Pharmaco-epidemiological evaluation of veterinary antimicrobial prescriptions for cattle, swine, small ruminants, poultry, rainbow trout, and food-producing horses in Umbria in 2014

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Veterinary antimicrobials, Antimicrobial monitoring, One Health, Antibiotic resistance, Veterinary pharmaco-epidemiology.

Summary
Veterinary antimicrobial use could lead to problems such as the spread of antimicrobial resistance or the presence of residues in animal-derived products for human consumption. Related to this, data on drug consumption is in strong demand. The aims of this study are therefore to evaluate a regional Defined Daily Dose (DDDvet_Umbria) for all of the antimicrobials prescribed in Umbria during 2014 and to analyse prescriptions for cattle, swine, small ruminants, poultry, rainbow trout, and food-producing horses. Consumption, prevalence, and intensity of use indicators are calculated. Swine, poultry, and fish were the most treated species during 2014. Beta-lactams were the most frequently consumed antimicrobials for these species. Critically important antimicrobials were mostly prescribed for swine, poultry, and cattle. Colistin was the most frequently used critically important antimicrobial to treat swine and poultry. This study helps to better understand antimicrobial consumption in food-producing animals by overcoming the limitations of other proposed approaches. Our data are useful for quantifying antimicrobial consumption, identifying problematic farms, and supports a comparison among different animal species. Results highlight that the critical sectors in drug consumption – where the highest use of antibiotics were found – are swine, poultry, and trout farms.

Valutazione farmaco-epidemiologica di prescrizioni antimicrobiche nell'Italia centrale, Umbria 2014

Parole chiave
Antimicrobici veterinari, Farmaco-epidemiologia veterinaria Monitoraggio, One Health, Restistenza antimicrobica, Sanità pubblica veterinaria.

Riassunto
La diffusione della resistenza antimicrobica e la presenza di residui nei prodotti di origine animale destinati al consumo umano possono essere conseguenze dell'uso degli antimicrobici in veterinaria. I dati sul consumo sono quindi molto richiesti. Gli obiettivi di questo studio sono di stimare una dose definita giornaliera regionale (DDDvet_Umbria) per tutti gli antimicrobici prescritti in Umbria nel 2014 e di analizzare le prescrizioni per bovini, suini, piccoli ruminanti, pollame, trote arcobaleno e cavalli destinati alla produzione alimentare. Le specie più trattate sono state nel 2014 i suini, il pollame e il pesce (le trote), per i quali sono stati utilizzati prevalentemente beta-lattamici. Gli antimicrobici di importanza critica sono stati prescritti oltre che per suini e pollame, anche per i bovini; la colistina è risultato essere l'antimicrobico più frequentemente usato nei suini e nel pollame. Superando i limiti di altri approcci proposti, questo studio indirizza la comprensione del consumo di antimicrobici negli animali da produzione alimentare. I dati sono utili per quantificare il consumo antimicrobico, identificare le fattorie problematiche e sostenere un confronto tra diverse specie animali.

Introduction

Veterinary antimicrobials are some of the veterinary drugs used as tools to prevent, control, and treat infections. They also protect animal welfare and health, and improve growth and production. Antibiotics must be used responsibly in order to guarantee public health by reducing the spread of antimicrobial resistance and the risk of residues in animal derived food products. (Economou and Gousia 2015). It is well known that any antibiotic administration both in animals and in humans could lead to the selection of resistant bacteria (Silbergeld *et al.* 2008); this has become an increasing problem worldwide for both veterinary and human medicine (Wassenaar 2005). The European Union is working towards the spread of antimicrobial resistance reduction by promoting regulations and guidelines. In 2006, the use of antibiotics for growth promotion was banned (European Commission 2003). Recently, a statement regarding the guidelines on the prudent use of antimicrobials in veterinary medicine was issued by the European Commission; it identified the need to monitor plans for various types of resistance in each production chain, as well as for pathogens, zoonotic and commensal bacteria, and for antibiotic consumption (European Commission 2015). Knowledge of both aspects is fundamental in assessing the relationship between resistance and the use of antimicrobials (van Rennings *et al.* 2015). The Directive 2003/99/EC makes it mandatory to monitor antimicrobial resistance in zoonotic bacteria; furthermore, European or national plans have been implemented for commensal and pathogen germs (Ministry of Health 2012, EFSA 2016). To date, no obligation regarding coordinated data-collection in Europe (van Rennings *et al.* 2015) has been defined, although some countries have recently developed their own strategies (van Rennings *et al.* 2015, AURES 2013, SVARM 2012, Merle *et al.* 2014, DANMAP 2014, MARAN 2015).

Since 2010, the European Medicines Agency launched the ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) project, which focuses on antibiotics. Specifically, the ESVAC initiative relates to 'collecting and developing a coordinated approach for the collection and reporting of data on the use of antimicrobial agents in animals from the European Union and European Economic Area Member States' (EMA/ESVAC 2015). The EMA/ESVAC group has provided a guideline on the standardisation of data collection and evaluation of veterinary drug consumption (EMA 2015) to overcome limits shown by other proposed units of measurements (Merle *et al.* 2014, EMA/ESVAC 2016). This guideline proposes 'standardised fixed units of measurement for the reporting of data on consumption by species that take into account differences in dosing' in order to compare consumption data between countries, animal species, and human (EMA 2015, EMA/ESVAC 2016). Defined daily doses (DDDvet) for each active ingredient per animal species and administration route are set as a reference parameter for evaluating veterinary active ingredients consumption and their comparisons across animal species and farming systems (EMA 2015, Postma *et al.* 2015, WHO 2013, EMA/ESVAC 2016). This information provides a valuable basis for decisions relating to the reduction of misuse of veterinary drugs, especially antibiotics, and may therefore be of interest to relevant Health Authorities. However, the list of DDDvet provided by the EMA/ESVAC for antimicrobials is reserved for swine, broilers, and cattle; and there is limited information about the registration and use of the veterinary drug handbooks in different member states, including Italy (EMA/ESVAC 2016). Nevertheless, this is an important step towards a standardised approach in quantifying antibiotics in Europe. The extension of the list to include other animal species and all active ingredients in veterinary medicine, through the use of information gathered from all the European countries, could improve our knowledge of drug utilisation in veterinary medicine.

The aim of this study is to begin addressing some of these gaps by providing data on antimicrobial consumption in cattle, swine, small ruminants, poultry, rainbow trout, and food-producing horses in Umbria, according to the methods proposed by the EMA/ESVAC (2016). Data are provided by the veterinary prescriptions received by the Umbrian public health authorities in 2014.

Materials and methods

General analysis

Information about the total number of farms and livestock animals per species present in Umbria during 2014 was obtained from a national database, which is available at www.vetinfo.sanita.it (BDN) (Table I). The BDN does not include information on antibiotic prescriptions in veterinary medicine. Data on antibiotic prescriptions were obtained from the hard copies of veterinary drug prescriptions stored by the veterinary public authorities responsible for veterinary drug control; these authorities receive veterinary prescription copies from drug vendors, a mandatory procedure under both European and national Italian law. Copies of veterinary drug prescriptions were collected on a monthly basis and transferred to Microsoft Excel and Microsoft Access. Prescriptions were split by species. The prescriptions admitted in this study were those for cattle, swine, small ruminants, poultry (defined according to council directive 2005/94/EC), rabbits, rainbow trout (fish), and food-producing horses. Damaged prescriptions, off-label antibiotic drugs registered for humans,

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Table I. *Number of farmed animals and farms in Umbria in 2014.*

		Umbria Region
Cattle	Farmed animals	56,694
	Farms	3,088
Swine	Farmed animals	212,105
	Farms	3,361
Small ruminants	Farmed animals	132,437
	Farms	3,510
Poultry	Farmed animals	7,774,832
	Farms	261
Fishes (trouts)	Farmed animals	-
	Farms	15
Total	Farmed animals	8,176,068
	Farms	10,235

and antibiotic drugs with topical administration for which it was impossible to evaluate a DDDvet_Umbria standard, were excluded from the study. For each prescription, the following information was transferred to the database: commercial name, posology, number and productive category of treated animals, days of treatment, and withdrawal periods. The active ingredient (a.i.) contained in each prescribed drug was considered a single record. Analysis was performed taking into consideration each class of antibiotic and the sub-group 'Critically Importance Antimicrobials' (CIAs), according to the World Health Organization (WHO 2011).

DDDvet_Umbria determination and prescribed DDDs evaluation

DDDvet_Umbria values were calculated according to the EMA indication (EMA 2015) for each a.i., and differentiated by animal species. Different DDDvet_Umbria values were evaluated for each administration route and for those a.is. prescribed in synergistic combination with other a.is. This means that each a.i. could have 2 or more different DDDvet_Umbria values according to different animal species usage, with a different administration route, and/or in a synergistic combination with other a.i. utilisation. A database with all the prescribed drugs in 2014 in Umbria was created by collecting information about the recommended dose according to each respective leaflet (including premixes for medicated feed) available from the Ministry of Health veterinary drug manual[1]. Each prescription drug entry was expressed differently for each administration route, in-line with (EMA/ESVAC 2016):

- Parenteral and oral route of administration: mg a.i. /kg body weight.
- Intra-mammary administration for treatment during lactation (cattle and small ruminants): the number of tubes per teat daily administered.
- Intra-mammary administration for dry therapy (cattle and small ruminants): the number of tubes per udder daily administered.
- Intrauterine administration: mg a.i./animal.

DDDvet_Umbria was calculated for each a.i. as the average value of recommended dosage reported in the various leaflets about each prescribed drug.

For those a.is. for which European Medecines Agency (EMA) has provided, DDDvet values for oral and parenteral administration for cattle, swine, and broilers, a ratio between DDDvet_Umbria and DDDvet was calculated.

Prescribed DDDs were evaluated by dividing the total amount of each a.i. in mg by DDDvet_Umbria of this a.i.

Consumption analysis

The following indicators of antibiotic consumption were evaluated:

- Defined daily doses (DDD) per 1,000 animals per day: the mean number of doses consumed every day by 1000 animals (DDDs/1,000 animals-*die*).
- DDDs per 1000 farms per day: the mean number of doses consumed every day by 1,000 farms (DDDs/1,000 farms-*die*).
- Prevalence of use: the number of drug users (farms) divided by the overall farms present in the Umbria region in 2014 (%).
- Intensity of use: the number of prescribed DDDs divided by the number of farms with at least 1 antibiotic prescription in 2014 (DDDs/farms).

Analysis was performed for each productive sector.

For food-producing horses and rabbits, no information was available in BDN regarding the number of animals and number of farms, while for rainbow trouts (fish), the only available information was related to farms. Therefore, for food-producing horses and rabbits, only prescribed DDDs were evaluated, while for rainbow trout (fish) only DDDs/1,000 farms-*die*.

Results

General consumption analysis

The total number of prescriptions that were analysed was 10,051, which corresponded to 23,146 antibiotic records. Partial or incomplete records accounted

[1] https://www.vetinfo.sanita.it/j6_prontuario/public/.

Table II. *Classification of antimicrobials prescribed in 2014 in Umbria.*

Classes	Active ingredients
Aminoglycosides	Apramycin, amikacin, dihydrostreptomycin, streptomycin, gentamicin, kanamycin, framycetin, nemoycin, spectinomycin, paromomycin
Amphenicols	Thiamphenicol, florfenicol
Cephalosporins, First Generation	Cefacetrile, cefopirin, cefazolin, cefalonium, cefalexin
Cephalosporins, Third Generation*	Cefoperazone, ceftiofur
Cephalosporins, Fourth Generation*	Cefquinome
Ionophore antimicrobials	Monensin
Lincosamides	Lincomycin
Macrolides*	Erithromycin, spiramicin, tilmicosin, tylvalosin, tulathromycin, tylosin, tildipirosin, gamithromycin
Nitrofurans	Furaltadone
Penicillin	Amoxicillin, amoxicillin + enzime inhibitor,penethamate hydriodide, phenoxymethylpenicillin, cloxacillin, dicloxacillin, benzylpenicillin, procaine penzylpenicillin, benethamine penicillin, ampicillin
Pleuromutilin	Tiamulin, valnemulin
Polymyxins and Polipeptidic antimicrobials*	Colistin, bacitracin
Quinolones/Fluoroquinolones*	Enrofloxacin, flumequine, oxolinc acid, danofloxacin, marbofloxacin
Rifaximins	Rifaximin
Sulfonamides and Trimethoprim	Sulfadiazine, sulfadimidine, sulfadimethoxine, sulfamethoxazole, sulfamonomethoxine, phthalylsulfathiazole, sulfathiazole, sulfamethoxypyridazine, sulfamerazine, sulfaguanidine, trimethoprim
Tetracyclines	Oxytetracycline, chlortetracycline, doxycycline

* Critically important antimicrobials.

for 2.47% of the total and off-label records accounted for 10.61% of the total. The number of antimicrobial records was 14,249, of which 3339 were for CIAs.

Poultry – especially game – showed the highest number of off-label records (58.35%), followed by rabbits (10.57%), swine and small ruminants (9.94%), rainbow trout (4.02%), food-producing horses (3.59%), and cattle (3.59%). The majority of prescriptions were mostly for swine (37.11%) and cattle (24.45%), followed by rabbits (17.48%), poultry (13.03%), small ruminants (6.85%), food-producing horses (0.60%), and rainbow trout (0.49%). Regarding rabbits, 98.08% of evaluated prescriptions were for animals bred for home consumption. Antimicrobials were the most prescribed type of drugs in 2014 (100% of prescribed records in rainbow trout, 66% in cattle, 63.72% in swine, 57.37% in rabbits, 50% in poultry, 47.17% in small ruminants, and 44.50% in food-producing horses).

A total of 285 DDDvet_Umbria values were evaluated in this study. Values referred to 65 a.is. classified in 16 antimicrobial classes[2] and differentiated by animal species, administration route, and synergistic combinations. The list of a.is. classified by classes of drugs is shown in Table II. Cattle (33.33%), swine (23.16%), and poultry (20.70%) showed the highest number of evaluated DDDvet_Umbria values; followed by rabbits (9.47%), small ruminants (8.42%), food-producing horses (3.16%), and fish (1.75%). The largest number of evaluated DDDvet_Umbria values was for oral administration (44.21%), followed by parenteral (40%), intra-mammary (12.63%), and intrauterine (3.16%).

A comparison between DDDvet_Umbria and DDDvet provided by EMA was performed for 118 a.is. (22 for broilers, 54 for swine, and 42 for cattle). The average value of DDDvet_Umbria/DDDvet was 1.05 (0.65 for cattle, 1.007 for poultry and 1.55 for swine).

Swine were the most treated animal species in Umbria in 2014 (11,930.02 x 10^5 prescribed DDDs), followed by poultry (2,853.64 x 10^5 prescribed DDDs), cattle (275.11 x 10^5 prescribed DDDs), rabbits (188.90 x 10^5 prescribed DDDs), aquaculture (188.28 x 10^5 prescribed DDDs), small ruminants (24.26 x 10^5 prescribed DDDs), and food-producing horses (1.48 x 10^5 prescribed DDDs) (Figure 1).

The results on antimicrobial consumption using

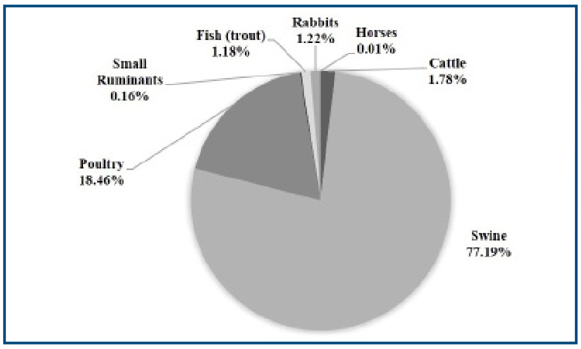

Figure 1. *Antimicrobials: prescribed Defined daily doses (% per animal species).*

[2] Lists of DDDvet_Umbria values are available from the authors.

DDDs/1,000 animals-*die* confirms swine as the most treated farm animal in 2014 (15.41 x 10^3 DDDs/1,000 animals-*die*), followed by cattle, poultry, and small ruminants (1.33 x 10^3; 0.10 x 10^3; 0.05 x 10^3 DDDs/1,000 animals-*die*, respectively). Poultry and fish farms instead showed a high consumption of antimicrobials (fish: 3,329.35 x 10^3; poultry: 2,995.47 x 10^3; swine: 972.48 x 10^3; cattle: 24.41 x 10^3; small ruminants: 1.89 x 10^3 DDDs/1,000 farms-*die*).

Data showing consumption, prevalence, and intensity of use for each animal species are found in Tables III, IV, and V.

CIAs were prescribed mostly for swine, poultry, and cattle (Table III, Table IV, Figure 2, and Figure 3). In prescribed DDDs, the highest percentage of CIAs was for swine (72.23%), followed by poultry (25.18%), cattle (1.82%), rabbits (0.73%), small ruminants (0.02%), rainbow trout (0.02%), and food-producing horses (0.001%).

A large number of prescriptions for polymixins (essentially colistin) and macrolides was found in swine, which relates to the number of farmed animals (Figure 2a). Macrolides were also prescribed for cattle. However, in this species, third-generation cephalosporines was the most used class of CIAs. Quinolones/fluoroquinolones and polymixins showed a moderate utilisation for cattle. A different type of behaviour could be observed in the consumption of CIAs per farm (Figure 2b). In this case, poultry showed the highest consumption of CIAs, particularly colistin, which is extensively prescribed for swine farms as well. Macrolides and quinolones/fluoroquinolones were also widely prescribed for poultry; a high use of macrolides was also indicated for swine. For both, animals and farms, the lowest use of CIAs was found in small ruminants and for these species, colistin was the most widely prescribed CIAs. Figure 3 shows prevalence (%) and intensity of use in reference to CIAs. Poultry showed the highest farm prevalence, especially for macrolides, quinolones/fluoroquinolones, and polymixins. Polymixins (essentially colistin) showed the highest intensity of use on farms, particularly on swine and poultry farms, followed by macrolides in swine, and quinolones/fluoroquinolones in poultry.

Antimicrobial consumption per animal species

Data on antibiotic consumption analysis per animal species are shown in Table III, Table IV, and Table V.

Table III. *Consumption of veterinary antimicrobials in Umbria in 2014 in food-producing animals.*

	Cattle		Swine		Poultry		Small Ruminants		Fishes (trout)
Class	DDDs/1000 animals-*die*	DDDs/1000 farms-*die* (x 10^2)	DDDs/1000 animals-*die*	DDDs/1000 farms-*die* (x 10^2)	DDDs/1000 animals-*die*	DDDs/1000 farms-*die* (x 10^2)	DDDs/1000 animals-*die*	DDDs/1000 farms-*die* (x 10^2)	DDDs/1000 farms-*die* (x 10^2)
Aminoglycosides	148.36	27.24	290.87	183.56	0.26	76.26	6.12	2.31	0
Monensin	143.47	26.34	0	0	0	0	0	0	0
First generation cephalosporins*	0.11	0.02	0	0	0	0	0	0	0
Thrid generation cephalosporins*	201.23	36.94	19.58	12.36	0	0	0	0	0
Fourth generation cephalosporins*	15.77	2.90	4.76	3	0	0	0	0	0
Quinolones/ fluoroquinolones*	83.09	15.26	98.05	61.88	5.71	1,697.06	0.88	0.33	850
Amphenicols	14.90	2.74	559.26	352.93	0.04	11.64	0	0	13,014.55
Beta-lactamase inhibitors	2.98	0.55	45.33	28.60	0	0	0	0	0
Lincosamides	34.87	6.40	3122.88	1,970.78	0.03	7.44	0.02	0.01	0
Nitrofurans	0	0	0	0	0	0.91	0	0	0
Macrolides*	105.52	19.37	1,425.45	899.57	6.51	1,935.98	1.02	0.38	0
Penicillin	287.62	52.81	3,972.34	2,506.85	38.50	11,446.70	8.60	3.24	0
Pleuromutilins	0	0	340.77	215.05	0.10	29.06	0	0	0
Polymixins*	42.42	7.79	3,205.10	2,022.66	32.98	9,805.99	3.21	1.21	0
Rifaximin	0.07	0.01	0	0	0	0	2.61	0.98	0
Sulfonamides	99.20	18.21	994.92	627.87	5.13	1,525.68	0.60	0.23	71,355.70
Tetraciclines	94.14	17.28	1,330.51	839.66	7.47	2,222.55	26.93	10.16	26,181.82
Trimethoprim	55.72	10.23	792.27	499.98	4.09	1,216.35	0.21	0.08	70,880

* Critically important antimicrobials.

Table IV. *Farm prevalence (%) and farm intensity of use [DDDs(Defined daily doses)/farms] of veterinary antimicrobials in Umbria in 2014 in food-producing animals.*

	Cattle		Swine		Poultry		Small Ruminants		Fishes (trout)	
Class	Prevalence (%)	DDDs/ farms (x 10^3)	Prevalence (%)	DDDs/ farms (x 10^3)	Prevalence (%)	DDDs/ farms (x 10^3)	Prevalence (%)	DDDs/ farms (x 10^3)	Prevalence (%)	DDDs/ farms (x 10^3)
Aminoglycosides	11.89	8.37	4.91	136.48	8.43	727.80	1.94	4.35	0	0
Monensin	0.45	212.07	0	0	0	0	0	0	0	0
First generation cephalosporins*	2.95	0.03	0	0	0	0	0	0	0	0
Thrid generation cephalosporins*	2.40	56.27	0.51	89.17	0	0	0	0	0	0
Fourth generation cephalosporins*	1.81	5.83	0.71	15.36	0	0	0	0	0	0
Quinolones/ fluoroquinolones*	6.06	9.20	3.69	61.22	29.89	16,196.96	0.74	1.63	26.67	21.25
Amphenicols	1.17	8.57	2.56	503.45	0.38	111.11	0.03	0.01	6.67	1,301.45
Beta-lactamase inhibitors	1.85	1.08	0.66	159.50	0	0	0.03	0.01	0	0
Lincosamides	2.79	8.39	4.55	1,580.18	2.68	71.00	0.03	1	0	0
Nitrofurans	3.24	21.84	4.02	817.45	39.46	18,477.26	0	0	0	0
Macrolides*	0	0	0	0	0.38	8.70	0.26	5.50	0	0
Penicillin	21.76	8.86	11.01	824.48	30.27	109,248.92	2.76	4.29	0	0
Pleuromutilins	0	0	2.26	347.13	1.53	277.34	0	0	0	0
Polymixins*	1.65	17.21	3.12	2,363.17	22.61	93,589.77	0.48	9.12	0	0
Rifaximin	2.33	0.02	0	0	0	0	0.06	63.08	0	0
Sulfonamides	5.31	12.52	3.66	626.22	21.84	14,561.28	0.23	3.62	20	2,378.52
Tetraciclines	2.9	22.65	3.60	851.29	26.05	21,212.30	3.13	11.83	33.33	523.64
Trimethoprim	2.72	13.73	2.59	705.01	19.16	11,609.02	0.03	10	33.33	1,417.60

* CIAs

Table V. *Prescribed DDDs (Defined daily doses) in Umbria in 2014 in horses and rabbits.*

	Prescribed DDDs (x 10^3)	
	Horses (food producing)	Rabbits
Aminoglycosides	41.11	279.51
Thrid generation cephalosporins*	3.82	0
Quinolones/fluoroquinolones*	2.00	366.00
Macrolides*	0	1,437.50
Penicillin	54.09	0
Pleuromutilins	0	3,795.57
Polymixins*	0	3,375.55
Sulfonamides	23.06	2,996.16
Tetracyclines	3.94	3,995.94
Trimethoprim	19.82	2,643.80

* Critically important antimicrobials.

With regard to antibiotics used for cattle, beta-lactams, and particularly penicillin either alone or in combinations, were the most prescribed classes of drugs and showed a high prevalence. Aminoglycosides and quinolones/fluoroquinolones showed a higher prevalence than cephalosporines, despite its prevalence being generally lower when compared to penicillin. A different kind of behaviour was discovered by evaluating the intensity of use, in that the highest value was shown by monensin, followed by third generation cephalosporins, tetracyclines, and macrolides.

Penicillin, polymixins, lincosamides, and macrolides were the most prescribed classes of drugs for swine both at animal and farm level. Both prevalence and intensity of use were high in the same classes of drugs, particularly regarding the prevalence of penicillin, lincosamides, and macrolides. Aminoglycosides have shown a prevalence value higher than other classes of drugs despite a low consumption expressed for both DDDs/1,000 animals-*die* and DDDs/1,000 farms-*die*. Polymixins showed the highest value of DDDs/farms, followed by lincosamides and tetracyclines.

Antibiotic consumption was principally related to penicillin and polymixins, both for single animals and single farms in poultry. Other classes of antimicrobials showed values of DDDs/1,000 animals-*die* and DDDs/1,000 farms-*die* far lower than penicillin and polymixins. Macrolides, penicillin, and quinolones/fluoroquinolones showed the highest values of prevalence. Penicillin and polymixins showed the highest values of intensity of use.

The most prescribed classes of antibiotics in small ruminants were tetracyclines, penicillin, and aminoglycosides. Tetracyclines also showed the highest value of DDDs/farms as referred to antimicrobials. Tetracyclines and penicillin had the highest prevalence of use.

Sulfonamides, either alone or in combination with trimethoprim, were the most prescribed class of drugs in rainbow trout; however, tetracyclines also showed a high value of prevalence, together with trimethoprim. Intensity of use was higher in sulfonamides, trimethoprim, and amphenicols. The last class of antibiotic was prescribed 100% off-labels. Quinolones/fluoroquinolones were the only CIAs prescribed in fish and showed the lowest values of consumption and intensity of use together with a high prevalence.

Aminoglycosides, penicillin and potentiated sulphonamides were the most prescribed classes of antimicrobials in food-producing horses, while tetracyclines and pleuromutilins were mostly used in rabbits. Third-generation cephalosporines were prescribed only for food-producing horses and were mostly prescribed for rabbits (polymixins, quinolones/fluoroquinolones and macrolides), as were other classes of CIAs.

Discussion

The collection of veterinary drug use data and their descriptive analysis are important for public health (Collineau *et al.* 2016). Although the EMA have recently provided DDDvet values for antimicrobials for cattle, swine, and broiler, in this study we decided to use regional DDDvet_Umbria data for these species in order to facilitate a comparison between the animal species admitted in this study. Comparing the values for swine, cattle, and broilers assigned by us, to the values assigned by the EMA in 2016 (EMA/ESVAC 2016) demonstrates the strength of this study. The

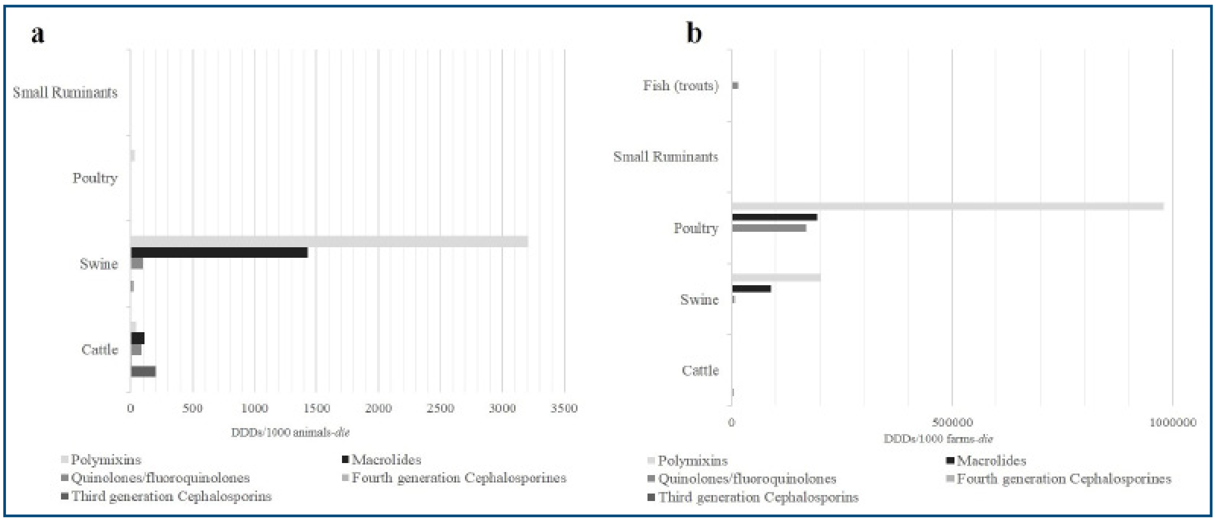

Figure 2. *Focus on Critically important antimicrobials.* **a.** DDDs (Defined daily doses)/1000 animals-*die*; **b.** DDDs/1000 farms-*die*.

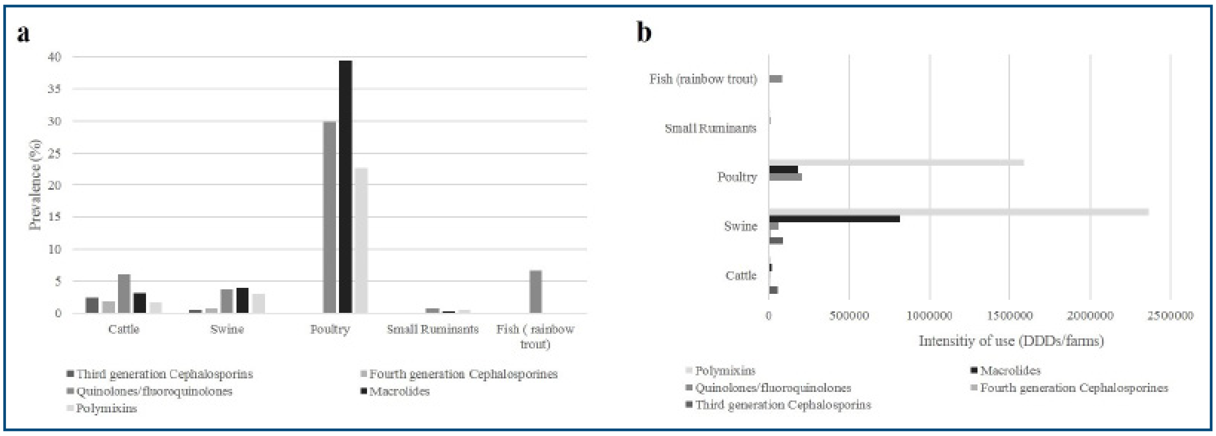

Figure 3. *Focus on Critically important antimicrobials.* **a.** Farm prevalence (%); **b.** Intensity of use [DDDs (Defined daily doses]/farms).

differences could be attributed to the high number of registered products used by the EMA for DDDvet determination, which are based on the veterinary drug handbooks of nine countries, compared to our values, which are based on the registered products prescribed in only 1 Italian region. It is well-known that there are differences in suggested doses provided by leaflets of commercial products which depend, for instance, on the severity and place of infection or age of the considered animals (Timmerman *et al.* 2006). The EMA's decision to evaluate DDDvet using nine veterinary drug handbooks is an attempt to minimise the above-mentioned differences. This consideration is particularly important for cattle and swine, which have the highest number of registered products – about 3,000 for both species (https://www.vetinfo.sanita.it/j6_prontuario/public/), compared with other food-producing animals. Furthermore, there are not many veterinarians working in Umbria and, those who do work in the region often prescribe the same commercial products for different farms breeding the same animal species. There were few evaluated differences for poulty, which could be due to the lower number of registered products available for these animals – about 900 (https://www.vetinfo.sanita.it/j6_prontuario/public/). Nevertheless, the DDDvet_Umbria/DDDvet average value, which is 1.05, confirms the integrity of our approach. A comparison of the swine values was performed not only with the EMA values but also with the DDD values assessed recently in four European countries (Postma *et al.* 2015) and in Denmark by the project DANMAP (DANMAP 2014). Values for the oral administration of colistin and for the parenteral administration of ampicillin were assessed by Postma and colleagues (Postma *et al.* 2015) and were found to differ by only a few decimals from the same active ingredients assigned in our study. Off-label prescriptions were mostly made for game, fish, and food-producing horses, and revealed a lack of registered veterinary products. The availability of veterinary drugs as 'registered products' should be increased in order to avoid problems such as mistakes in dosage and in withdrawal periods, as well as to gain a better understanding about the safety and efficacy of prescribed drugs for all bred animals.

The analysis of antibiotic consumption is often evaluated by considering animal body weight. However, in this study we chose to relate antibiotic consumption to the number of farms and bred animals in Umbria in 2014. This could facilitate an easier comparison with human medicine, where antibiotic consumption is expressed in DDDs/1,000 inhabitants-die, which is similar to our units of measurement (DDDs/1,000 animals-*die* and DDDs/1,000 farms-*die*) (Agenzia Italiana Farmaco 2016). Furthermore, Collineau and colleagues have recently indicated DDDs/1,000 animals-*die* as the most suitable unit of measurement to assess the relationship between antibiotic consumption and antibiotic resistance. This would be an appropriate follow-up study to the work presented here (Collineau *et al.* 2016).

Beta-lactams, especially penicillin, were the most prescribed class of antimicrobials of all animal species monitored in 2014. This could be due to the lower cost of these drugs, short withdrawal periods (EFSA 2016, EMA/ESVAC 2015, De Briyne *et al.* 2014), and broad spectrum of activity, which is sometimes obtained through the association with clavulanic acid. The use of broad-spectrum antibiotics is another critical area relating to the spread of antibiotic resistance, especially when these are prescribed without any laboratory indications about bacterium sensibility (European Commission 2015).

Swine and cattle were the animal species with the highest number of prescriptions in 2014. Together with small ruminants, these are the most bred species in Umbria; however, small ruminants are treated less than other livestock, probably for economic reasons and types of farming (Santman-Berends *et al.* 2014). The analysis of prescribed DDDs, DDDs/1,000 animals-*die* and DDDs/1,000 farms-*die* evaluated in 2014 in Umbria, confirmed the high use of veterinary drugs in swine but showed a lower drug use in cattle compared to poultry and fish, especially where drug consumption concerns farms. With cattle, the low antibiotic consumptions, expressed in prescribed DDDs, DDDs/1,000 animals-*die*, and DDDs/100 farms-*die*, could be explained by taking into account the fact that the units of measurement were influenced by the strength of each antimicrobial a.i. and in cattle, antibiotics with a high dosage were more often prescribed. Swine, poultry, and aquaculture represent 3 crucial livestock industries referred to drug consumption because of group treatments, high use of medicated feed (in swine and rainbow trout), and rapid growth of animals, especially for poultry and swine. These aspects could lead to an under- or over-estimation of live weight and consequently to mistakes in the drugs dosage calculation (Timmerman *et al.* 2006, González *et al.* 2010, Mancini *et al.* 2010, Persoons *et al.* 2012, Zonca and Cagnardi 2012, Di Cesare *et al.* 2013, Trauffler *et al.* 2014). This problem could also influence the occurrence of antimicrobial resistance (Catry *et al.* 2003) in antibiotics in a positive sense. Our results confirm the high use of antimicrobials in swine and poultry and the potential influence that these livestock species can have on the spread of antibiotic resistance. Furthermore, swine and poultry showed a high consumption of CIAs, especially polymixins (colistin). Other studies highlight the use of colistin in pigs and poultry as the main class of CIAs for curing diarrhea, especially in piglets (De Briyne *et al.* 2014, Callens *et al.* 2012). Colistin should be used responsibly, in accordance with EMA recommendations (EMA 2013) in veterinary medicine. Furthermore, the EMA has recently provided information on the impact of colistin use in veterinary medicine on human medicine and antimicrobial resistance (EMA 2016). Data from this study could be useful to identify farms, veterinaries, and/or areas with a high consumption of CIAs, which in turn would be useful in guiding intervention efforts to encourage a more rational use of CIAs based on antibiogramme.

Another important class of CIAs, mostly used in swine and poultry in other countries in 2014, was macrolides (Merle *et al.* 2014, Trauffler *et al.* 2014, van Rennings *et al.* 2015). This class of CIAs is usually used for the respiratory diseases and gastrointestinal diseases of swine (De Briyne *et al.* 2014), which represent the main pathologies for this species. Even if macrolides were included in the CIAs listed by the WHO, because of the possibility of selecting macrolides-resistant *Campylobacter* spp. (WHO 2011), their use could be preferable to colistin, which is now one of the last resources in human medicine for the treatment of different kinds of infections caused by multidrug-resistant bacteria (EMA 2016).

In the field of aquaculture in Italy, our results confirm the high use of antimicrobials. In farmed fish, antimicrobials were the only class of drug used in Umbria in 2014. This is in contrast with national and European policies, which tend to reduce antimicrobial use by increasing prevention practices such as vaccination (Ministero della Salute 2012, DANMAP 2014). One of the problems related to aquaculture is the small number of registered active ingredients; for example, neither anti-parasitic products nor florfenicol and erythromycin could be prescribed in Italy in 2014. Florfenicol and erythromycin can be prescribed only off-label, which is fundamental because they are elective drugs for some pathologies such as flavobacteriosis and lactococcosis (Zonca and Cagnardi 2012). However, it is necessary to consider that florfenicol was recently registered for farmed fish in order to guarantee animal health and production. In farmed fish, potentiated sulfonamides and tetracyclines were the most widely prescribed drugs in 2014 in Umbria. These were administered by medicated feed, with possible impacts on the spread of antibiotic resistance and environmental pollution (Zonca and Cagnardi 2012, Di Cesare *et al.* 2013, Lim *et al.* 2013). The same consideration could be made for quinolones/fluoroquinolones used in farmed fish in Umbria, since they are classified as CIAs.

Third- and fourth-generation cephalosporins were prescribed mostly for cattle and were probably principally related to the treatment of mastitis and/or dry-cow therapy, as has already been stated in other countries (Lanza *et al.* 2012, De Briyne *et al.* 2014, Merle *et al.* 2014). Cephalosporins are frequently used during dry periods to prevent mastitis and this practice continues to be considered important for reducing the spread of this invalidating pathology in dairy animals (Scoppetta *et al.* 2016). Dry-cow therapies could impact the spread of antibiotic resistance, although literature on this association is limited (Rajala-Schultz *et al.* 2009). This could represent a serious public health concern, considering that third and fourth generation cephalosporins are among the few available possible therapies for serious *Salmonella* and *E. coli* infections in humans, especially children (WHO 2011).

Lack of information concerning horses in BDN and problems related to non-computerisation of veterinary prescriptions limited our evaluation to prescribed DDDs only. Although prescribed DDDs in Umbria for 2014 for food-producing horses were lower with respect to other animal species, the lack of indicators for consumption in this area lead to a lack of available data for assessing horse treatment impact on the spread of antimicrobial resistance (Bowen and Clegg 2015, Weese 2015). The same considerations could be taken into account for rabbits, although, for this species, the most prescribed classes of antibiotics were tetracyclines and pleuromutilins, which are not considered CIAs.

One of the biggest problems related to the quantification of drug use is linked to the differences among each national database referring to any single species. This includes a lack of information about the number of rabbit farms and the number of farmed rabbits or the number of farmed fish in each single aquaculture farm. Moreover, different animal identification systems, which are more specific in cattle compared to other species – especially sheep or poultry, ensure a greater reliability of cattle BDN with respect to others. General descriptive studies regarding drug use are important as a reference point for planning further studies and strategies that address antibiotic resistance and improper drug usage.

In our consideration of drug prescriptions, no information about the diagnosis stating whether antimicrobial susceptibility tests were used to select the antimicrobial of choice were reported. This made it difficult to assess the appropriateness of the prescribed therapy and its compliance with prudent principle usage (European Commission 2015).

Conclusion

The description of veterinary drug usage through a DDDvet_Umbria approach, allowed us to overcome the limits of the report of national sales of veterinary antimicrobials produced annually by the EMA/

ESVAC. Moreover, it facilitated drug consumption comparisons between human and veterinary medicines, especially insomuch as they related to antibiotics and CIAs. It should be noted that the non-computerisation of veterinary prescriptions makes it more difficult to analyse antibiotic consumption in veterinary medicine; for example, some prescriptions could have been missed in the data transmission system. This underlines the necessity for the implementation of electronic prescriptions in veterinary medicine in order to obtain complete data more rapidly.

Making data available is useful for carrying out risk assessments based on drug consumption – especially antimicrobials – in food producing animals, and enables the identification of problem farms where controls could be carried out. Our results highlight this critical area of drug consumption. Moreover results of this study suggest that the spread of antibiotic resistance in veterinary medicine could include swine, poultry, and rainbow trout farms, where the highest use of antibiotics and, in particular, CIAs, was observed. This data could additionally be particularly useful in guiding the implementation of plans to reduce any irrational use of antibiotics and veterinary drugs, promoting prevention by using vaccines, and improving farm management by improving knowledge on antibiotic resistance and responsible use of antibiotic drugs in veterinary medicine.

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