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ORIGINAL RESEARCH

Comparison of metrics to assess antibiotic use in small ruminants at a university referral clinic between 2005 and 2019

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Abstract

Background: Monitoring antibiotic use is essential to provide a framework enabling veterinarians to use antibiotics prudently.

Methods: Electronic medical records from the University of Veterinary Medicine's Clinic for Ruminants in Vienna were analysed with respect to sheep and goat antibiotic doses administered over a 15-year period (2005–2019). Antibiotic use was assessed using total milligrams per kilogram (mg/kg), total milligrams, number of doses administered, defined daily doses (DDD) for cattle and estimated DDD for sheep.

Results: A total of 5113 antibiotic doses were recorded over the 15-year period. Urinary tract disorders required the highest number of doses administered per animal (mean 16.9; median 16.0). Antibiotic use patterns varied according to the metrics used for analysis. By mg/kg, the largest proportion of antibiotics administered were penicillin/streptomycin (43.0% of the total mg/kg), followed by tetracyclines (17.3%) and sulphonamide/trimethoprim combinations (15.2%). By number of doses administered, the most frequently used antibiotics were penicillins (excluding combinations with streptomycin) (33.9% of total number of doses administered), fluoroquinolones (25.1%), third/fourth-generation cephalosporins (13.6%) and penicillin/streptomycin (13.4%).

Limitations: As the university clinic was a city-based referral centre, this analysis cannot be compared directly with antibiotic use in commercial herds or flocks.

Conclusions: The considered choice of antibiotic use metrics is essential for an effective and meaningful analysis of the responsible use of antibiotics by veterinarians in practice.

INTRODUCTION

Antibiotic sales for use in livestock production have been monitored on a voluntary basis in the European Union (EU) since 2009; however, given that veterinary medicinal products are often licensed for use in many species of animals, it has been impossible to analyse sales data by species.[1] To allow consideration of varying livestock populations with respect to national antibiotic sales, the population correction unit (PCU) is calculated for the European Sales of Veterinary Antimicrobial Agents (ESVAC) report, which is based on an estimate of the livestock biomass in kilograms of national livestock herds and slaughter numbers in each country assessed. In 2021, sheep and goats made up just 13.2% of the total PCU over 31 European countries.[2] National variations in the small ruminant proportion of the PCU varied from 0.4% in Denmark to 38.7% in the UK and 60.1% in Greece.[2] In Austria, the PCU for sheep and goats was 3.9% of the country's total (made up of a reported 402,000 sheep and 101,000 goats[3]), while national antibiotic data determined that small ruminants accounted for just 0.2% of all antibiotics dispensed for use in food-producing animals in the country in 2021.[4]

Due to their apparently small contribution to agricultural production and the relatively low economic value of the individual animals to farmers, veterinarians and pharmaceutical companies, many antibiotics are not specifically licensed for use in minor species such as sheep and goats. Therefore, the use of antibiotics to treat small ruminants poses a number of problems. Due to the limited choice of antibiotic agents, veterinarians often find themselves having to use drugs 'off-label' based on the EU cascade rule. The dosage is then frequently estimated on the basis of clinical experience or pharmaceutical formularies.[5,6]

There are a variety of classifications for antibiotics based on their importance to both human and veterinary medicine. The European Medicines Agency (EMA) has introduced a set of categories for the prudent use of antibiotics in veterinary medicine.[7] These range from Category A (not licensed for use in veterinary medicine) to Category D (first-choice antibiotics, which should still be used prudently).

A number of studies of antibiotic use have considered the importance of the different metrics used to quantify such use.[8–11] While national antibiotic monitoring data commonly use mass-based metrics, such as tonnes, milligrams or milligrams per kilogram (mg/kg) or PCU, this is primarily due to data availability (often only sales data are recorded and are lacking species-specific information), ease of analysis and to allow some level of comparison between countries.[11,12] However, a number of researchers, such as Mills et al.,[8] have noted that mass-based indicators display some antibiotic use (such as higher potency modern generation cephalosporins, which are used at a lower dose than older low potency drugs) in a more favourable light than other antibiotics. For this reason, in the present study, it was decided to provide a comparison of antibiotic use in mass-based, defined daily dose ('DDD sheep' or 'DDD goat')-based and numerical units, such as the number of doses administered.

The study presented here aimed to analyse antibiotic doses administered to small ruminants at the University of Veterinary Medicine's ruminant referral clinic in Vienna over an extended period. Trends with respect to both the quantity and the type of antibiotics used were examined from 2005 to 2019. Particular attention was given to variations in antibiotic use patterns visualised by a variety of metrics. In addition, antibiotics used were divided into EMA categories,[7] with a particular focus on Category B 'restricted' antibiotics. It was hypothesised that the use of these critical antibiotics, in particular, would have reduced over time, given the publication of a number of local and pan-European prudent use recommendations for veterinary medicine during the observed study period. Furthermore, it was assumed that the use of different antibiotic use metrics would lead to very diverse use patterns, illustrating the need for caution when comparing analyses of antibiotic use between countries, farms or veterinary practices.

MATERIALS AND METHODS

Data source

As a basis for this retrospective observational analysis, data from all sheep and goats listed in the Animal Hospital Information System (TIS, Agfa HealthCare Group) between 2005 and 2019 were used. This computerised system has been used by the University of Veterinary Medicine in Vienna since 2001 to keep digital records of patient and owner data, clinical history, diagnostics and therapy of treated animals. As only retrospective patient data were analysed, in accordance with local legislation, no ethics committee approval was required for this study.

Data extraction

All data concerning doses administered to sheep and goats were exported from the database of the University Clinic for Ruminants into an Excel spreadsheet (Microsoft Excel, Microsoft Corporation). Case data from 1 January 2005 to 31 December 2019 were included in the analyses. These data were then filtered to include only antibiotic treatments administered.

The data exported included the case number generated by the hospital information system, species, breed, sex, date of birth and animal identification number of each patient. In addition, the date and time of drug application, the antibiotic class, the trade name of the drug, the administered dose and the mode of administration were extracted. Furthermore, the initial and final diagnoses, as well as the animal's condition upon clinic discharge, were noted. In order to be able to calculate the age of the animal at the time of treatment, the dates of the clinic stay were also accessed. No personal data (e.g., name, address and telephone number) of the animal owners were extracted or analysed.

Antibiotic dosage information

Information regarding the concentration and dosage of the medicinal products administered was obtained primarily via the 'Summary of Product Characteristics' (SPC) available online from the Austrian federal register of medicinal products (https://aspregister.basg.gv.at/aspregister/faces/aspregister.jspx). If the marketing authorisation of the medicinal products in Austria had expired or had never been granted, the required information was obtained from the data of the medicinal products authorised in Germany, which was accessed via the website of the Federal Institute for Drugs and Medical Devices (https://portal.dimdi.de/amguifree/am/search.xhtml). For combination preparations, all active ingredients and dosages were noted.

If possible, licensed dosages were documented for small ruminants. If the drug was not approved in these minor species, then the dosages for cattle or pigs were

TABLE 1 European Medicines Agency categorisation of veterinary antibiotics

A ('avoid')	B ('restrict')	C ('caution')	D ('prudent use')
Not authorised for veterinary use in the European Union	Critically important for human health	Alternatives exist in human medicine	First-line treatments but only when medically necessary
- Carbapenems - Glycopeptides - Drugs used solely to treat tuberculosis, etc.	- Cephalosporins (third and fourth generation) - Polymyxins - Fluoroquinolones	- Aminoglycosides - Aminopenicillins (combinations with β-lactamase inhibitors) - Cephalosporins (first and second generation) - Amphenicols - Lincosamides - Pleuromutilins - Macrolides - Rifaximin	- Aminopenicillins - β-Lactamase-sensitive and resistant penicillin - Sulphonamides (and combinations, including trimethoprim) - Tetracyclines - Nitrofuran derivatives - Spectinomycin - Bacitracin - Fusidic acid - Metronidazole

Source: Modified from Ref. 7

used. Furthermore, information on the antibiotics used was taken from the published German-language formulary 'Dosing recommendations for medications for small ruminants and South American camelids'.[6] If multiple different doses were published in the above-mentioned sources, the mean dose was calculated. In addition, the unit of the medicines administered was included in the dataset.

Classification of veterinary antibiotics

Antibiotic classes were grouped into categories from A to D according to the template of the EMA.[7] For details, see Table 1.

Diagnosis coding

In Austria, veterinary diagnoses in dairy cattle enrolled in national milk recording systems are collected, analysed and published annually in the 'Health monitoring' (Gesundheitsmonitoring—GMON) report.[13] In the present study, this diagnosis coding system was used to categorise sheep and goat disease, with some minor alterations made for small ruminants. A summary of the health monitoring coding system is provided in Table S1.

The veterinary hospital software included a text box entry for an initial diagnosis and a diagnosis on clinic discharge. These entries were made by the responsible veterinarian and were not standardised. Diagnosis coding based on these entries was primarily performed by H. K., with assistance from the remaining authors for any unclear cases.

Liveweight calculations

Where available, the liveweight of the animals was filtered from the clinical records and transferred to an Excel spreadsheet. Given the large differences between breed sizes in sheep and goats (ranging from an adult pygmy goat weighing 25–30 kg to adult Tyrolean mountain sheep weighing 100–130 kg), liveweight for all animals was also estimated using the Brody growth curve dependent on sheep or goat breed standards.[14–16] The breed and sex of the patient were taken from the clinical records. The breed-specific liveweight of adult animals was taken, where possible, from the book 'The colour atlas of domestic livestock breeds (Farbatlas Nutztierrassen)'.[17] In individual cases and for rare breeds, data from specialist breeding websites were used. The baseline standardised liveweight for all sheep and goat breeds included in this dataset can be found in Table S2.

Total mg/kg calculations

For each antibiotic class, the total milligrams administered were summed and then divided by the total liveweight for all animals treated with the substance. Similar to the milligrams per PCU metric used in the ESVAC report,[2] this was a descriptive unit of antibiotic use and could not be directly linked to dosages administered.

Defined daily doses

As no recommended DDD values have been assigned for sheep or goats by the EMA, an estimation of a DDD was calculated here by dividing the total milligrams of antibiotic administered to the animal by the recommended and licensed dose taken from the SPC of each medication (Table S3). Prior to this, the dataset was filtered to include only antibiotics that were licensed for use in sheep or goats in Austria or Germany or had a recommended therapeutic dose in a published formulary[6] at the time of the study. These values were then summed to give the total number of 'DDD sheep' or 'DDD goat' for each licensed antibiotic. If more than one licensed dose was available for an antibiotic, then the mean dose was used. As not all antibiotics administered at the clinic during the study period were licensed for use in sheep or goats, only certain antibiotics could be analysed in this manner.

A DDDvet for cattle has been published and was available from the EMA for all of the included antibiotics.[18] This DDDvet for cattle was therefore

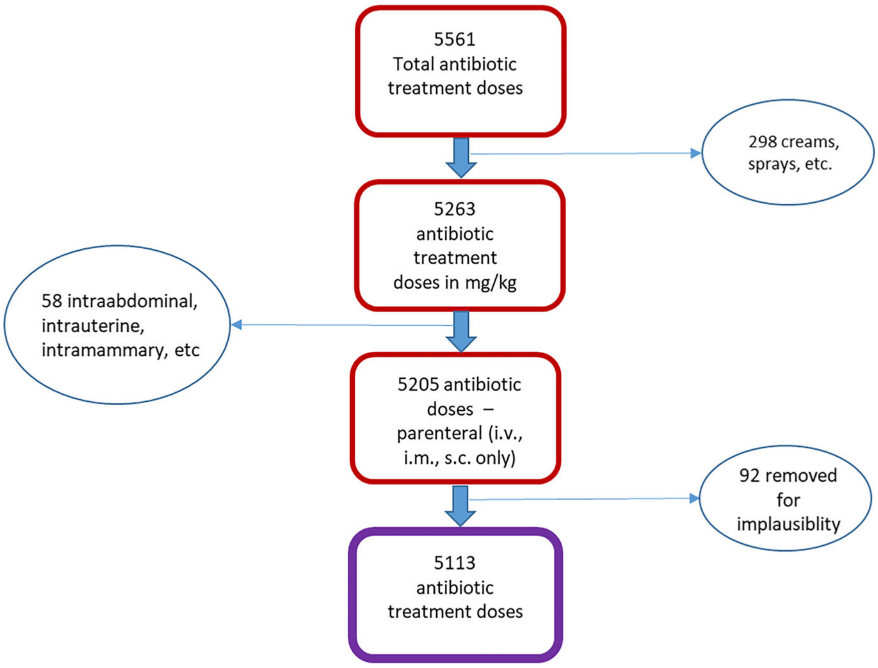

FIGURE 1 Flowchart of antibiotic treatment doses included in the study dataset. (i.m., intramuscular; i.v., intravenous; s.c., subcutaneous)

used to provide a comparison to the study-based estimates of 'DDD sheep' or 'DDD goat'.

RESULTS

Demographics

Over the 15-year study period, 1129 individual animals (503 sheep and 626 goats) were treated at the university referral clinic. Of these, 84.6% (955/1129) were treated with antibiotics. Antibiotics were administered to 84.3% (424/503) of sheep and 84.8% (531/626) of goats. The highest number of individual small ruminant patients treated with antibiotics was reported in 2008, namely, 58 sheep and 48 goats. Some patients were treated in more than 1 year and may be counted twice as unique patient numbers were not always given to the same animals year on year. The mean age of the study population was 36 months at the time of treatment (median age 31 months). Animals ranged from newborn lambs and kids (0 month old) to a castrated male pygmy goat aged 22 years.

Antibiotic doses administered

In total, over the 15-year period, 5561 antibiotic doses were administered to the 955 patients (Figure 1). A treatment dose refers to an application of antibiotic, which may have occurred daily, twice daily or more/less frequently. Of these, 298 treatments were creams, eye drops or sprays that could not be adequately quantified in milligrams. As intrauterine, intrabdominal and intramammary treatments are primarily administered in tablets or tubes as milligrams per unit, these treatment doses (n = 58) were also excluded from the final dataset. The remaining 5205 doses administered were defined in mg/mL and administered in mL/kg; as such, a mg/kg dose could be calculated.

To ensure that all remaining treatments were plausible, the amount of antibiotic administered in milligrams was divided by the recommended dose in mg/kg to obtain the putative liveweight of the animals. A box plot was then created based on the individual animal's liveweight according to this calculation (Figure S1). All values up to the upper whisker (equivalent to Q3 +1.5 interquartile range) were included in this dataset. Values above the upper whisker were more than 200 kg. The authors considered it implausible that an individual sheep or goat would reach this liveweight, and as such, these extreme outlying treatments (n = 71) were excluded. (*Note*: It is likely that these apparent 'overdoses' were actually a number of individual treatments given to the owners to administer at home; however, the hospital software did not record this information.) Furthermore, to take pygmy goats and dwarf sheep into account, all drug administrations reported at 50 mg/kg or more were considered implausible and excluded (n = 21).

After data cleaning and final preparation, a total of 5113 antibiotic doses administered remained in the dataset (Figure 1). As a large number of actual liveweights were missing from this dataset (2881/5113; 56.3%), the standardised liveweight for each sheep or goat breed was calculated for all animals in this study using the Brody growth curve[14–16] and used to calculate the total mg/kg of antibiotic administered.

Number of antibiotic doses administered per animal over time

Based on the final dataset (N = 5113), the number of doses administered per animal and year are shown in Table 2. A total of 168 out of 926 individual animals received only one antibiotic dose (18.1% of

TABLE 2 Number of antibiotic doses administered per animal

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Number of patients	52	86	100	106	49	52	77	58	74	52	53	46	53	50	41
Median number of doses administered	3.0	3.0	3.0	4.5	3.0	3.5	3.0	4.0	3.0	3.0	3.0	3.0	3.0	2.0	2.0
Minimum	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Maximum	18	40[a]	50[a]	51[a]	8	24	39[a]	19	16	16	30	18	23	13	17
Total number of doses administered	233	479	564	1185	153	269	412	295	299	212	254	170	285	148	155

[a]These maximum number of doses administered per animal per year were recorded for repeated hospital visits within that year, for example, in 2008, one goat was treated with antibiotics for a 14-day and 23-day period, respectively.

TABLE 3 Number and proportions of doses administered by European Medicines Agency (EMA) category and antibiotic class

EMA category	Antibiotic class	Number of doses administered	Proportion of total doses administered ($N = 5113$)
Category B—overall		1982	38.8%
	Fluoroquinolones	1285	25.1%
	Cephalosporins—third/fourth generation	697	13.6%
Category C—overall		758	14.8%
	Penicillin/aminoglycoside combinations	686	13.4%
	Fenicols	38	0.7%
	Macrolides	26	0.5%
	Aminoglycosides	8	0.2%
Category D—overall		2373	46.4%
	Penicillins	1734	33.9%
	Tetracyclines	387	7.6%
	Sulphonamide/trimethoprim	252	4.9%

all doses administered included here). The median number of doses administered ranged from a low of two doses administered per animal in 2018 and 2019 to a high of 4.5 doses administered per animal in 2008.

Table 3 shows the number of doses administered over the entire 15-year period by EMA category and antibiotic class. Category D (first-choice antibiotics) were used most frequently (46.4% of all doses administered), with penicillin use being most common (33.9% of all 5113 doses administered).

Most frequent diagnoses treated with antibiotics in small ruminants

By number of treatment doses, the most frequent diagnoses treated with antibiotics at the university referral clinic were disorders of the urinary tract (35.8% of all treatments), followed by doses administered due to disorders of the gastrointestinal tract (11.0% of all doses administered) and respiratory disease (7.6%) (Table 4).

By species, both sheep and goats were most frequently treated with antibiotics for urinary tract disorders (Table 4). Of 1829 doses administered, the vast majority (n = 999, 54.6%) were attributed to urolithiasis, with a further 157 (8.6%) doses administered for 'urinary retention' (with no mention of urolithiasis) and 109 (6.0%) doses administered for cystitis (with no mention of urolithiasis). Furthermore, a total of 17 sheep were treated with antibiotics in 2008 in relation to a laparoscopic-assisted cystotomy following a urinary tract disorder, making up 25.7% (470/1829) of doses administered in this category. Over a distinct 5-year period from 2008 to 2012, sulphonamide/trimethoprim combinations were often used to treat these disorders; however, overall, the most frequently used antibiotics for urinary tract disorders (by number of doses administered)

TABLE 4 Number and proportions of antibiotic doses administered by recorded diagnoses

	Total number (%) of antibiotic doses administered	Number of sheep doses administered	Percent of sheep doses administered ($N = 2546$)	Number of goat doses administered	Percent of goat doses administered ($N = 2567$)
Urinary tract disorders	1829 (35.8%)	1147	45.1%	682	26.6%
Gastrointestinal tract disorders	562 (11.0%)	224	8.8%	338	13.2%
Respiratory disease	387 (7.6%)	227	8.9%	160	6.2%
Other	370 (7.2%)	155	6.1%	215	8.4%
Central nervous system and sensory organ disorders	365 (7.1%)	197	7.7%	168	6.5%
Abscesses and bites	346 (6.8%)	144	5.7%	202	7.9%
Surgery	328 (6.4%)	124	4.9%	204	7.9%
Locomotory disease	297 (5.8%)	128	5.0%	169	6.6%
Unclear diagnosis (not otherwise specified)	187 (3.7%)	62	2.4%	125	4.9%
Udder disease	177 (3.5%)	52	2.0%	125	4.9%
Disorders of the skin and horns	107 (2.1%)	20	0.8%	87	3.4%
Reproductive tract disorders	76 (1.5%)	38	1.5%	38	1.5%
Metabolic disease	48 (0.9%)	25	1.0%	23	0.9%
Cardiovascular disease	34 (0.7%)	3	0.1%	31	1.2%
Total	5113	2546	100.0%	2567	100.0%

TABLE 5 Number of patients, mean, median, minimum and maximum number of antibiotic doses administered by recorded diagnoses (excluding 'other' and 'not specified')

Recorded diagnosis	Number of animals treated[a]	Number of antibiotic doses administered				
		Total	Minimum	Mean	Median	Maximum
Gastrointestinal disorders	160	562	1	3.5	3.0	14
Surgery	135	328	1	2.4	2.0	14[b]
Urinary tract disorders	108	1829	1	16.9	16.0	57[c]
Respiratory disease	97	387	1	4.0	3.0	16
Central nervous system and sensory organ disorders	78	365	1	4.7	3.5	18
Abscesses and bites	71	346	1	4.9	3.0	47[d]
Locomotory disease	66	297	1	4.5	4.0	27[e]
Udder disease	41	177	1	4.3	4.0	11
Metabolic disease	21	48	1	2.3	1.0	6
Disorders of the skin and horns	16	107	1	6.7	4.0	25[f]
Reproductive tract disorders	17	76	1	4.5	5.0	14
Cardiovascular disease	13	34	1	2.6	3.0	6

[a]Some animals were treated for more than one disorder over the entire study period, so the total number of animals is larger than the study population.
[b]Fourteen doses were administered to one animal due to scrotal complications following castration.
[c]Fifty-one of these doses were administered in 2008, during two different treatment periods over 14 and 23 days.
[d]Forty-seven doses were administered over 4 months to one goat as palliative care for abscesses and infections in connection with a tumour.
[e]Twenty-seven doses were administered over 27 consecutive days to a goat with exungulation and necrosis of the claw.
[f]Twenty-five doses were administered over 25 consecutive days to a goat with a skin infection in 2007.

were fluoroquinolones and third/fourth-generation cephalosporins.

By the number of animals treated, gastrointestinal disorders were the most common disorders treated with antibiotics (160 animals over the 15-year period), followed by doses administered due to surgery (135 animals) and urinary tract disorders (108 animals) (Table 5). Urinary tract disorders received the highest number of doses administered per animal (mean number of doses administered 16.9; median 16.0), followed by disorders of the skin and horns (mean 6.7; median 4.0) and reproductive tract disorders (mean 4.5; median 5.0). Although surgical procedures made up a large proportion of treated animals (n = 135), the mean and median numbers of antibiotic doses administered were 2.4 and 2.0, respectively (Table 5).

As shown in Table 3, Category B antibiotic doses made up 38.8% of all antibiotic doses administered

TABLE 6 Number and proportions of Category B antibiotic doses administered by recorded diagnoses

	Number (%) of Category B antibiotic doses administered	Number (%) of doses administered with third/fourth-generation cephalosporins	Number (%) of doses administered with fluoroquinolones
Urinary tract disorders	886 (44.7%)	79 (4.0%)	807 (40.7%)
Gastrointestinal tract disorders	227 (11.5%)	135 (6.8%)	92 (4.6%)
Other	175 (8.8%)	31 (1.6%)	144 (7.3%)
Udder disease	147 (7.4%)	70 (3.5%)	77 (3.9%)
Respiratory disease	135 (6.8%)	84 (4.2%)	51 (2.6%)
Abscesses and bites	93 (4.7%)	68 (3.4%)	25 (1.3%)
Locomotory disease	76 (3.8%)	64 (3.2%)	12 (0.6%)
Disorders of the skin and horns	58 (2.9%)	19 (1.0%)	39 (2.0%)
Unclear diagnosis (not otherwise specified)	56 (2.8%)	45 (2.3%)	11 (0.6%)
Reproductive tract disorders	53 (2.7%)	43 (2.2%)	10 (0.5%)
Central nervous system and sensory organ disorders	52 (2.6%)	36 (1.8%)	16 (0.8%)
Surgery	14 (0.7%)	14 (0.7%)	0
Metabolic disease	6 (0.3%)	6 (0.3%)	0
Cardiovascular disease	4 (0.2%)	3 (0.2%)	1 (0.1%)
Total	1982	697 (35.2%)	1285 (64.8%)

TABLE 7 Number of patients, mean, median, minimum and maximum number of Category B antibiotic doses administered by recorded diagnoses (excluding 'other' and 'not specified')

		Number of antibiotic doses administered				
Recorded diagnosis	Number of animals treated[a]	Total	Minimum	Mean	Median	Maximum
Urinary tract disorders	89	886	1	10.0	10.0	25[b]
Gastrointestinal disorders	57	227	1	4.0	3.5	14
Respiratory disease	36	135	1	3.8	3.0	16
Udder disease	32	147	1	4.6	5.0	11
Locomotory disease	20	76	1	3.8	3.0	10
Reproductive tract disorders	14	53	1	3.8	4.0	10
Abscesses and bites	13	93	1	7.2	5.0	30[c]
Central nervous system and sensory organ disorders	11	52	1	4.7	4.0	13
Disorders of the skin and horns	7	58	1	8.3	4.0	25[d]
Surgery	3	14	2	4.7	5.0	7
Metabolic disease	3	6	1	2.0	1.0	4
Cardiovascular disease	2	4	1	2.0	2.0	3

[a]Some animals were treated for more than one disorder over the entire study period, so the total number of animals is larger than the study population.
[b]Twenty-five doses were administered over 25 consecutive days in 2007 in a Merino ram with urolithiasis, cystitis and bloody diarrhoea.
[c]Thirty doses were administered over 4 months to one goat as palliative care for abscesses and infections in connection with a tumour.
[d]Twenty-five doses were administered over 25 consecutive days to a goat with a skin infection in 2007.

over the 15-year observation period. Details of Category B antibiotic doses administered by recorded diagnoses are provided in Tables 6 and 7. Third- and fourth-generation cephalosporins (namely, ceftiofur and cefquinome) were most frequently administered for gastrointestinal disorders (6.8% of all Category B doses administered) and respiratory disease (4.2%). Fluoroquinolones (namely, enrofloxacin and marbofloxacin) were most frequently used to treat urinary tract disorders (40.7% of all Category B doses administered) (Table 6).

The highest number and proportion of animal patients were treated with Category B antibiotics for urinary tract disorders (89 [82.4%] out of all 108 animals treated for urinary infections over the 15-year period). Urinary tract disorders also had the highest mean and median number of Category B antibiotic doses administered, namely, 10 doses administered per animal. Abscesses and bites were treated in 13 animals over the study period, with the mean number of Category B doses administered being 7.2 per animal, (median 5), and disorders of the skin and horns

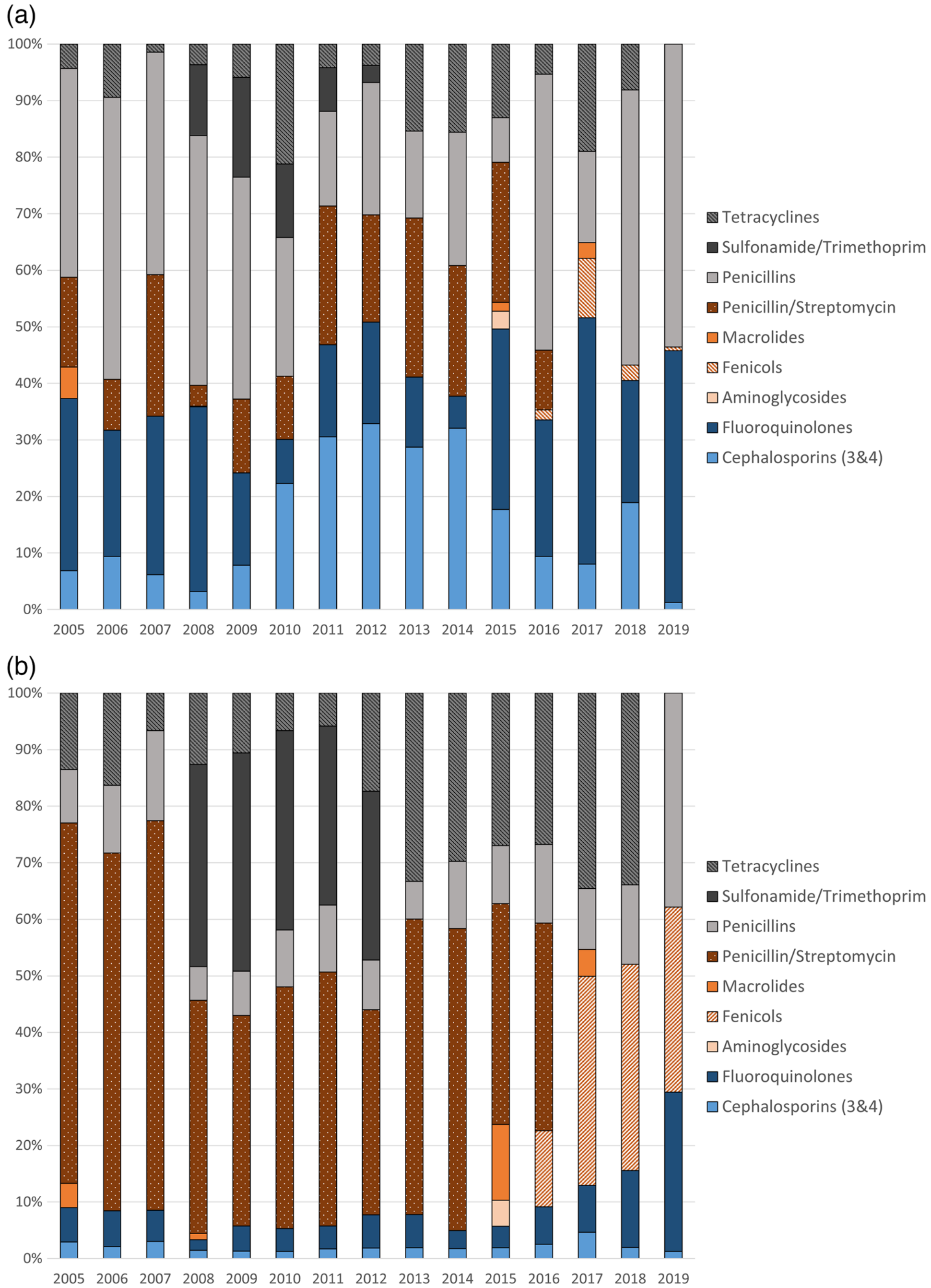

FIGURE 2 Comparison of the relative proportions of antibiotic use in small ruminants over time as analysed by: (a) number of antibiotic doses administered by antibiotic class; (b) mg/kg per antibiotic class. Category B antibiotics are shown in blue tones, Category C in orange tones and Category D in grey tones

were treated in seven animals, requiring a mean of 8.3 Category B doses administered per animal (median 4) (Table 7). In relation to surgical procedures, only three animals received Category B antibiotics (i.e., 2.2% of all 135 patients in this category, the remainder of which received either Category C or D antibiotics).

Comparison of antibiotic use in total mg/kg and number of doses administered

Trends in treatment at the university clinic were visualised in total milligrams of antibiotic per kilogram of standardised liveweight by breed over this 15-year period, as well as in the number of doses administered per antibiotic class and year (Figure 2). By number of doses administered, penicillins (excluding combinations with streptomycin) made up 33.9% (1734/5113), followed by fluoroquinolones with 25.1% (1285/5113), third/fourth-generation cephalosporins with 13.6% (697/5113) and penicillin/streptomycin combinations with 13.4% (686/5113) (Figure 2A and Table 3). Penicillins (excluding combinations with streptomycin) made up 53.5% of all doses administered in 2019.

When analysed by total mg/kg, third/fourth-generation cephalosporins made up only 2.0% of the total mg/kg administered, whereas the largest

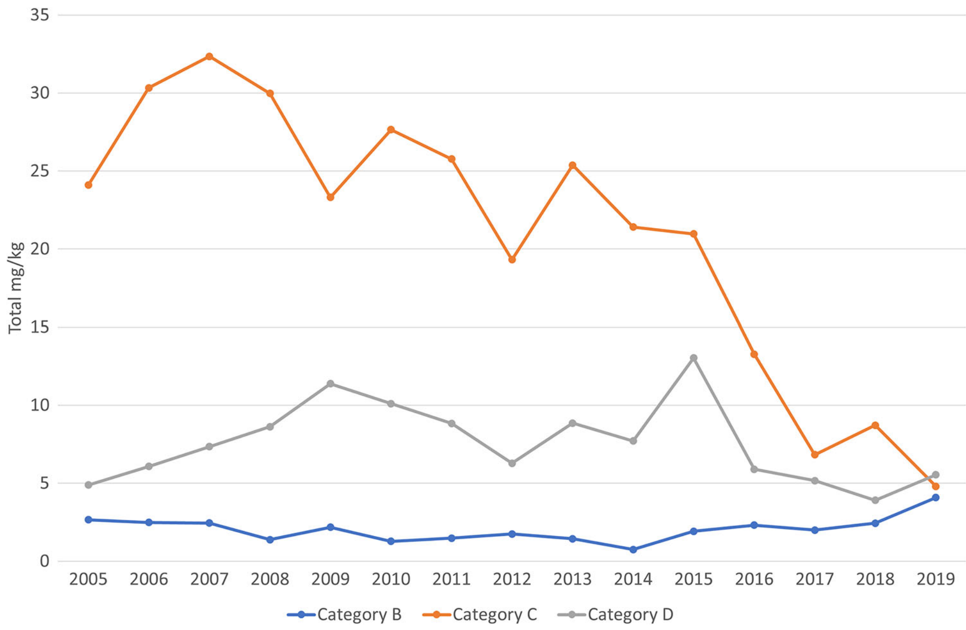

FIGURE 3 Trends in antibiotic category use in total mg/kg over time

proportion was found to be penicillin/streptomycin combinations (43.0%), followed by tetracyclines (17.3%) and the combination of sulphonamide and trimethoprim (15.2%) (Figure 2B).

Over time, patterns in antibiotic use varied greatly by year. Third- and fourth-generation cephalosporins reached a peak (32.9% of the total number of doses administered) in 2012 and have generally fallen since, reaching a low of 1.3% in 2019 (Figure 2A). By both the number of doses administered and mg/kg, fluoroquinolones have fluctuated over the 15-year period and have increased over more recent years (up to a maximum of 44.5% of the total number of doses and 28.2% of the total mg/kg in 2019) (Figure 2A,B). Tetracycline use reached a maximum of 21.2% of the total number of doses administered in 2010 and 34.6% of the total mg/kg in 2017 but was no longer used in 2019 (Figure 2A,B). Similarly, penicillin/streptomycin was only used up to 2016.

Comparison of EMA antibiotic categories over time

By total mg/kg per year, Category C antibiotics, which should be used with 'caution', were used at the highest level, reaching a peak of 32.3 mg/kg in 2007 and falling to 4.8 mg/kg in 2019. Category D antibiotics ranged from a high of 13.0 mg/kg in 2015 to a low of 3.9 mg/kg in 2018. Category B antibiotics (the most restricted category available in veterinary medicine) were used at a relatively low level, by total mg/kg, ranging from 0.8 mg/kg in 2014 to 4.1 mg/kg in 2019 (Figure 3). Category C antibiotics in this case were primarily penicillin/streptomycin combinations (90.5%; 686/758), where only streptomycin is a Category C drug, but the combination is classed as Category C as a whole.

When the total number of doses administered was analysed per year, however, Category C antibiotics were administered much less frequently; Category B products made up 24.2% of doses administered in 2009, rising to a maximum of 51.6% of doses administered in 2017 (Figure 4). Over the entire 15-year period, Category B antibiotics made up 38.8% of all doses administered, and Category C made up only 14.8% (Table 3).

Comparison of antibiotic metrics for all drugs licensed for use in sheep in Austria

Data were selected to include only sheep and antibiotics licensed for sheep for this part of the analysis, and a total of 484 doses administered and five antibiotics were analysed. When comparing the different metrics for each antibiotic, it is clear that the choice of metric has a large influence on the apparent distribution of proportions of antibiotic use in this sheep population (Figure 5). For example, oxytetracycline made up varying proportions of each metric, ranging from a minimum of 28.7% of the total number of doses administered to a maximum of 47.9% of the total nDDDvet (cattle). Similarly, florfenicol made up only a very small proportion of the total number of doses administered (1.9%; 9/484) but ranged from a minimum of 1.5% of the total nDDD(sheep) to a maximum of 3.3% of the total milligrams administered (Figure 5).

With respect to EMA prudent use categories, the choice of metric also leads to substantial differences, which is particularly important when trying to demonstrate a reduction in the use of

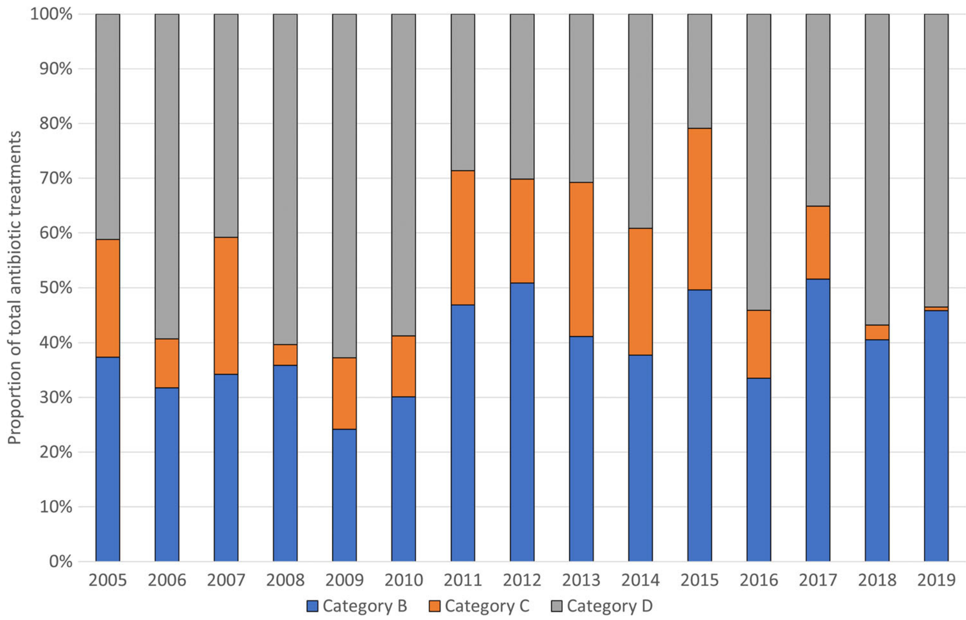

FIGURE 4 Trends in antibiotic category use by relative proportions of the total number of doses administered per year

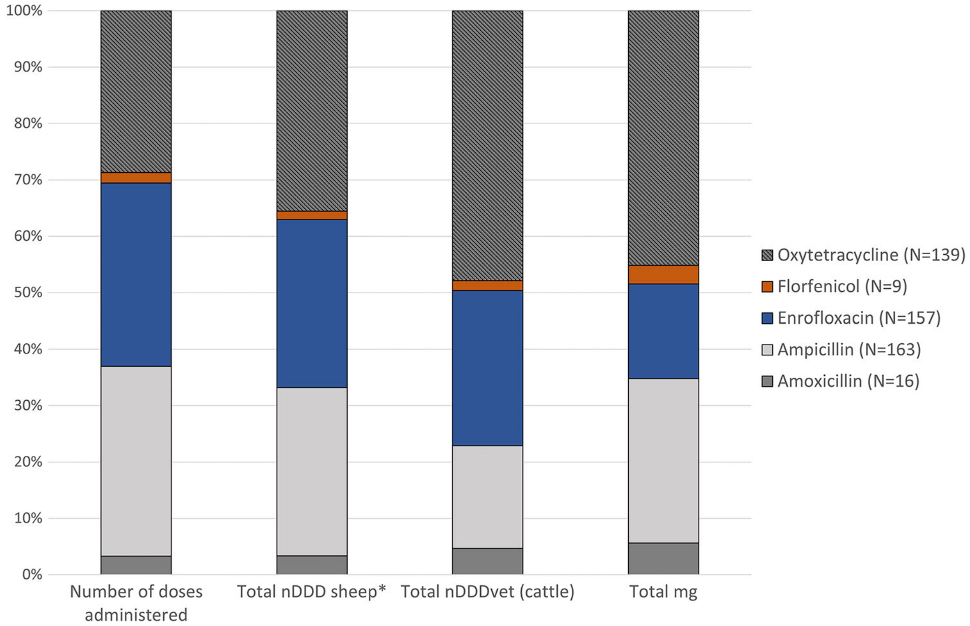

FIGURE 5 Comparison of antibiotic use metrics to describe the five antibiotics licensed for use in sheep at the time of this study. *nDDD sheep was calculated based on the mean licensed dose for sheep in Austria or Germany. (DDD, defined daily dose)

Category B drugs (Figure 6). In the case of Category B antibiotics, namely, enrofloxacin, the relative proportion doubled from a minimum of 16.7% as total milligrams administered to a maximum of 32.4% of the total number of doses administered (Figure 6).

Comparison of antibiotic metrics for all drugs licensed for use in goats in Austria

Data were selected to include only goats and antibiotics licensed for goats for this part of the analysis and only one antibiotic (enrofloxacin) remained. For this reason, a comparison of metrics was not carried out for goats.

DISCUSSION

This study aimed to illustrate trends in antibiotic use over time at a university referral clinic for the treatment of bacterial infections in small ruminants, as well as the differences the choice of antibiotic metrics can make in the visualisation of antibiotic use data. The condition for which the highest number of sheep and goat patients were treated with antibiotics over this 15-year period was gastrointestinal disorders. However,

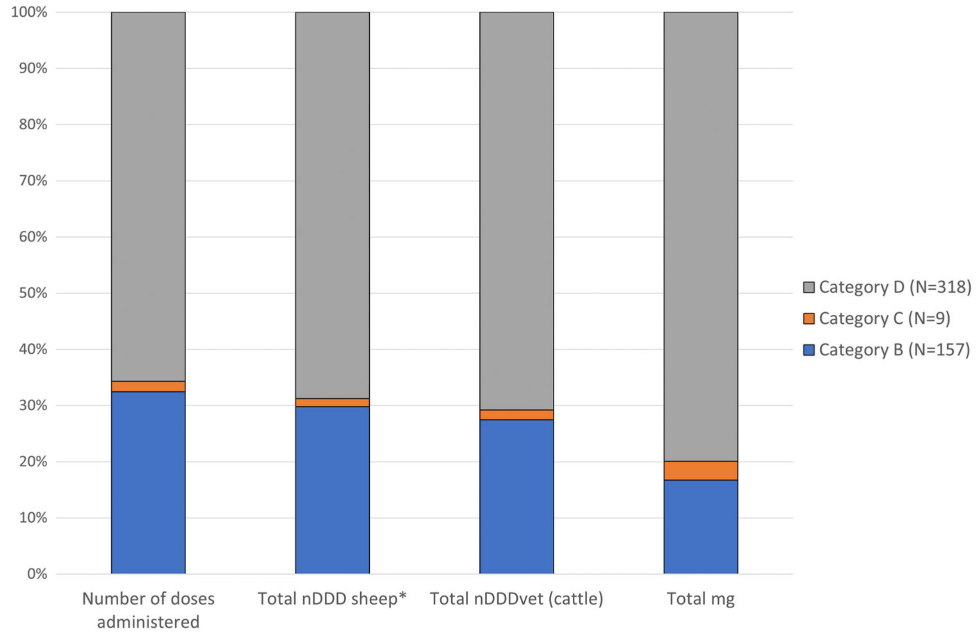

FIGURE 6 Comparison of antibiotic use metrics to describe the European Medicines Agency prudent use categories of antibiotics licensed for use in sheep at the time of this study. *nDDD sheep was calculated based on the mean licensed dose for sheep in Austria or Germany. (DDD, defined daily dose)

the largest proportion of antibiotic doses administered over this period were administered for disorders of the urinary tract (including urolithiasis). This is to be expected, as the vast majority of the patients treated by this city-based referral clinic were hobby/smallholder animals. Pet sheep and goats have often been reported to be at high risk of developing urolithiasis and other urinary tract disorders due to incorrect feeding and poor animal husbandry.[19,20] A limitation of the current study, therefore, is that these results cannot be compared with antibiotic use in commercial herds or flocks of small ruminants. Nevertheless, the long observational period enables us to demonstrate some interesting trends in treatment decisions from 2005 to 2019.

Prudent use guidelines with respect to veterinary medicine were first published in Austria in 2013.[21] As such, it was expected that substantial changes in antibiotic use patterns would be visible from 2014 onwards. The EMA published their prudent antibiotic use categories in 2019.[7] While Category C (to be used with 'caution', primarily penicillin/streptomycin combinations) use reduced continuously (particularly when analysed in mg/kg) in this retrospective analysis from 2005 to 2019 and Category D (to be used 'prudently') use appeared to increase in 2015, Category B (to be 'restricted', in this case third- and fourth-generation cephalosporins and fluoroquinolones) use did not noticeably decrease over time.

As with all analyses of antibiotic use, the metric chosen to illustrate such use can lead to extreme differences when comparing data.[8,9,11,22,23] In this study, when using total mg/kg, an overall reduction in antibiotic use was seen over time, and this change was particularly apparent with respect to Category C drugs. However, when this antibiotic use was analysed by the number of doses administered over the entire period, Category B antibiotics made up 38.8% of all doses administered and Category C made up only 14.8%. This discrepancy between mass-based and numerical-based units is often due to the much lower dose rate (i.e., higher potency) of Category B drugs (such as cephalosporins) compared to Category C and D drugs (such as oxytetracycline), which have a much higher mg/kg dose requirement.[8,23] Similarly, when comparing Category B antibiotics with Categories C and D over time in total mg/kg, the overall Category B usage was so low (reaching a maximum of just over 4 mg/kg, compared to 32 mg/kg for Category C antibiotics) that any changes were hardly visible. The differences in EMA category proportions are important to note, as total mg/kg-equivalent metrics are often used for European or national statistics, such as milligrams per PCU in the ESVAC report[2] or mg/kg in the Veterinary Antimicrobial Resistance and Sales Surveillance (VARSS) reports in the UK, where targets for prudent antibiotic use are given in mg/kg of national antibiotic use.[24]

Likewise, when comparing the same antibiotic use data by a variety of antibiotic quantification metrics, large discrepancies were visible. Differences between metrics for the Category B antibiotics, which should be restricted in veterinary medicine, were particularly pronounced. If the total administered milligrams of enrofloxacin was used as a metric instead of the total number of doses administered or DDD, then the apparent use of these restricted antibiotics was halved. For this reason, it is essential that caution is taken when choosing metrics for prudent use schemes.

Overall, at the university referral clinic, penicillins (and their combinations), sulphonamide/trimethoprim combinations and tetracyclines made up the largest proportion of antibiotic use in mg/kg. Published data on antibiotic use in small ruminants are scarce, but this corresponds with findings from Greece, where self-reporting by farmers showed that penicillin and streptomycin combinations, amoxicillin and oxytetracycline were most frequently used to treat a variety of bacterial infections, such as mastitis, pneumonia, enzootic abortion and diarrhoea, and were given prophylactically to newborn lambs and kids.[25] A Dutch study also reported that in small sheep flocks and goat herds (<32 animals), penicillin was used most frequently, while on larger goat farms (≥32 animals), aminoglycosides were used most frequently.[26] Davies et al.[22] in the UK also determined that the most commonly prescribed antibiotic on 207 commercial sheep farms was oxytetracycline, followed by penicillin and aminoglycosides. Similarly, in the USA, Landfried et al.[27] reported that, 46% of the veterinarians they surveyed prescribed penicillin to small ruminants, while 46% prescribed tetracyclines and 45% prescribed cephalosporins.

For the treatment of urinary tract disorders, which made up 35.8% of all antibiotic doses administered between 2005 and 2019, fluoroquinolones and third- and fourth-generation cephalosporins were the most frequently used antibiotics over all years and for both species. These two antibiotic classes are classified as Category B antibiotics and are critical to human medicine. The reasons for the use of a relatively high proportion of Category B antibiotics are unclear from the electronic data records. As a referral clinic, most of these animals had previously been treated by their local veterinarian prior to transfer, which may mean that resistance to first-choice antibiotics was more likely to have developed. Ideally, fluoroquinolones (used for 91.1%; 807/886 of urinary tract disorder doses administered here) should only be used when antimicrobial susceptibility testing demonstrates resistance to Category C and D antibiotics. However, an additional complication is that, under European law at the time of the study, the first-choice drug for the veterinarian should be one that is licensed in the target species. Fluoroquinolones, while Category B antibiotics, are one of few antibiotics licensed for use in both sheep and goats, although, with respect to prudent use guidelines, they should no longer be considered as a first-choice drug. At the university referral clinic, urinary tract infections were commonly determined to be caused by *Escherichia coli*, which is intrinsically resistant to penicillins and had an acquired resistance to tetracyclines, meaning that fluoroquinolones are often the only effective drug available in these cases, which is why their use has not fallen as much as expected. Of course, prevention of urolithiasis cases through improved education of animal owners, particularly those with hobby smallholdings or pet animals, would be the best way to reduce overall antibiotic use for urinary tract disorders, and while information on husbandry and nutrition was always provided to the owners of these animals, it is unknown how effective such recommendations were.

As an alternative to Category B antibiotics, sulphonamide/trimethoprim combinations were frequently used over a 5-year period, but this use then dwindled to zero. Possible reasons for this include changes in clinical staff over time, susceptibility testing results or clinicians being unsatisfied with clinical efficacy, as sulphonamide/trimethoprim combinations have been reported to have poor pharmacokinetic properties in small ruminants compared to cattle.[28–30]

Over the 15-year period observed here, antibiotic use by mg/kg was reduced in most EMA categories. Mass-based metrics (such as total milligrams, tonnes or mg/kg) are often very low with respect to modern antibiotics that are critical to human medicine, such as cephalosporins, and it is possible to skew the results of prudent use programmes by actually using more of these Category B drugs rather than older Category D antibiotics, such as tetracyclines. However, dose-based metrics are often more difficult to calculate and compare unless they are standardised. While EMA has published DDDvet values for cattle, pigs and poultry,[18] no such metrics exist for sheep and goats at present. There is no perfect metric for quantifying antibiotic use in veterinary medicine, and the comparisons of mass-based, dose-based and numerical antibiotic doses administered provided here demonstrate the difficulties in using one specific metric to illustrate changes in antibiotic use, particularly with respect to critical categories. Nevertheless, while the direct link between antibiotic use and antimicrobial resistance remains controversial, the World Health Organization/World Organisation for Animal Health/Food and Agriculture Organization tripartite recommends monitoring antibiotic use in veterinary medicine,[31] particularly for critically important antibiotics, as much as possible, and a number of studies and reports have shown that reducing antibiotic use in farm animals can be beneficial in reducing antimicrobial resistance overall.[32–34] For this reason, critically choosing the right metrics to quantify antibiotic use nationally, internationally or even on a farm or in a veterinary practice will remain an essential step for providing the right tools for antimicrobial stewardship.

AUTHOR CONTRIBUTIONS

Clair L. Firth contributed to study conception and design, data analysis and interpretation, and writing of the manuscript. Hanna Keppelmüller contributed to data cleaning, data analysis and interpretation, and drafting of the manuscript. Alexandra Hund contributed to data collection, data analysis and interpretation, and drafting of the manuscript. Annemarie Käsbohrer contributed to data interpretation, supervision and drafting of the manuscript. Thomas Wittek contributed to study supervision, data collection and interpretation, and drafting of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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The authors received no specific funding for this work. All authors were employees (Clair L. Firth, Alexandra Hund, Thomas Wittek and Annemarie Käsbohrer) or students (Hanna Keppelmüller) of the University of Veterinary Medicine, Vienna at the time of the study.

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy/ethical restrictions.

ETHICS STATEMENT

As only retrospective patient data were analysed, in accordance with local legislation, no ethics committee approval was required for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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