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PRACTICAL USE OF REGISTERED VETERINARY MEDICINAL PRODUCTS IN MACEDONIA IN IDENTIFYING THE RISK OF DEVELOPING OF ANTIMICROBIAL RESISTANCE

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ABSTRACT

The use of antimicrobial agents is the key risk factor for the development and spread of antimicrobial resistance. It is therefore generally recognized that data on the usage of antimicrobial agents in food-producing animals are essential for identifying and quantifying the risk of developing and spreading of antimicrobial resistance in the food-chain. According to the WHO guidelines, the Anatomical Therapeutic Chemical system for the classification of veterinary medicines (ATC-vet) is widely recognized as a classification tool. The aim of this work is to analyze the list of registered veterinary medicinal products in R. Macedonia and to evaluate the quality and practical use of this list according to the ATC-vet classification in order to identify the risk of developing and spreading of antimicrobial resistance.

Key words: antimicrobial agents, antimicrobial resistance, veterinary medicinal products, ATCvet classification system

INTRODUCTION

Antimicrobials are valuable tools in the preservation of animal health and animal welfare, and must be cherished as they may save lives and prevent animal suffering (1). But the use of antimicrobial agents is the key risk factor for the development and spread of antimicrobial resistance (AMR). It is therefore generally recognized that data on the usage of antimicrobial agents in food-producing animals (and companion animals) are essential for identifying and quantifying the risk of developing and spreading of AMR in the food-chain (2). The World Health Organization has indicated the follow up of antimicrobial resistance as one of the three top priorities (1). Antimicrobial resistance is defined as the ability of a microorganism to grow or survive in the presence of an antimicrobial at a concentration that is usually sufficient to inhibit or kill microorganisms of the same species. Antimicrobial consumption in animals selects for antimicrobial resistant bacteria in animals, leading to therapy failure of bacterial infections. Yet it might also endanger human health through either transfer of resistant bacteria or their resistance genes from animals to humans. The magnitude of this risk still needs to be quantified while increasing evidence of resistance transfer between environments is found (1). This was also acknowledged by the European Council in 2008 through the Council Conclusions on Antimicrobial Resistance, which called upon the Member States to strengthen surveillance systems and improve data quality on antimicrobial resistance and on use of antimicrobial agents within both human and veterinary sectors (3). Having this in mind we decided to respond to the latest and to estimate the use of antimicrobial agents in veterinary sector in the Republic of Macedonia (RM) by analyzing the List of Registered Veterinary Medicinal Products (VMPs) and evaluating of the quality and practical use of this list according to the

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Anatomical Therapeutic Chemical System for the Classification of Veterinary Medicines, with the aim of identifying the risk of development and spread of antimicrobial resistance.

ATCvet classification system

To harmonize the veterinary antimicrobial agents to be included in the material, the Anatomical Therapeutic Chemical System for the Classification of Veterinary Medicines (ATCvet) was applied. According to the WHO guidelines, the ATCvet is widely recognized as a classification tool. This system is based on the same overall principles as the ATC system for substances used in human medicine (4). In most cases an ATC code exists which can be used to classify a product in the ATCvet system. The ATCvet code is created by placing the letter Q in front of the ATC code. In some cases, however, specific ATCvet codes are created, e.g. Immunologicals (QI) and Antibacterials for intramammary use (QJ51) (4). In both the ATC and the ATCvet systems, medicinal products are divided into groups, according to their therapeutic use (1st level) (see the Table below).

ATCvet ▶

ATCvet	Anatomical groups (1st level)	*ATC*
QA	Alimentary tract and metabolism	A
QB	Blood and blood forming organs	B
QC	Cardiovascular system	C
QD	Dermatologicals	D
QG	Genito-urinary system and sex hormones	G
QH	Systemic hormonal preparations, excl. sex hormones and insulins	H
QI	Immunologicals	-
QJ	Anti-infectives for systemic use	J
QL	Antineoplastic and immunomodulating agents	L
QM	Musculo-skeletal system	M
QN	Nervous system	N
QP	Antiparasitic products, insecticides and repellents	P
QR	Respiratory system	R
QS	Sensory organs	S
QV	Various	V

◀ ATC/DDD

Within most of the 1st level groups, medicinal products are subdivided into different therapeutic main groups (2nd level), coded for example as QA01, QA02, QA03 etc. Two levels of chemical/therapeutic/pharmacological subgroups (3rd and 4th levels), e.g. QA02A, QA02B etc. at the 3rd level and QA02AA, QA02AB etc at the 4th level, provide further subdivisions. At a 5th level, e.g. QA02AA01, chemical substances are classified. This subdivision does not apply to QI – Immunologicals (4).

Distribution of veterinary medicines in RM

The first step in setting up surveillance of veterinary antimicrobial agents in some country is to identify and describe of the distribution system for veterinary antimicrobial agents (8). In our country, all VMPs containing antimicrobial agents are prescription-only medicines. This includes medicated premixes containing pharmaceutically active substances like antimicrobial agents. VMPs containing antimicrobial agents are provided

by Wholesaler Distributors (WD) to retailers of veterinary medicinal products (veterinary pharmacies) and veterinary organizations. Wholesaler-distributors obtain the VMPs from a wholesaler or from the Marketing Authorization Holder (MAH)/manufacturers.

Antimicrobial VMPs are only available to animal owners/farmers by delivery from a pharmacy on veterinary prescription or directly from the veterinary organizations. Only veterinarians are entitled to sell VMPs to animal owners/farmers. Veterinarians have to confirm the distribution of veterinary drugs to owners of food-producing animals if used for food production. Sales of VMPs by pharmacies account for a negligible amount of sales for farm animals. Medicated feeds have to be prescribed by veterinarians and manufactured either by authorized feed mills or by authorized farms. They are also may be imported to Macedonia. Medicated feeds containing antimicrobials are prepared from authorized premixes that are distributed through wholesaler-distributors. From feed mills, only farmers are receivers. Medicated feeds are used primarily for pig and poultry production.

Legal basis for the monitoring of sales of VMPs in RM

The collection of sales data by MAH/WDs is based on the national Law on veterinary medicinal products (Official Gazette of the Republic Macedonia No. 42/2010- article 37)(10). MAH/WDs are obliged to keep records of all sales and to deliver these records (by template for the amount of sold out VMPs) to the Sector for Public Veterinary Health in Food and Veterinary Agency (FVA) on a yearly basis (11). The fact that many antimicrobial products are registered for use in different animal species and that there are currently no data available on the proportions of products used in the different species makes extrapolation up to animal species level unachievable at this very moment. The MAH of the products do provide estimated proportions to be included in the periodic safety update reports, yet these estimates are not always at hand, and are often based on limited data. For these reasons it was not feasible to use these data.

MATERIALS AND METHODS

Data of all registered/renewed VMPs on the Macedonian market are collected from the web site of FVA (12), pharmaceutical companies (n=37) producing or importing VMPs and from MAH/WDs (n=16) that are assigned by the FVA to distribute them. The registered/renewed VMPs in last five years in Macedonia are classified according to composition of active component/s and main therapeutic indications regarding to the system of organs to which are intended to act on. An appropriate code from ATCvet Index 2013 provided from WHO Collaborating Centre for Drug Statistics Methodology at Norwegian Institute of Public Health (4) was designated to each VMP. On this way we have created a list of registered/renewed VMPs with appropriate ATCvet code and made a detailed analysis of the number of registered VMPs classified by the system of organs and qualitative analysis of specific groups of VMPs. In particular, we analyzed groups of antimicrobial agents in different therapeutic main groups (see Table 3) in order to estimate the use of antimicrobial agents in veterinary sector in the RM and to identify the risk of developing and spreading of antimicrobial resistance.

RESULTS AND DISCUSSION

In Macedonia, 318 VMPs were registered or renewed during the period from 01.01.2008 to 31.12.2012. Figure 1 shows the number of registered/renewed VMPs per year and manufacturers. All registered VMPs are from import, mainly from 37 manufacturers from 16 European countries (Holland 18.2%, Serbia 17.0%, Croatia 15.0 %, Bulgaria 7.2 %, Slovenia 7.2 %). In the period of 15 years, about 850 VMPs were registered/renewed or approximately 45 – 50 per year. In 2009 and 2012, a little reduction in the number of registered/renewed VMPs on the Macedonian market is observed, largely due to newly adopted legislation for registration and the impossibility of MAH/WD in quick time to adjust to the new regulations.

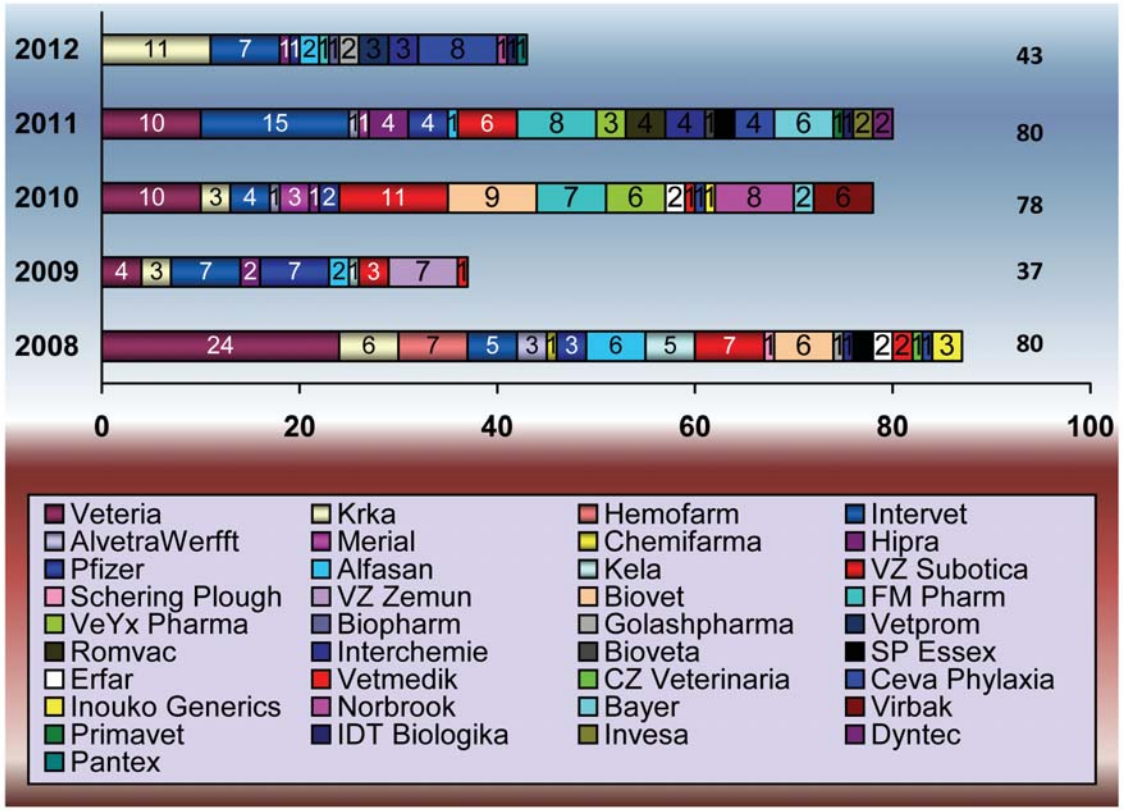

Figure 1. Number of registered/renewed VMPs in RM per year and manufacturers

Table 1 shows the number of registered/renewed VMPs on the Macedonian market this moment according to their therapeutic use. The largest number of registered VMPs are from group QJ – Anti-infectives for systemic use (n = 93), while on the other hand there are no VMPs registered for primary therapeutic effect on cardiovascular system (group QC), for treatment of neoplasm (group QL-Antineoplastic and immunomodulating agents) and for treatment of diseases of eyes and ears (group QS - Sensory organs). Some of the anatomical groups like a group QB - Blood and blood forming organs, group QM - Musculo-skeletal system and group QR - Respiratory system were represented by insignificant number of VMPs.

Table 1. Number of registered VMPs in RM according to their therapeutic use

Anatomical groups (1st level)		No. of VMPs
QA	Alimentary tract and metabolism	**38**
QB	Blood and blood forming organs	**4**
QC	Cardiovascular system	**0**
QD	Dermatologicals	**9**
QG	Genito-urinary system and sex hormones	**17**
QH	Systemic hormonal preparations, excl. sex hormones and insulins	**13**
QI	Immunologicals	**74**
QJ	Antiinfectives for systemic use	**93**
QL	Antineoplastic and immunomodulating agents	**0**
QM	Musculo-skeletal system	**2**
QN	Nervous system	**11**
QP	Antiparasitic products, insecticides and repellents	**53**
QR	Respiratory system	**2**
QS	Sensory organs	**0**
QV	Various	**2**
	Total:	**318**

From the total number of the registered VMPs, pharmaceuticals are 76.7% (n=244) while immune-preparations are 23.3% (n=74). The amount of antimicrobial agents and their combinations is 32.7% (n=104), while the amount of antiparasitic is 16.7% (n=53). From the total number of registered immune-preparations greater number are vaccines for poultry and swines. In RM the use of antimicrobial agents is expanded, contrary to the immune-preparations. The above mentioned data are partly in coordination with the data for the registered VMPs in other European countries (5,6,7). Small market for specific VMPs results in lack of interest of the pharmaceutical companies to register VMPs with low or no commercial value, creating serious problem for the veterinary practitioners. Table 2 provides an overview of the number of registered/ renewed antimicrobial pharmaceuticals and the number of antimicrobial medicated premixes per year on the Macedonian market for the period 2008 - 2012.

Table 2. Overview of the number of registered/renewed antimicrobial products on the Macedonian market in period 2008 - 2012

	2008	**2009**	**2010**	**2011**	**2012**
Number of antimicrobial pharmaceuticals	18	8	30	17	15
Number of antimicrobial medicated premixes	7	2	4	2	1
Total number of registered/renewed antimicrobial products on the market	25	10	34	19	16

In the period of 5 years, 104 antimicrobial products were registered and renewed or approximately 20 per year. In RM the use of parenteral forms of antimicrobial products (inj. sol.; inj. susp.) is expanded 51% (n=53), contrary to antimicrobial medicated premixes 15.4% (n=16). The amount of intramammary products is 6.73% (n=7), while the amount of intrauterine products is 2.9% (n=3). With exception of macrolide antibiotics tulathromycin and tilmicosin (since 2009 and 2012) and third generation cephalosporin ceftiofur (since 2009), no additional active substances were registered on the market in the reported years. Thus the observed number in available products is largely due to the marketing of new formulations or new generic products based on existing active substances. Table 3 provides an overview of the number of antimicrobial agents from different therapeutic main groups available on the Macedonian market this moment.

Table 3. Groups of antimicrobial agents and corresponding ATCvet codes available on the Macedonian market this moment

Groups of antimicrobial agents	**ATCvet codes**	**Total**
Antimicrobial agents for intestinal use	QA07AA; QA07AB	4
Antimicrobial agents for dermatological use	QD06AA; QD06BA	4
Antimicrobial agents for intrauterine use	QG51AA; QG51AC; QG51AE; QG51AX QG51BA; QG51BC; QG51BE	3
Antimicrobial agents for systemic use	QJ01	86
Antimicrobial agents for intramammary use	QJ51	7
Antimicrobial agents for use in sensory organs	QS01AA; QS01AB QS02AA QS03AA	0
Antimicrobial agents for use as antiparasitic	QP51AG	0

Antimicrobial products which are used as antiparasitic agents (group QP51AG) and for use in sensory organs were not registered. Some group of the antimicrobial agents like a group QA07 – Antibacterials for intestinal use, group QD06 - Antimicrobial agents for dermatological use, group QG51- Antibacterials for intrauterine use and group QJ51 - Antibacterials for intramammary use were represented by insignificant number of VMPs. The ATCvet codes (ATC level 3 or 4) included in each antimicrobial class are listed in Table 4.

Table 4. ATCvet codes included in the different classes of antimicrobials

Class of antimicrobials	ATCvet codes included	Total
Aminoglycosides	QA07AA01 (1) QJ01GA01 (1), GB03 (1), GB04 (1)	4
Cephalosporins	QG51AA05 (1) QJ01DA90 (3); DB01 (1) QJ51DA01 (1)	6
Amphenicols	QJ01BA52 (1); BA90 (3)	4
Macrolides	QJ01FA90 (1), FA91 (1), FA94 (1)	3
Penicillins	QJ01CA04 (5); CE30 (4); CR02 (3) QJ51RC (1)	13
Polymyxins	QA07AA10 (1)	1
Quinolones	QJ01MA90 (12) QJ01MB07 (1)	13
Sulfonamides and trimethoprim	QA07AB (2) QJ01EQ (4); EW (6)	12
Tetracyclines	QD06AA (3) QD07C (1) QG51AA01 (1); AA08 (1) QJ01AA02 (1), AA03 (2); AA06(9)	18
Pleuromutilins	QJ01XQ01 (7)	7
Combinations of antibacterials	QJ01RA01(penicillins)/QJ01RA95(polymyxins)(1) QJ01RA01(penicillins)/QJ01RA97(aminoglycosides) (8) QJ01RA02 (sulfonamides)/QJ01RA90(tetracyclines) (1) QJ01RA02/QJ01RA90/QJ01RA97 (2) QJ01RA90 (tetracyclines + tiamulin) (3) QJ01RA94 (lincosamides + spectinomycin) (1) QJ01RV01 (penicillin+polymyxin+corticosteroid) (1) (penicillin+aminoglycos+corticosteroid) (1) QJ51RC23 (penicillin+aminoglycosides) (2) QJ51RV01 (cephalosporin+corticosteroid) (1) (penicillin+aminoglycosides+ corticosteroid)(1) tetracyclin+aminoglycosid+bacitracin+corticosteroid)(1)	23

Tetracyclines (n=25), penicillins (n=27) and quinolones (n=13) are the top three antimicrobial classes, comprising approximately 62.5 % of all registered antimicrobial agents. Generally, tetracyclines and/or penicillins accounted for the highest proportion of the use in the reporting period. For antimicrobial agents considered to be critically important antimicrobials in human medicine, such as the 3rd and 4th-generation cephalosporins, macrolides and the fluoroquinolones, an overall increase in usage is observed. These classes of compounds are used for food producing animals and could potentially influence the prevalence of resistance. 3rd and 4th-generation cephalosporins and fluoroquinolones are considered as particularly important in human medicine because they are among the only alternatives for the treatment of certain infectious diseases in humans. Measures to

counter a further increase and spread of resistance in animals should therefore be considered.

Although there is a legal basis for the collection of sales data on VMPs on an annual basis from MAH/WDs to the FVA in this moment the data is not available to us. It should be emphasized that sales of antimicrobial agents (mg per population correction factor - PCU) are not indicators for the level of exposure (9). The main goal of calculating the amount of antimicrobial agents is to adjust trends in the use within a country for possible changes in the size of animal livestock population and number of slaughtered animals (7). Also, the sales data on veterinary antimicrobial agents cover all species, while the population correction factor does not include companion animals or minor species.

DISCUSSION

The use of antimicrobial agents is an important risk factor for the development of antimicrobial resistance. Monitoring of use of antimicrobials is one of the important sources of information used for the assessment and management of risks related to antimicrobial resistance. Our work provides the first data on the usage of antimicrobial drugs in animals in Macedonia for the given period and shows a high usage of antimicrobials in veterinary sector. Many European countries have been reporting these already for several years. Moreover it has recently become a European engagement from member states to report on the level of antimicrobial consumption in animal production (7). Also in the context of methicillin resistant Staphylococcus aureus, extended spectrum beta-lactamase, and other emerging resistance traits, comparable and evolutionary data on antimicrobial consumption are needed. This work can thus also be seen as a starting point for continuous monitoring of using the antimicrobial agents in future. The reported table will also be used as a reference for comparison and to evaluate effects of policy measures.

As the data presented in this work are aggregated per antimicrobial class, they do not allow for more in-depth analysis. The types and incidences of infectious diseases vary considerably between animal species and production category (e.g. veal versus dairy cattle), and consequently the sales of veterinary antibacterial agents are thought to be influenced by animal species demographics. To identify the factors underlying the differences observed, there is a need for detailed sales data of each antimicrobial VMPs. As a first step, the use of the standardized ESVAC template for the collection of data (9) will provide detailed data at package level, including information on administration form and herd treatment versus individual treatment, allowing for more detailed analysis than can be done using the aggregated data. As some agents are administered in much higher dosages than others (e.g. tetracyclines versus cephalosporins), there is a need to continue to refine the tools for analyzing the data on sales of antimicrobial agents. The next steps should be to analyze the data taking into account variance in the dosing and the treatment duration of each antimicrobial VMPs.

CONCLUSIONS

The extended and uncontrolled use of antimicrobial agents in Macedonia is representing the main risk factor for the development of antimicrobial resistance. Data on the usage of antimicrobial agents particularly in food producing animals is essential for identifying and quantifying this risk in the food-chain. The ATCvet classification gives a detailed view on the real quantity of the different classes of registered VMPs. It is practical tool for identification of different groups of VMPs for the veterinary practitioners as well as all subjects involved in production, trade and distribution of VMPs. The results obtained given an overall picture of trends in the use of veterinary antimicrobial agents in R. Macedonia. Currently data indicate a high use of antimicrobials indicating that this class of VMP should be monitored closely to avoid the appearance of antimicrobial resistance and possible consequences for animal and human health. Nevertheless, such data should be interpreted with caution, with further analysis to assess exposure trends and the effect of policy measures for prudent use.

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