0	0.0
Total	**14.4**	**5.6**	**3.4**	**15.1**	**14.9**	**2.0**	**3.3**

TABLE 13. PERCENTAGE OF MDR SAMPLES OUT OF ALL ISOLATED *PSEUDOMONAS* SPECIES FROM 2013-2019.

In 2018, *Enterococcus* sp. were isolated 13 times out of 1206 bacterial culture samples (1.1%), of which 10 samples confirmed to be *E. faecalis* (76.9%; 10/13) and 3 samples *E. faecium* (23.1%; 3/13). 12 of these bacterial cultures were labelled as resistant (92.3%; 12/13), with 8 labelled as MDR (66.7%; 8/12). 8 out of 13 samples were obtained from dogs (61.5%) and 5 out of 13 were obtained from cats (38.5%). Most *Enterococcus* sp. isolates were obtained from urine samples (69.2%; 9/13). Resistance to antimicrobials was highest for ryfamicines (100%; 13/13). In 2019, *Enterococcus* sp. was isolated 19 times out of 1082 bacterial culture samples (1.8%), with 10 samples confirmed to be *E. faecalis*, 8 samples of *E. faecium* and 1 sample of *E. hirae*. All isolates were labelled as resistant to at least one antimicrobial (100%; 19/19), with 11 labelled as MDR (57.9%; 11/19). 12 samples were obtained from dogs (63.2%; 12/19) and 7 from cats (36.8%; 7/19). Most isolates were obtained from urine samples (52.6%; 10/19). Resistance to antimicrobials was highest for fluoroquinolones (100%; 19/19).

	2013	2014	2015	2016	2017	2018	2019
Dog	0.0	21.4	40.0	18.2	62.5	50.0	50.0
Cat	0.0	0.0	60.0	33.3	0.0	80.0	71.4
Exotic	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	**0.0**	**20.0**	**46.7**	**23.5**	**41.7**	**61.5**	**57.9**

TABLE 14. PERCENTAGE OF MDR SAMPLES OUT OF ALL ISOLATED *ENTEROCOCCUS* SPECIES FROM 2013-2019.

The last researched bacterial culture sample *Acinetobacter* sp. was isolated 3 times in 2018 (0.2%; 3/1206). 1 *Acinetobacter lwoffii* (33.3%), 1 *Acinetobacter baumannii* (33.3%) and 1 undefined *Acinetobacter* species (33.3%). 2 out of 3 samples were labelled as resistant to at least one antimicrobial (66.7%), with 1 labelled as MDR. 2 samples were obtained from dogs (66.7%; 2/3) and one from a cat (33.3%; 1/3). Most *Acinetobacter* sp. bacterial culture isolates were obtained from urine samples (66.7%; 2/3). In 2019, *Acinetobacter* sp. was isolated 3 times out of 1082 samples (0.3%). 2 *Acinetobacter baumannii* (66.7%) and 1 *Acinetobacter pitti* (33.3%). All *Acinetobacter* species were tested as MDR (100%; 3/3). All samples were obtained from dogs (100%; 3/3), with 2 ear canal swab samples (66.7%) and 1 wounds and abscesses sample (33.3%).

	2013	2014	2015	2016	2017	2018	2019
Dog	0.0	71.4	0.0	0.0	0.0	50.0	100.0
Cat	0.0	0.0	0.0	100.0	0.0	0.0	0.0
Exotic	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	**0.0**	**71.4**	**0.0**	**50.0**	**0.0**	**33.3**	**100.0**

TABLE 15. PERCENTAGE OF MDR SAMPLES OUT OF ALL ISOLATED *ACINETOBACTER* SPECIES FROM 2013-2019.

In total, 4.15% (50/1206) bacterial isolates cultured from clinical specimens in 2018 were tested as MDR. Most of these (30%; 15/50), were obtained from ear canal swab samples, followed by samples obtained from wounds and abscesses (26%; 13/50). The majority of samples tested as MDR were submitted by the General Surgery division at the CSCA (70%; 35/50), followed by the Internal Medicine division (10%; 5/50). In 2019, a total of 3.2% (35/1082) bacterial isolates cultured from clinical specimens were tested as MDR, most obtained from ear canal swabs (31.4%; 11/35), followed by urine samples (20%; 7/35). The majority of samples tested as MDR were submitted by the General Surgery division (54.3%; 19/35), followed by the Intensive Care Unit (17.1%; 6/35) and the Internal Medicine division (17.1%; 6/35). 50 samples tested as MDR in 2018 was the highest number since 2013 (53). After 33 samples in 2014, the 35 MDR samples in 2019 were the lowest number from 2013 to 2019. 1206 bacterial isolates cultured in 2018 from clinical specimens submitted by veterinarians working at the CSCA was the highest number from 2013 to 2019, followed by 1130 samples submitted in 2016. The least samples were submitted in 2015 (987).

Material	2013	2014	2015	2016	2017	2018	2019
Ear canal	20	8	8	17	9	15	11
Urine	10	7	4	8	18	8	7
Skin	3	6	8	15	10	2	4
Wounds and abcesses	7	3	8	5	2	13	6
Free fluid	4	2	2	0	1	0	0
Respiratory tract	3	1	0	0	3	2	1
Synovial fluid	1	0	0	0	3	0	0
Genital tract	0	0	2	0	1	0	0
Unspecified puncture specimen	5	6	4	0	0	5	6
All Other	0	0	0	0	0	5	0
Total	**53**	**33**	**36**	**45**	**47**	**50**	**35**

TABLE 16. MATERIAL OF ALL MDR SAMPLES FROM 2013-2019.

Division	2013	2014	2015	2016	2017	2018	2019
General Surgery	39	22	18	22	27	35	19
Dermatology	3	6	12	15	8	2	3
Intensive Care Unit	7	4	1	4	6	0	6
Internal Medicine	3	1	2	4	3	5	6
Ophthalmology	1	0	0	0	2	2	0
Reproductive Medicine	0	0	2	0	0	0	0
Zoological Medicine	0	0	0	0	1	3	1
Emergency Clinic	0	0	0	0	0	1	0
Oncology	0	0	0	0	0	1	0
Diagnostic imaging	0	0	0	0	0	1	0
Total	**53**	**33**	**35**	**45**	**47**	**50**	**35**

TABLE 17. MDR SAMPLES DIVIDED BY DIVISIONS FROM 2013-2019.

Questionnaire

The questionnaire was filled out by the A-team's clinical pharmacist, microbiologist and animal caretaker. All staff members indicated the usefulness of the research by van Bree, F.P.J. et al., by observing a noticeable increased awareness and knowledge of Antimicrobial Stewardship amongst their colleagues (van Bree, F. P. J., Broens et al. 2018). They all expected the DDDAs of 2018 and 2019 to have decreased compared to the years before. Recommendations made by the A-team included setting up a full ASP for the CSCA and a clinic-specific formulary based on the KNMvD formulary; raising awareness to the importance of hygiene in antimicrobial resistance and continuous monitoring, reporting and feedback- follow up of antimicrobial usage, antimicrobial resistance in general and on an individual base in case of complicated patients and/or extraordinary results.

Discussion

The usage of antimicrobials at the CSCA at Utrecht University expressed in DDDAs was 3.77 in 2018 and 3.08 in 2019. There was a decrease of 18,3% in 2019 (3.08) compared to

2018 (3.77). The DDDA of 2019 (3.08) compared to the DDDA of 2013 (5.01) had dropped 38.5%. This means that the average number of days per year an average patient at the CSCA was treated with antimicrobials in 2018 and 2019 had largely lowered compared to the years before. The main goal of the A-team and its ASP at the CSCA at Utrecht University is to prevent an increase in antimicrobial resistance by, among other things, monitoring antimicrobial usage. The downward trend in the DDDA shows the A-team has persisted its goal over the last two years.

The DDDA at the CSCA at Utrecht University can most reliably be compared to itself and not to other veterinary clinics in the Netherlands, because of the variable patient population and its function as veterinary referral centre. The DDDA outcome is also difficult to compare to other international veterinary clinics because of its way of calculation. In various researches, different values have been used to calculate the DDDA. For example, in a study by Redding, E.L., et al., the unique weight per animal was used to calculate the DDDA, instead of an average animal weight per species (Redding, Grunwald et al. 2020). The calculation method in this research has been repeated from the research from 2013 to 2017 (van Bree, F. P. J., Broens et al. 2018). By calculating the DDDA in the exact same way, the most accurate comparison over the years has been made.

In this calculation, the treated weight*day is an average of the canines and felines value when calculating for the Intensive Care Unit, Nursing Wards, Operating Rooms, Outpatient Clinic, Emergency Clinic and individual prescription for cats and dogs. With this average, it has not been taken into account that the distribution of dog and cat patients is not equally divided. In fact, the ratio dog versus cat patients on average in 2018 and 2019 was 71.7% to 28.3%. The antimicrobial usage in DDDA could be calculated more precisely if this ratio would be taken into account, but in practice, the treated weight*day of canines and felines in the Netherlands does not differ in the majority of antimicrobials. Different values can only be found in the active substances clindamycin, nitrofurantoin, florfenicol, rifampicin and a doxycycline injection (Table 1).

The largest contributor of all sub-departments to the DDDA in 2018 and 2019 was the Intensive Care Unit, followed by the Emergency Clinic. Both contributed to the number of DDDA with over 10% of all antimicrobial usage. This high percentage is related to the high importance of combatting bacteria in critical patients. The most used antimicrobials at the Intensive Care Unit were cascade-drugs. This is due to the high usage of the active substance amoxicillin/clavulanic acid as injection powder (AMOXI/CLAV 500/50MG INJPDR). This cascade use of a human labelled product is necessitated because of the lack of intravenously administrable veterinary medicinal products with the active substance amoxicillin/clavulanic acid. Intravenously administrable antimicrobials are of high importance at the Intensive Care Unit due to the possibility to administer higher dosages than when administered orally, the faster and better effectiveness because of the immediate and full administration to the bloodstream, the most likely unpleasant feeling of multiple intramuscular and subcutaneous injections per day and the difficulty to orally administer medication to critically ill patients. The most used antimicrobials at the Emergency Clinic were second-line drugs. This number is caused by the high usage of amoxicillin/clavulanic acid tablets and suspensions.

There was a decrease in antimicrobial usage between 2013 and 2019. A decrease in antimicrobial usage can be accomplished by prescribing antimicrobials to fewer patients and by shortening the course of antimicrobials when prescribed to patients. Compared to the 14.1% in 2013 (1093/7739), the ratio of patients treated with antimicrobials had decreased with 5.1% in 2018 (9.0%; 910/10,063) and 4.8% in 2019 (9,3%; 1014/10,849). Less unique patients presented at the CSCA were treated with antimicrobials, which is one of the main set goals by the A-team to reduce antimicrobial resistance. This number only covers individual prescription and not antimicrobials used at the different sub-departments. The antimicrobial quantity of all sub-departments and individual prescription in total did decrease with 17.2% (54,924/66,343) from 2013 to 2019. This shows that AMS has been successfully applied in practice to decrease the usage of antimicrobials at the CSCA.

Another goal set by the A-team was to have comparatively more samples submitted for antimicrobial susceptibility tests by veterinarians working at the CSCA, to monitor antimicrobial resistance rates. But instead of an increase in the percentage of samples submitted per total patients at the CSCA, there was a decrease from 14.1% in 2013 to 10.0% in 2019. This number is caused by the increase of unique patients presented at the CSCA in 2018 and 2019 combined with the roughly same amount of submitted samples in these years (1089 in 2013 and 1082 in 2019). Although a peak of samples was submitted in 2018 (1206), this number had decreased again in 2019 with 10.3% (1082). An explanation for this could be a patient population with different health problems. For instance, patients with gastrointestinal or metabolic problems will have fewer samples submitted than patients with dermal issues. Unfortunately this information could not be extracted from the available data.

The percentage of MDR bacteria amongst submitted samples decreased from 4.38% (47/1073) in 2017 to 4.15% (50/1206) in 2018 to 3.23% (35/1082) in 2019. This shows the multi-drug-resistance percentage has decreased in 2018 and 2019, but the lowest percentage was actually reached in 2014 with 3.15% (33/1049). Unfortunately, due to this low difference and the few submitted samples, a significant conclusion cannot be drawn. To get the most reliable number of multi-drug-resistance, all patients prescribed antimicrobials should have samples submitted for antimicrobial susceptibility tests. This way, the most accurate percentage of multi-drug-resistance at the CSCA can be calculated. In addition, antimicrobial usage can be reduced if the most effective type of antimicrobial is selected by using antimicrobial susceptibility tests. Thus, unnecessary usage of non-functioning antibiotics can be prevented and the clinic's DDDA can be reduced.

The questionnaire filled out by the members of the A-team summarised the importance of an ASP to prevent antimicrobial resistance from increasing by lowering the antimicrobial usage at the CSCA. It is important for the A-team at the CSCA to create a clear ASP for its employees. This way, the importance of Antimicrobial Stewardship can be emphasised to stimulate employees to reduce antimicrobial usage and to be more careful when administering antibiotics.

Conclusion

In conclusion, the compliance of Antimicrobial Stewardship at the CSCA at Utrecht University can be endorsed by the positive results. The prescription of antimicrobials in number of DDDA's has decreased and awareness of careful antimicrobial usage seems to have increased amongst employees. The number of culturing and antimicrobial susceptibility tests appears to have decreased and the attitude towards testing might need to be brought to the attention of the veterinarians at the CSCA, in order to further optimise their antimicrobial prescriptions when needed. To optimise Antimicrobial Stewardship at the CSCA, its ASP should be endorsed and reminders of its importance should be consistently carried out. The A-team, pharmacy and the CSCA should collaborate and exchange information about antimicrobial usage and resistance. With recent and accurate data, employees can track improvement or deterioration and be stimulated to contribute to better results.

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