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RESEARCH ARTICLE

Antimicrobial veterinary drug sale pattern in correlation with critically important antimicrobials for human use: A five-year study in Montenegro

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ABSTRACT

Antimicrobial resistance (AMR) poses a significant threat in veterinary medicine due to the excessive and inappropriate use of antimicrobial agents, compromising the effectiveness of these drugs. To combat AMR, the collection of data on the consumption of antibiotics is paramount, as there is a well-established connection between antibiotic use and AMR in both humans and food-producing animals. Hence, the current study aimed to generate measurable data concerning the sales patterns of antimicrobial drugs used in animal treatment in Montenegro over a five-year period (from 2017 to 2021). Furthermore, the study aimed to compare these sales figures with the overall sales of antimicrobial veterinary medicine products (AMVMPs) during the same period, with particular emphasis on the utilization of critically important antimicrobials (CIAs) for human use. Data on AMVMPs consumption from 2017 to 2021 were expressed in euros and were sourced from the Institute for Medicines and Medical Devices of Montenegro (CInMED) annual reports, complying with the regulatory framework of the Law on Medicines in this country. Research results indicate that the sales of AMVMPs increased from 2017 to peak in 2019, followed by a stable decline of 21.79% in 2021. However, the portion of selected CIAs AMVMPs in total sales experienced a minor decline from 2017 to 2019, followed by a noticeable 6.11% increase from 2019 to 2021. In order to address AMR challenges, these findings emphasize the importance of enhancing surveillance and monitoring of veterinary antimicrobial use, as well as CIAs for human use.

KEYWORDS

antimicrobial resistance, antimicrobial use, critically important antimicrobials

INTRODUCTION

As a global public health challenge, antimicrobial resistance (AMR) requires monitoring of antimicrobial drug use in both human and veterinary medicine [1]. Although the principal cause of AMR in humans is the widespread use of antibiotics, the inappropriate use of falsified and counterfeit antimicrobial substances in animal husbandry has contributed to the emergence and alarming increase of antibiotic-resistant bacteria originating from animals [2]. Furthermore, humans are exposed to antimicrobial-resistant pathogens of animal origin through the consumption of animal food products and via direct or indirect contact with livestock and companion animals [3]. Besides, resistant strains of bacteria can also reduce the therapeutic effect of drugs used to treat infections in humans and animals [4].

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In order to obtain information on the progression of resistance to antibiotics, the collection of data on the consumption of antibiotics is a prerequisite since there is well established connection between antibiotic use and antibiotic resistance both humans and food-producing [4, 5] animals. Therefore, the European Commission published the action plan against the rising threats from AMR in 2011, which recommends that gathering of standardized data on the use of antimicrobials should be done, ideally stratified by animal species and production categories, as well as for different therapeutic indications [6, 7]. Additionally, in order to ensure that the most essential drugs are used judiciously in both human and veterinary medicine, as well as to navigate their use, public and animal health organizations have created competing lists of "critically important antimicrobials" (CIAs) where these drugs are classified according to their importance in human and veterinary medicine, respectively [8, 9]. Moreover, in 2018, the WHO released guidelines to preserve the effectiveness of medically important antimicrobials; in these guidelines it is recommended that drugs classified as Highest Priority Critically Important Antimicrobials for Humans (HPCIAs) should not be used for the treatment of food-producing animals with clinically diagnosed infectious disease [10]. According to the WHO, antimicrobial classes termed as critically important are used to treat infections caused by bacteria possibly transmitted from non-human sources, or those with resistance genes from non-human sources and which represent the sole, or one of limited available therapies to treat serious bacterial infections in people [11]. Since no or limited alternatives exist for the treatment of serious infectious diseases in humans, in particular for diseases caused by bacteria that may be transmitted to people from non-human sources, substances such as fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and glycopeptides have been classified as HPCIAs [12].

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project collects information on how antimicrobial medicines are used in animals across the European Union (EU), which is essential for the identification of possible risk factors that could lead to the development and spread of AMR in animals [13]. Since Montenegro is not part of ESVAC, it is important to quantify antimicrobial use consumption in veterinary medicine at a national level. Thus, the Institute for Medicines and Medical Devices has the authority to perform collecting and processing data on marketing and consumption of veterinary medicine products (VMPs) in Montenegro, according to the Law on Medicines [14]. The report on the total value of sales for all veterinary medicines, as well as the volume of sales per packaging of individual medicines is submitted to the Institute according to the anatomical – therapeutic – chemical veterinary classification code (ATCvet) prescribed by the World Health Organization [15].

Insight in the antimicrobial drug sale pattern as a part of antimicrobial stewardship programme could give important data on prescriptions habits of veterinarians which could be used for tailored interventions focused on the AMR decrease. Furthermore, as a consequence of huge AMR increase, there is a huge pressure from EU legislatives to ban critically important antibiotics for human use in veterinary practice, such us an obligatory requirement for antimicrobial susceptibility testing prior to use of high priority critically important antimicrobials (CIAs) [16].

Hence, the aim of this study was to create quantitative evidence of antimicrobial drug sale pattern used in animal treatment in Montenegro in a five-year period, from 2017 to 2021, compared to total antimicrobial VMPs sales in the same period, with special consideration of the use of CIAs for human use.

MATERIALS AND METHODS

Collection of data

Information about the consumption of antimicrobial veterinary medicine products (AMVMPs) was obtained from the annual reports of the Institute for Medicines and Medical Devices of Montenegro (CInMED) for a five-year period (from 2017 to 2021). Actually, in this study the regulatory framework for the reporting of sales volumes of antimicrobial agents authorized as VMPs in Montenegro was used, which was formed by amendments of the Law on Medicines [14].

Annual reports from 2017 to 2019 were compiled according to the Articles 93. and 107. of the Law on Medicines [17], while the period 2020 and 2021 were complied according to the Articles 131. and 150. of the Law on Medicines [14]. In the database of the Institute for Medicines and Medical Devices of Montenegro for the antimicrobial VMPs consumption monitoring, veterinary drugs are classified according the classification given by World Health Organization (WHO) by anatomic-therapeutic-chemical veterinary (ATCvet) groups, as well as by international non-protected names (INNs). Pharmaceutical companies and wholesalers are obliged to annually report the volumes of VMPs sold to practices and clinics in Montenegro that operate a veterinary dispensary. They submit these reports to Institute for Medicines and Medical Devices in Montenegro. Hence, these records are used for quantitative evidence of animal antimicrobial usage patterns in Montenegro vs. total VMPs in five year period, from 2017 to 2021.

Analysis of data

Based on the submitted reports the data on total consumption of VMPs were expressed as a total amount in euros according to wholesale prices. Special attention and focus was given to the critically important antimicrobials for human use. Actually, the antibiotics which were taken in consideration were selected based on WHOs classification of critically important antimicrobials for human use [11].

RESULTS

Listing and categorization of antimicrobials used in human medicine is given by WHO Advisory Group on Integrated

Surveillance of Antimicrobial Resistance (AGISAR) [11]. CIAs for human medicine from this document are given in Table 1 along with WHO ATCvet classification [15]. According to the data from this table, CIAs for human use in overall AMVMPs in Montenegro are determined.

Research results show that the overall sale trend of AMVMPs increased from 2017 reaching its peak in 2019, followed by a stable decline with a decrease of 21.79% in 2021 (Fig. 1).

Sale records were extrapolated for amoxicillin sole or in combination with other substances (clavulanic acid, colistin and prednisolone), ampicillin sole or in combination with cloxacillin, and gentamicin. Because of its significance, regarding its categorization as HPCIA, data on colistin in combination with amoxicillin were presented separately, since this was the only recorded colistin preparation sold for veterinary use. In general, sale trends of these selected antimicrobial substances remain stable in the five-year period, 2017 – 2021 respectively, showing slight increase or decrease annually, with exception of ampicillin which sale increased 60.2% from 2018 to 2021 (Fig. 2). After a minor decrease in portion of selected CIAs in the total sale of AMVMPs from 2017 to 2019, an increase of 6.11% was noticeable from 2019 to 2021 (Fig. 3).

DISCUSSION

To the best of our knowledge, this is the first study describing the drug sale pattern of antimicrobials used in veterinary medicine in Montenegro with special consideration of the CIAs. The use of CIAs, especially of HPCIAs poses the risk of developing resistance to these antimicrobials in bacteria, which may affect a high absolute number of people with extremely limited treatment options [7]. Furthermore, if HPCIA-resistant bacteria spread to human populations through food products, direct contact with animals, or via the environment, the resulting infections could be more difficult to treat if antibiotics of the same class or different classes of antimicrobials are used in both animals and in human medicine, leading to increased burdens of morbidity and mortality, and increased costs for healthcare [12, 18]. Moreover, some of the same antibiotics or classes are in use in food animals and in human medicine, as well as carrying the risk of emergence and spread of resistant bacteria, including those capable of causing infections in both animals and people [19]. This is the reason why in this study, special attention was paid to critically important antimicrobials defined by the WHO [11].

Montenegro national strategy for antibiotic resistance control for the period from 2017 to 2021, among other interventions, emphasis the antibiotics sales control, as well as monitoring the resistance of bacteria to antibiotics in human and veterinary medicine [20]. On the other hand, inconsistent and poor record keeping is a pervasive problem in veterinary medicine, as well as human medicine [21]. Besides, although the most countries in the European region, such as Montenegro, monitor antimicrobial consumption, these countries are urged to invest in comprehensive surveillance

Table 1. Critically important antimicrobials for human medicine [11, 15]

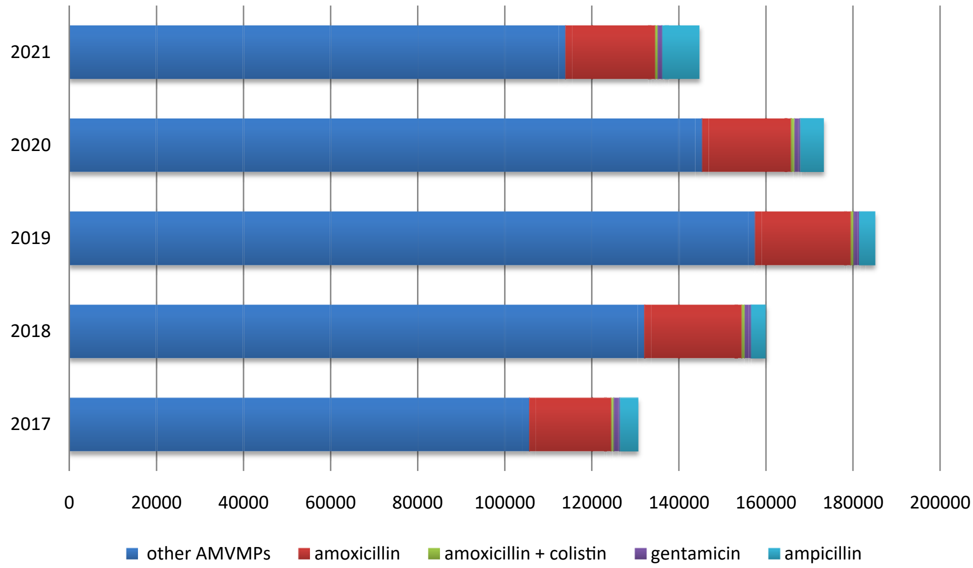
Antimicrobial class	Example of antimicrobial(s)	ATCvet code(s)
Aminoglycosides	gentamicin	QA07AA91, QD06AX07, QG01AA91, QG51AA04, QJ01GB03, QJ51GB03, QS01AA11, QS02AA14, QS03AA06
Ansamycins	rifampicin	QJ04AB02, QJ54AB02
Carbapenems and other penems	meropenem	QJ01DH02
Cephalosporins (3rd, 4th and 5th generation)	ceftriaxone, cefepime, ceftaroline, ceftobiprole	QJ01DD04, QJ01DE01, QJ01DI02, QJ01DI01
Glycopeptides	vancomycin	QA07AA09, QJ01XA01, QS01AA28
Glycylcyclines	tigecycline	QJ01AA12
Lipopeptides	daptomycin	QJ01XX09
Macrolides and ketolides	azithromycin, erythromycin, telithromycin	QJ01FA10, QS01AA26 QD10AF02, QD10AF52, QJ01FA01, QJ51FA01, QJ51RF02, QS01AA17
Monobactams	aztreonam	QJ01DF01
Oxazolidinones	linezolid	QJ01XX08
Penicillins (antipseudomonal)	piperacillin	QJ01CA12, QJ01CR05
Penicillins (aminopenicillins)	ampicillin	QG51AG04, QG51AG05, QG51AG07, QJ01CA01, QJ01CA02, QJ01CA06, QJ01CA14, QJ01CA15, QJ01CA51, QJ01CR01, QJ51CA01, QJ51CA51, QJ51CR01, QJ51RC20, QJ51RC21, QS01AA19
Penicillins (aminopenicillin with beta-lactamase inhibitors)	amoxicillin-clavulanic-acid	QJ01CR02
Phosphonic acid derivatives	fosfomycin	QJ01XX01, QS02AA17
Polymyxins	colistin	QA07AA10, QA07AA98,

(continued)

Table 1. Continued

Antimicrobial class	Example of antimicrobial(s)	ATCvet code(s)
Quinolones	ciprofloxacin	QG51AG07, QJ01XB01, QJ51XB01 QJ01MA02, QJ01RA10, QJ01RA11, QJ01RA12, QS01AE03, QS02AA15, QS03AA07
Drugs used solely to treat tuberculosis or other mycobacterial diseases	isoniazid	QJ04AC01

systems to fully understand the patterns of prescription and antibiotic consumption [22]. This is pointed out in the WHO report on the implementation of national action plan on antimicrobial resistance from 2021 [22]. Hence, this is a reason why research such as ours is so valuable. Moreover, several guidance documents on the rational use of antibiotic in the treatment of bacterial infections have been published on the website of the Ministry of Health of Montenegro, but the application of these guidelines in practice is unsatisfying. The system for controlling the use of antibiotic in health care institutions is not sufficiently developed [23]. Thus, the national strategy for the AMR control needs constant improvement engaging both human and veterinary medicine trough One Health collaboration. One of the reasons for this situation is that in the past antibiotics have been used not only to control infections, but also in the prevention of the



AMVMPs – antimicrobial veterinary medicine products

Fig. 1. The ratio of selected CIAs in the overall AMVMPs sales in euros from 2017 to 2021

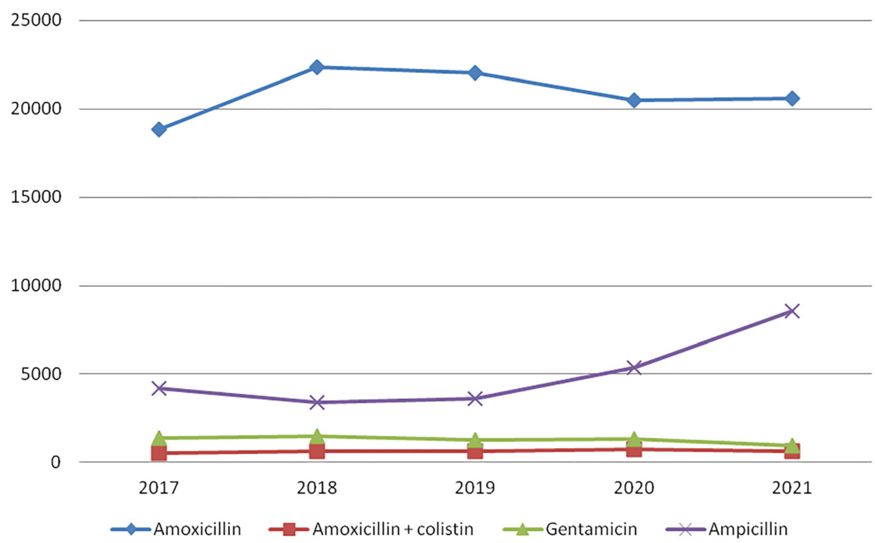


Fig. 2. The sale trends of selected CIAs from 2017 to 2021 expressed in euros

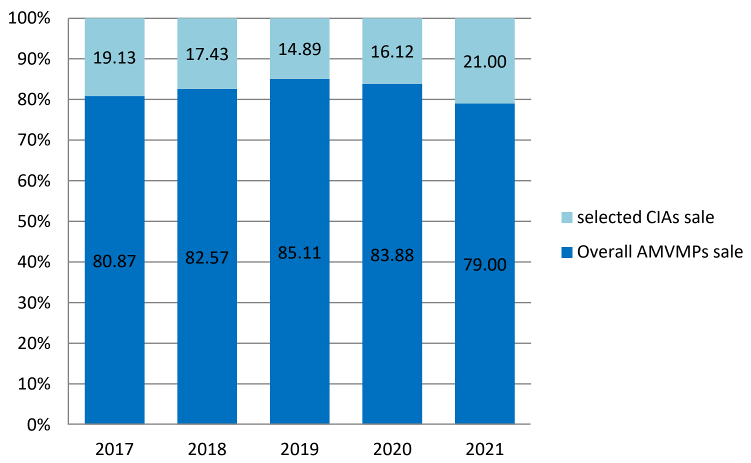


Fig. 3. The overall ratio of CIAs in overall AMVMPs sale ratio from 2017 to 2021

pathologies and improvement of the animal health status, without limits on their use or AMR prevalence control [24].

The CAESAR network was founded in 2012 as a collaborative effort by the WHO Regional Office for Europe, the WHO Collaborating Centre for AMR Epidemiology and Surveillance at RIVM and ESCMID with the goal to assist countries in the WHO European Region (excluding EU/EEA) in setting up or strengthening national AMR surveillance. As of 2022, 21 countries are engaged in the CAESAR network, including Montenegro [25] and the results from this network clearly show that AMR continues to be widespread in the WHO European Region despite the limitations (distinct country surveillance systems). Moreover, the presence of specific AMR patterns across clinical settings covered by the surveillance networks is apparent [25].

Dogs and cats are considered an important potential source of AMR, posing a risk to public health. Although harmonized control and monitoring programs are not established in the EU, it is important to highlight the need to create a joint plan to combat the evolution of AMR in companion animals under the One Health concept [26]. In order to mitigate the companion animal contribution to AMR it is important to put our focus on improving antimicrobial prescription, as a part of antimicrobial stewardship, especially through the development and implementation of evidence-based antimicrobial prescribing guidance [27]. In the study conducted at the veterinary teaching hospital indicate medical encounters of antibiotics were dispensed with no evidence in 38.4% of infection, just suspected evidence of infection in 44.1%, while in only 17.5% of them they were dispensed for an infection that was confirmed and documented in the medical record indicating that clinicians are frequently prescribing antibiotics without proper documentation in the medical record or without indication for their use [21]. Furthermore, study conducted in Finland reviles that antibiotic use in dogs is less strict than in food animals since it is not strictly regulated and is driven by people's emotional attachment to their individual pets' needs [21, 28].

In the future, in the AMR control programs in veterinary medicine special attention have to be given to the implementation of the interventions in large animal practice veterinarians since antibiotics are used in greater quantities in food producing animals than in the treatment of disease in human patients [19]. Actually, the amount of antibiotics used in animal husbandry worldwide is almost double that are used in human medicine [29]. Moreover, antibiotics mass administration is extensively used in animal husbandry for disease prevention and as growth promoters [24]. Besides growth promotion, antibiotics are used in three other ways in animals: therapy, metaphylaxis and prophylaxis [30]. Usually, antimicrobials in such large animal groups are administered when single animals of the group present with symptoms of the disease, as it is expected that most of the group will become affected [31]. This practice constitutes the main difference between the use of antibiotics in the animals and in the humans. Interestingly, in an European-wide survey, when veterinarians all over the Europe were asked to specify the indications for which they most commonly prescribed antibiotics, HPCIAs were the most frequently cited therapy in cattle for respiratory diseases (45%), diarrhoea (29%) and locomotion disorders (31%) [32].

Although the volume of sales of antimicrobials for use in food-producing animals in Europe fell by more than 43% between 2011 and 2020 [13], our research results have shown stable trend in the sale of VMPs in Montenegro during the period from 2017 to 2021. As for the data across Europe, they vary a lot. Out of the 25 countries, in the time period from 2011 to 2020, 19 countries reported a decrease of more than 5% in the sales amount of VMPs. On the other hand, 4 countries noted an increment of more than 5% while two countries documented increase or decrease in total volume of sales less than 5%. Significant decline in several countries suggest that there is also a chance for sales reduction in other countries [13].

Besides, this ESVAC report from 2021, shows that sales of antimicrobials considered critically important in human medicine decreased between 2011 and 2020 by: 33% for third and fourth generation cephalosporins, 77% for polymyxins, 13% for fluoroquinolones and 85% for other quinolones. On the other hand, our research results in period from 2017 to 2019 have showed that after a minor decrease in portion of selected CIAs in the total sale of AMVMPs, an increase of 6.11% was noticeable comparing year of 2019 to year of 2021. Contrary to our findings, a surveillance conducted in Germany in period from 2011 to 2018 regarding monitoring of the total sales volumes of antimicrobials for veterinary use have shown considerable reduction amounting to 983 tons (58%). Moreover, in order to determine sales volumes, it is important to take into account factors that could have influence on it, such as in animal demographics and prescription patterns [33, 34]. However, changes in animal demographics are not taken into account by the German system [35]. Such large reductions are most likely easier to achieve in developed countries, as it is the case in Germany. However, more data are needed to better understand how antimicrobials are used in animal agriculture to find opportunities for further reduction along with additional recommendations and regulations that have to be put in place to curtail the use of antibiotics helping in the reduction of antimicrobial use in food animal production [8]. One of the regulations could be the controlled use of antimicrobials [31], since antimicrobials for animal growth promotion can generally be purchased without veterinary control even in the European Union. Furthermore, high sanitation, by controlling the microbial burden in the farm is a key factor to help to ban antimicrobial misuse [36]. Hence, multidisciplinary studies aimed at finding the most adequate strategies for antibiotics use in animal and human medicine are necessary. Thus, prior to performing group treatment, the causative bacterial pathogen should be identified and an effective antimicrobial agent should be chosen on the basis of its antimicrobial sensitivity [30]. Some research results pointed out that there is a lack of antimicrobial sensitivity testing in human medicine also. For example, in a study conducted in 2021, that included all patients from 10 hospitals in Montenegro which were treated with antimicrobials during the survey, results showed that only 1.7% out of all participants received microbiologically targeted antimicrobial therapy [37]. Therefore, to preserve the effectiveness of the antimicrobial drugs focus of the educational campaigns of all health workers have to be on raising knowledge and awareness about this important issue. Besides, this is crucial since the same resistance mechanism confers resistance to veterinary and human antibiotics. For example, CTX-M beta-lactamase production leads to resistance to both ceftiofur (veterinary use) and cefotaxime (human use) cephalosporins [31]. Unlike third-generation cephalosporins, which in outpatient settings can only be used as an extension of hospital treatment, the use of fluoroquinolones has no limitations, which could be an additional selective pressure of this class of antibiotics. Furthermore, analysis of outpatient consumption might contribute to explaining the high rate of resistance to fluoroquinolones [38]. Besides, link between animals and humans in antimicrobial consumption and AMR emphasizes the need for integrated control methods that aim to prevent transmission across different One Health domains [39].

In veterinary medicine, colistin sulfate is often used in oral preparations because it displays good activity against *Escherichia coli* and *Salmonella* spp. and presents poor absorption after oral administration and low rates of resistance. On the other hand, acquired resistance on these pathogens to polymyxins has been attributed to the substitution of phosphate groups in membrane lipopolysaccharides [31]. Oral use of this drug enabled wide use as growth promoters in veterinary medicine, as well as in prophylaxis. Since 2006, the use of colistin as a growth stimulator has been banned in the EU, but it is still used in prophylaxis and is one of the five best-selling antibiotics in veterinary medicine in Europe [40, 41].

In our study, the consumption of colistin, as the only presented HPCIA, was processed together with amoxicillin, considering that it is the only recorded pharmaceutical formulation in veterinary use in Montenegro. It sales, along with the other selected CIA, remained stable in the calculated period, showing slight increase or decrease annually, with exception of ampicillin which sale increased 60.2% from 2018 to 2021. Amoxicillin, alone or in combination with other substance, was by far the most widely used antibiotic of the selected ones. These results are consistent with the results in the European countries where amoxicillin alone or in combination with clavulanic acid is the most frequently prescribed medication [42].

CONCLUSION

For years, Montenegro was among the European countries with the highest rate of antimicrobial consumption. Constant efforts on the establishing monitoring systems for antimicrobial usage will enable the development of effective and tailored antimicrobial stewardship programs in order to prevent and control the spread of AMR. Since high resistance to some CIAs for human medicine is established, veterinarians have to restrict their use, so educations of current and future veterinarians on this issue will promote prudent antimicrobial use. Furthermore, antimicrobial therapy is rarely targeted in both human and veterinary medicine. Thus, antibiotic susceptibility testing has to be crucial part of successful and appropriate antibiotic therapy targeting the cause of infection. Further research on the local levels, integrating contextual information, could usefully explore some of the drivers behind the prescribing antimicrobial patterns reported here.

Conflict of interest: The authors declare that there is no conflict of interest.

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