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Original article

Off label use of human approved drugs in treatment of dogs in the Republic of Serbia

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Abstract

Since drug companies are driven by the need to produce profit they are unwilling to make large investments in the development of new drugs if there is no market large enough to justify such investment. For this reason, veterinarians face a major obstacle – the veterinary drug market is not very profitable, which sometimes leads to not having a licensed drug available for treatment in veterinary practice. In this case, the cascade procedure allows veterinarians to, under certain circumstances, prescribe human approved drugs. The aim of our study was to analyze the pattern of human approved drugs prescription for 150 medical records of dogs participating in the survey. The results show that antimicrobial agents were the most commonly prescribed drugs for animals (50%) of all human approved drugs, and beta-lactams (38.6%) were the most widely used antibiotic classes. The most common general conditions for therapeutic use of antimicrobials in this study were digestive, skin and respiratory disorders. Our study shows that the frequency of bacterial culture, susceptibility testing and cytology was very low. Even though the off-label use of human approved drugs in animal practice is regulated by law, the results of this study indicate the need for more specific strategies and guidelines for such use. This may represent a potential for improvement by raising veterinarians' awareness toward more prudent use of human drugs.

Key words: off label use, human drugs, dogs, cascade procedure, antimicrobials

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Introduction

The world drug market share of veterinary drugs is only 4-5%. According to estimation, this share is even smaller in Serbia, probably around 2%. In general, the veterinary market is a "dwarf" in relation to the "human giant" (Filipovic 2008). The costs of developing and validating novel drugs in relation to safety and efficacy are very high, both in money and time. Hence, companies are reluctant to make such an investment if the market is not large enough to justify the costs. Although certain veterinary drugs, such as ivermectin and carprofen, generate vast profits, many of them do not (Rollin 2002). Drugs approved for use in humans are frequently used for treating infections in companion animals, such as dogs and cats, known as "off label" use (Hölsö et al. 2005). Off-label use is defined as the use of a drug outside the scope of its approved label (EMA/CVMP 2017). A more suitable drug formula, the strength, package size or non-availability of a comparable veterinary product may be reasons why human drugs are so widely used in companion animal practice (Hölsö et al. 2005). According to a study conducted by Gómez-Poveda and Moreno (2018) there were several drugs where practitioners could prescribe either veterinary or human products but chose the human product because of its lower price; this was also mentioned by Escher et al. (2011). In addition, the use of human authorized products in dogs is not restricted by considerations of drug residues as in food-producing animals. Therefore, the use of human approved drugs is more common in pets. Also, it is possible that newer generation drugs are being adopted for small animal practice without clear justification (Rantala et al. 2004, EMA/CVMP 2017). Moreover, although in some cases the dosage must be extrapolated regarding experience in humans, pharmacokinetic and pharmacodynamic data in animal species are often available (EMA/CVMP 2017). The mechanism of action of a drug is often the same in humans and other mammalian species, whereas the intensity and duration of the effects can vary. This implies that, in most cases, species variations in response to a fixed dose of drug can be due to differences in pharmacokinetic processes (Van Miert et al. 1986). In contrast, the use of human drugs in the treatment of animals in the economic production of milk and meat can affect the food safety, because no drug used in human medicine has a defined withdrawal period that would make it safe for use (Hölsö et al. 2005, Filipovic 2008).

In accordance with European Union rules (Anonymous 2001), the first treatment option should be a veterinary drug approved for the particular animal species to be treated. If such a product is not available, another veterinary drug approved for another animal species should be used. A human drug is allowed only if a suitable veterinary drug for another animal species does not exist, known as the cascade procedure (Hölsö et al. 2005, Anonymous 2012).

The main aim of the present study was to estimate the use of human approved antimicrobials in dogs, as well as to analyze pattern of this consumption in Serbia.

Materials and Methods

Data collection

The study was conducted at a private veterinary clinic in Novi Sad, Serbia during a period of 5 months, from January to May, 2020. One hundred and fifty medical records were used; all of them included dogs. Although the majority of veterinarians in Serbia keep computerized records on the disease history of animals and antimicrobial prescriptions, the documented information is not standardized, and therefore it was difficult to analyze. Regarding the estimation of the use of human approved drugs in dogs, the following data were collected: animal species, drug brand name, active substance, pharmaceutical form, dosage, duration of the treatment and indication, route of administration and prescription type. The results obtained in the study were processed using MS Office Excel v2019 and Statsoft Statistica v12.5 software.

Study design

Data were sorted by animal species (dogs) and whether the drug is prescribed by veterinarians or sold over-the-counter. Antimicrobial agents were further divided into subgroups according to their active substances, and the mean treatment period for different groups were calculated. According to the treatment, prophylactic and therapeutic were distinguished. When an animal received a pharmaceutical for a condition, this was classified as a therapeutic treatment, whereas when an animal was treated with a pharmaceutical as a part of a surgical procedure (administration prior, during or after the surgical procedure), the administration was classified as prophylactic. Therapeutic treatments were grouped according to the main systems/organs (digestive tract, respiratory tract, skin, ear, eye, urinary and other), and prophylactic treatments according to similar criteria (obstetrics, orthopedic, dental and other). They are also divided according to the route of application (peroral, parenteral or topical).

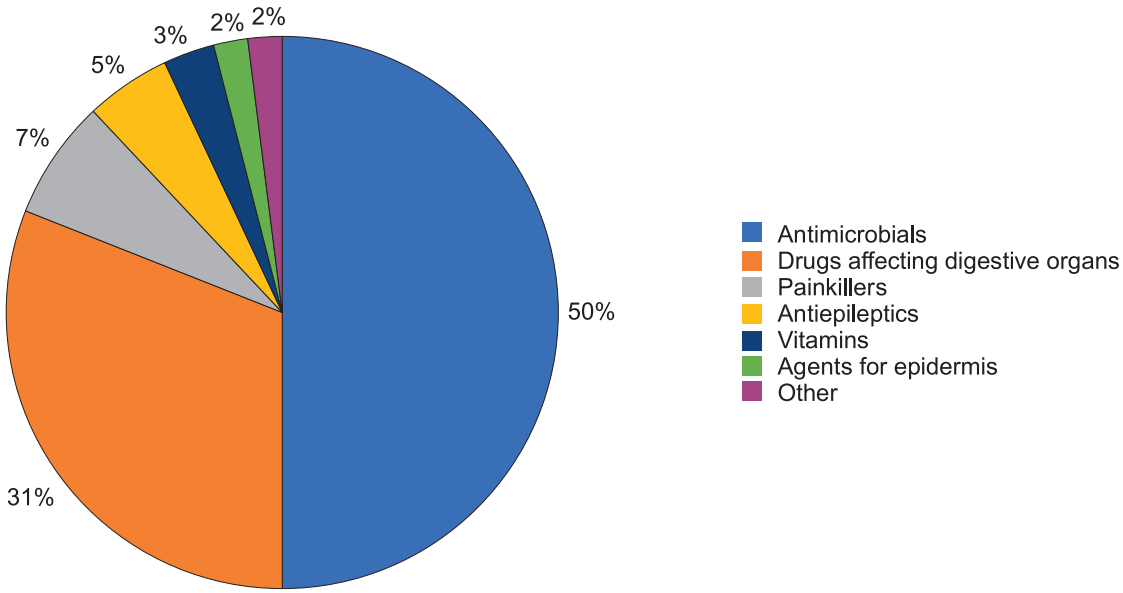

Fig. 1. Distribution of human approved drugs prescribed to dogs in survey period.

Table 1. Distribution of pharmacological class and subclass of 176 antimicrobials prescribed to 150 dogs.

Class and subclass of antibiotics	(N)	%
Beta-lactams	**68**	**38.6**
Amoxicilin/Clavulanic acid	19	28.0
Cephalexin	12	17.6
Cefixime	9	13.2
Ceftriaxone	28	41.2
Nitroimidazole	**36**	**20.5**
Metronidazole	29	80.6
Nifuroxazide	7	19.4
Aminoglycoside	**33**	**18.7**
Tobramycin	18	54.5
Gentamicin	15	45.5
Tetracycline	**15**	**8.5**
Doxycycline	15	100.0
Macrolides-lincosamides	**10**	**5.7**
Azithromycin	3	30.0
Clindamycin	7	70.0
Fluoroquinolones	**7**	**3.9**
Ofloxacin	5	71.4
Ciprofloxacin	2	28.6
Sulfonamides	**7**	**3.9**
Sulfamethoxazole/trimethoprim	7	100.0
Total	**176**	**100%**

Results

Of the 150 dogs participating in the survey, 79 (52.6%) were male and 71 (47.4%) were female. Their age ranged from three months to 17 years. The dogs were classified into 12 breeds, and 46 of the dogs (30.6%) were crossbreeds. Antimicrobial agents were the most commonly prescribed drugs for these animals and represented 50% of all human approved drugs (Fig. 1). During the survey, 176 medical products containing antimicrobials from the medical records of 150 dogs, prescribed between January and May 2020 were documented. One hundred and twenty-eight dogs were treated with one product, eighteen dogs with two products, and four dogs were treated with three medical products.

Table 1 shows 176 products with 14 different antimicrobials used in the treatment of dogs, beta-lactams

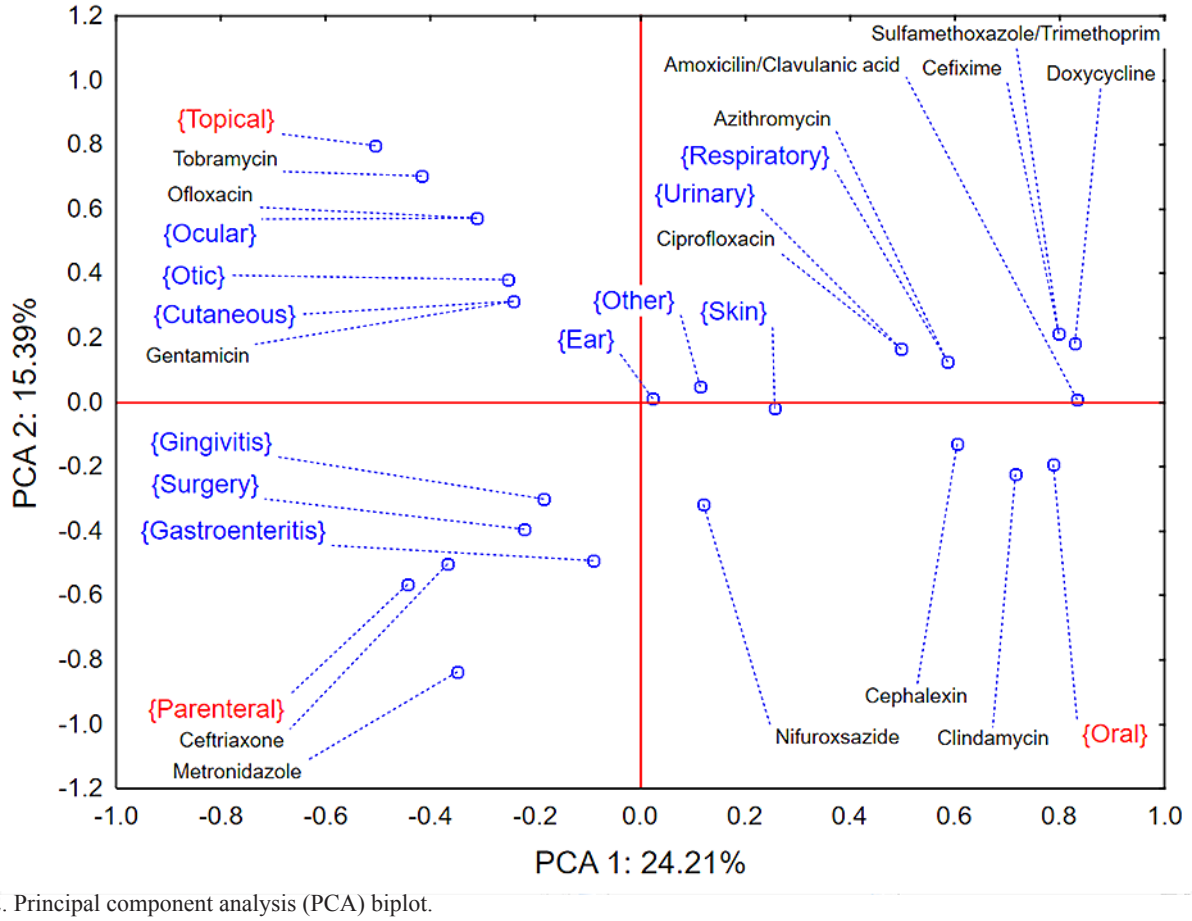

Fig. 2. Principal component analysis (PCA) biplot.

(68/176; 38.6%) being the most widely used antibiotic class, followed by nitromidazoles (36/176; 20.5%) and aminoglycosides (33/176; 18.7%). Regarding the active ingredients, metronidazole was the most common, followed by ceftriaxone and amoxicillin with clavulanic acid.

Regarding the distribution of antimicrobials according to the administration route, most of them were for systemic (oral or parenteral) or topical (skin, eye, ear) use (Fig. 2). Beta-lactams, macrolides, lincosamides, tetracyclines, sulfonamides, and metronidazole were always used systemically (Table 2 and 3), whereas tobramycin, gentamicin and ofloxacin were only used topically (Table 4). The most common administration route was oral (97/176; 55.1%; Table 2), followed by parenteral (41/176; 23.3%; Table 3) and topical (38/ 176; 21.6%; Table 4).

Conditions (Treatment Indication)

One hundred and twenty two of 150 dogs (81.3%) received a therapeutic treatment with an antimicrobial product, whereas 28 out of 150 dogs (18.7%) received a prophylactic (perioperative) treatment (15 after surgery, 8 during the intervention and 5 prior to surgery). Surgical procedures included the following interventions: obstetrical (10/28; 35.8%), orthopedic (7/28; 25%), dental (9/28; 32%), and other (2/28; 7.2%) (Table 5). The most common general conditions for therapeutic use of antimicrobials were digestive, skin and respiratory disorders (Table 6).

The specific diseases that were more frequent in the digestive system were periodontitis and gastroenteritis; in the skin, dermatitis and pyoderma; in the respiratory tract, kennel cough and pneumonia; in the ear, external otitis; in the eye, conjunctivitis, and in the urinary tract, cystitis. The majority of the betalactams were used for treatment of skin or wound infections and digestive infections. The indications for nitroimidazole were digestive disorders such as gastroenteritis and periodontitis. Aminoglycoside antimicrobials were used in topical treatment of canine skin, ear or eye infections. Doxycycline was indicated for wound and respiratory infections and in treatment of dirofilariasis. In the group of macrolides-lincosamides azithromycin was used for respiratory disorders and clindamycin for periodontal infections. Some respiratory and urinary infections were treated with trimethoprim-sulfonamides.

The application of Principal Component Analysis (PCA) on the dataset describing the route of application of different antibiotics for treatment of specific conditions reveals that the first two principal components

Table 2. Distribution of pharmacological class and subclass of 97 peroral antimicrobials to 150 dogs according to organ/system (conditions) treated.

Class and subclass of antibiotics	Respiratory (N)	Digestive		Urinary (N)	Skin (N)	Ear (N)	Surgery (N)	Other (N)
		Gastroenteritis (N)	Gingivitis (N)					
Beta-lactams	**16**	**9**		**5**	**6**			
Amoxicilin/ Clavulanic acid	5	4		3	3	**1** 1		**3** 3
Cephalexin	4	5			3			
Cefixime	7			2				
Nitromidazole		**16**	**4**				**3**	
Metronidazole		9	4				3	
Nifuroxsazide		7						
Tetracycline	**3**			**2**	**8**			**2**
Doxycycline	3			2	8			2
Macroldies-linkosamides	**3**		**4**				**3**	
Azithromycin								
Clindamycin	3		4				3	
Sulfonamides	**4**			**3**				
Sulfamethoxazole/ Trimethoprim	4			3				
Fluoroquinolones				**2**				
Ciprofloxacin				2				

Table 3. Distribution of pharmacological class and subclass of 41 parenteral antimicrobials according to organ/system (conditions) treated, to 150 dogs.

Class and subclass of antibiotics	Respiratory (N)	Digestive		Urinary (N)	Skin (N)	Ear (N)	Surgery (N)
		Gastroenteritis (N)	Gingivitis (N)				
Beta lactams		**9**					**19**
Ceftriaxone		9					19
Nitroimidazole		**5**	**5**				**3**
Metronidazole		5	5				3

Table 4. Distribution of pharmacological class and subclass of 38 topical antimicrobials according to administration route and conditions treated, to 150 dogs.

Class and subclass of antibiotics	Ocular (N)	Otic (N)	Cutaneus (N)
Aminoglycosides			
Tobramycin	8	10	
Gentamicin			15
Fluoroquinolones			
Ofloxacin	5		

describe more than 39% of sample variability. The position of the examined variables (applied antibiotics), route of application and treated organ/system/condition (Fig. 2) in the space described by the first two principal components (PCA1 and PCA2), allows us to identify the most common antibiotics applied for treatment of certain conditions. Namely, based on the grouping in the positive part of PCA1, the association of different antibiotics administered orally in the treatment of respiratory, urinary, skin and ear infections can be noticed. On the other hand, in the negative part of PCA1 a grouping of antibiotics applied topically and parenterally

Table 5. Distribution of pharmacological class and subclass of 28 antimicrobials for perioperative use according to type of surgery.

Surgery	Cephalosporins (N)	Nitroimidazole (N)	Lincosamide (N)
Obstetrical	Ceftriaxone (10)		
Orthopedic	Ceftriaxone (7)		
Dental		Metronidazole (6)	Clindamycin (3)
Other	Ceftriaxone (2)		

Table 6. The most common disorders for therapeutic use of antimicrobials (N, %).

Disorders	N	%
Digestive	52	42.6
Skin	29	23.7
Respiratory	26	21.3

was noted. Further separative localization was based on the variability described by PCA2. Namely, in the negative part of PCA2 parenterally applied antibiotics administered for treatment of gingivitis, gastroenteritis and pre/post surgery. On the other hand, in the positive part of PCA2 were noted antibiotics applied topically in the treatment of different ocular, cutaneous and otic condition.

In the study, the mean duration of the treatment period of the most frequently used oral antimicrobial agents varied from 9 to 14 days. Long treatment with cephalexin was recorded in cases of pyoderma (3-4 weeks) and mastitis (10-14 days) and especially with doxycycline in the treatment of dirofilariasis (30 days). Bacteriological culture had been performed in 13.1% (16/122) of the dogs receiving a therapeutic treatment (five urinary, three skin, two ear, two digestive conditions and four miscellaneous conditions) and antimicrobial susceptibility test had been performed in 9% of the cases (11/122) (five urinary, three ear and three skin conditions). Cytology testing had been performed in 14.8% (18/122) (eight ear, five skin, two urinary, and three miscellaneous conditions).

Discussion

All over the world antimicrobials approved for human use are more frequently prescribed for companion than for other animals. There is, however, no prescription surveillance report from Serbia regarding this issue. This is the first study conducted in this country using veterinary practice electronic records in a private database to access the pattern of use of human approved antimicrobials in the treatment of dogs. Moreover, the availability of similar studies in the literature is very limited. Prescription surveys have been conducted in Norway and Sweden (Odensvik et al. 2001), Finland (Hölsö et al. 2005), Italy (Escher et al. 2011), the UK (Singleton et al. 2017), Japan (Tanaka et al. 2017), and Spain (Gómez-Poveda and Moreno 2018) using electronic records, prescription paper records or internet databases. A seven-month survey of prescriptions conducted in Spain revealed that 37.2% of the total antimicrobial prescriptions were for human approved drugs, whereas 62.8% of the prescriptions were approved for companion animals (Gómez-Poveda and Moreno 2018). In contrast to this, a study conducted in Finland showed that only 17% of drugs prescribed were approved for human use (Hölsö et al. 2005). Escher et al. (2011) reported off-label use in 23.8% of cases in Italy, most of them because of labeling of the drugs for human use. A Norwegian study has shown that 50% of antimicrobials used in dogs were human medicines, while in Sweden this percentage was lower (20%) (Odensvik et al. 2001).

An EMA reflection paper (EMA/CVMP 2017) shows that the proportion of use of human drugs in cats and dogs ranges from 13 to 80%. These differences may be caused either by different regulations, or differences in approved drugs in each country (Odensvik et al. 2001, Hölsö et al. 2005), different survey periods, different animal populations and different therapy choices for aged companion animals (Tanaka et al. 2017).

According to our results, the most used antimicrobial group of drugs in dogs were beta lactams, which is in accordance with other studies (Rantala et al. 2004, Hölsö et al. 2005, Regula et al. 2009, Escher et al. 2011, Murphy et al. 2012, Hardefeldt et al. 2017). Ranked from the most to the least commonly prescribed, after beta-lactams, antimicrobials differ between countries. As in our study, in the UK and Spain the next most common were nitroimidazoles (Gómez-Poveda and Moreno 2018). In Sweden and Norway (Odensvik et al. 2001) and in Finland (Hölsö et al. 2005) amoxicillin with clavulanic acid was followed by trimethoprim-sulphonamides, macrolides and lincosamides, fluoroquinolones and metronidazole. An Italian study ranked

fluoroquinolones as second after beta-lactams (Escher et al. 2011), which is also reported in the study conducted in Spain (Gómez-Poveda and Moreno 2018). Interestingly, prescription of fluoroquinolones in Italy and Spain differs from results shown in our study, where only a few percent of prescriptions belong to this antimicrobial group.

Hölsö et al. (2005) and Gómez-Poveda and Moreno (2018) reported that systemic antimicrobials were the most commonly prescribed medicines for animals in Finland and Spain, which is in agreement with our study where oral antimicrobials were the most commonly prescribed medicines for dogs, followed by parenteral. Our results revealed that veterinarians in Serbia follow similar patterns in human approved antimicrobial prescriptions used in dogs.

Our data highlight that most common general conditions for therapeutic use of antimicrobials were digestive, skin and respiratory disorders. These results are similar to those reported by Gómez-Poveda and Moreno (2018) where skin was the most common condition, followed by respiratory and digestive disorders. The beta-lactams class (penicillins and cephalosporins) were at the top of the prescription list for several specific conditions affecting the skin, gastrointestinal tract, respiratory system, and genitourinary system (Rantala et al. 2004, Escher et al. 2011, De Briyne et al. 2014, Gómez-Poveda and Moreno 2018). Cephalexin (Rantala et al. 2004, Holloway et al. 2013, Gómez-Poveda and Moreno 2018) and amoxycillin-clavulanate (Beco et al. 2013) were reported to be the most commonly prescribed drugs for pyodermas and traumatic wounds, which is in agreement with the results obtained in our study.

Our data ranked imidazole derivatives after beta-lactam. Metronidazole is commonly used in small animal practice (Lutz et al. 2020, Robbins et al. 2020) as it is believed to reduce the duration of clinical signs and the severity of diarrhea, although evidence is lacking. Metronidazole was the most used antimicrobial for digestive disorders in our study, in agreement with the European data (Gómez-Poveda and Moreno 2018, Lutz et al. 2020) and a study conducted in Canada (Murphy et al. 2012). However, current guidelines only recommend the use of antimicrobials in dogs with acute diarrhea if clinical or laboratory signs of sepsis are present (Jessen et al. 2019, Lutz et al. 2020). As was recommended in Holloway et al. (2013) for periodontitis, metronidazole and clindamycin are preferred over amoxicillin-clavulanate because they reach more effective levels within the biofilm in the vicinity of the periodontal space, which is in agreement with our study.

Lutz et al. (2020) reported the use of antimicrobials for abscesses and bite wounds, which corresponds to the results of our study where beta-lactams and tetracyclines were mostly used. According to the guidelines, drainage of abscesses and a local treatment (Jessen et al. 2019, Lehner et al. 2020) is the most important part of treatment and antimicrobials are indicated for bite wounds penetrating the epidermis and for abscesses only in case of fever, signs of systemic disease, highly contaminated wounds or lesions close to fragile tissues (Lehner et al. 2020, Lutz et al. 2020), potential joint involvement or in immunosuppressed individuals (Bergvall et al. 2009, Jessen et al. 2019). Aminoglycosides were the most commonly used topical antimicrobial class in our study for treating skin, eye and ear conditions, although some guidelines (Gómez-Poveda and Moreno 2018) recommend that "antibiotics should not be used to treat otitis conditions that are not actually infected with bacteria".

In cases with kennel cough, our study reported that beta-lactams were commonly prescribed as also presented in Lutz et al. (2020). According to Jessen et al. (2019) most cases of kennel cough are self-limiting and do not require antimicrobial treatment if it is not associated with signs of systemic disease, suggesting that most kennel cough treatments in our study should have been avoided. Holloway et al. (2013) reported that amoxicillin-clavulanate which was sometimes used in our study, is a less satisfactory choice because, being charged and water soluble, it tends not to reach sufficiently high levels in respiratory mucous. Otherwise, doxycycline is recommended as a first-line empirical treatment, being well tolerated by dogs and due to its efficacy (Holloway et al. 2013, Lappin et al. 2017, Jessen et al. 2019, Lutz et al. 2020). In stable patients with pneumonia, amoxicillin/clavulanate is an appropriate first choice, which is in agreement with our study (Jessen et al. 2019).

The treatment of urinary infections such as cystitis is consistent with Rantala et al. (2004) and Holloway et al. (2013) since trimethoprim-sulphonamides and amoxyciline-clavulanate were the most used in therapy. According to De Briyne et al. (2014), fluoroquinolones were highly ranked for skin, genitourinary and respiratory infections in dogs in some parts of Europe. In our survey, however, fluoroquinolones were mostly used to treat diseases affecting the eye, such us conjunctivitis, but also to treat diseases associated with the urinary tract when no other drug is effective.

Perioperative antimicrobial prescription is also a controversial and not well regulated subject of prudent antimicrobial use (Gómez-Poveda and Moreno 2018). Guidelines for the prudent use of antimicrobials in veterinary medicine (Anonymous 2015) recommend that perioperative use of antimicrobials should be minimized by using aseptic techniques, which was also sug-

gested by Lehner et al. (2020). Danish guidelines emphasize the dog's status and expected surgery as the main criteria for perioperative use of antimicrobials (Jessen et al. 2019). Antibiotics are considered unnecessary for routine short surgeries conducted under sterile conditions, such as routine desexing (Holloway et al. 2013). In Serbia, there is a lack of guidelines on this issue and our study confirmed that routine perioperative treatments are still used by some veterinarians.

For antimicrobials that were administered orally, in our study the mean duration varied from 9-14 days, which was similar to studies conducted by Hölsö et al. (2005), Murphy et al. (2012) and Joosten et al. (2020). On the other hand, our study has shown that chronic or recurrent conditions were treated significantly longer, similar to a study conducted by Murphy et al. (2012).

Studies conducted in companion animals demonstrated a high use (Gómez-Poveda and Moreno 2018, Joosten et al. 2020) without clear justification (Hölsö et al. 2005) of broad-spectrum antimicrobials such as amoxicillin with clavulanic acid and first generation cephalosporins. Their high use is associated with a low rate of bacterial culture and antimicrobial susceptibility testing (Escher et al. 2011, Gómez-Poveda and Moreno 2018). Our study shows that frequency of bacterial culture (13.1%) and susceptibility testing (9%) was also low. Cytology, as another valuable diagnostic tool for bacterial infection (Gómez-Poveda and Moreno 2018), was rarely used according to our survey (14.8%), similar to a study conducted in Canada (Murphy et al. 2012). Sensitivity testing in general practice is usually restricted to more difficult cases (Jessen et al. 2019) or in the case of a poor response after initial therapy (Gómez--Poveda and Moreno 2018). Increased use of antibiotic sensitivity testing could reduce the empiric prescription of broad-spectrum antimicrobials, in favor of equally effective narrow-spectrum antimicrobials (Murphy et al. 2012, Anonymous 2015, Gómez-Poveda and Moreno 2018). Our study revealed that the lack of proper laboratory testing can be associated with excess use of antimicrobials, representing a critical issue not only for public health, but also for animal welfare.

According to the Guidelines for the prudent use of antimicrobials in veterinary medicine (Anonymous 2015), some human approved antimicrobials are critical for preventing or treating life-threatening infections in humans. Their use should be limited to cases where no other alternative is available and when laboratory testing has confirmed that no other antimicrobials will be effective and if ethical reasons justify such treatment. As in our study, the antimicrobial classes classified as critically important antimicrobials for human medicine by WHO experts (WHO 2018), such as third- and fourth-generation cephalosporins, amoxicillin clavulanate acid, aminoglycosides and macrolides, were the most frequently prescribed drugs, which is similar to results reported in Escher et al. (2011). Less than 4 per cent of the antimicrobials prescribed for dogs were fluoroquinolones (7 of 176), indicating that the use of these agents is adequately controlled. Even though fluoroquinolones represent valuable agents with favorable pharmacokinetic properties, their efficiency is threatened by the rapid spread of resistance. In order to maintain its efficacy, it is important to restrict their use to serious infections only (Lehner et al. 2020). Consequently, there is a potential risk of transmission of resistant genes from companion animals to humans (Pomba et al. 2017, Schwarz et al. 2017), giving more reasons for veterinarians to be more careful with antibiotics used in these animals.

In conclusion, off-label use of human drugs in animals is one of the most clearly regulated issues of prudent use. However, the results of this study indicate that part of the antimicrobial use may not be in compliance with the guidelines for prudent use and there is a need for further surveys about the patterns of antimicrobial use in small veterinary practices. These types of studies are rare, and the use of different methods makes comparison between countries quite difficult. In Serbia, except for legal regulation there is no national recommendations and there is a lack of guidelines and specific strategies supporting the prudent use of antibiotics in companion animals.

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