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The use of the "Highest Priority Critically Important Antimicrobials" in 75 Austrian pig farms – Evaluation of on-farm drug application data

Der Einsatz von „Highest Priority Critically Important Antimicrobials" in 75 österreichischen Schweinebetrieben – Auswertung von betriebsbezogenen Arzneimitteldaten

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Summary

The World Health Organization lists antimicrobial substances which are essential for the treatment of specific infections in humans as "highest priority critically important antimicrobials" (HPCIAs): macrolides, fluoroquinolones, 3rd and 4th generation cephalosporins as well as glycopeptid antibacterials. The use of these substances in livestock husbandry should be restricted in order to minimise the risk of antimicrobial resistance. To date, there is little knowledge about the amounts of HPCIAs used in animal husbandry and the different animal species and diagnoses these antimicrobials are prescribed for.
In a retrospective study, drug application data recorded from 2008 until 2011 from 75 conventional pig farms were evaluated. Data were assessed directly by the farmer at farm-level. The annual antimicrobial consumption was expressed in "weight of active substance(s) in [mg]" and "number of Daily Doses". Results were referred to the animal biomass, evaluated per pig age class (piglets, weaners, fattening pigs < 60 kg biomass; fattening pigs > 60 kg biomass, sows, boars) and broken down to some variables such as the substance class and the therapy indication. The focus was especially laid on the HPCIAs.
The total usage of the HPCIAs in the study population was on average 3.0 mg/kg/year; 1.1 UDD_{kg}/kg/year; 0.2 ADD_{kg}/kg/year and 0.6 $PrDD_{kg}$/kg/year. This represents about 9%, 22%, 12% and 22% of total antimicrobial consumption, respectively, depending on the unit of measurement. Fattening farms showed the highest consumption of the named substances. The main part of the HPCIAs ($nADD_{kg}$/year) was applied to weaners, piglets and fattening pigs < 60 kg. They played an important role in the therapies of piglets (approximately 40% of the total antimicrobial consumption in piglets).
Macrolides played the major role within the HPCIAs and were mainly used for digestive tract diseases. A not negligible portion of macrolides was prescribed for metaphylactic and prophylactic measures.

Keywords: antimicrobial consumption, critically important antimicrobials, antimicrobial resistance, pig, Daily Dose

Zusammenfassung

Die Weltgesundheitsorganisation hat antimikrobielle Substanzen, die für die Behandlung spezifischer Infektionen beim Menschen gebraucht werden, als „Wirkstoffe mit höchster Priorität" („highest priority critically important antimicrobials" – HPCIAs) eingestuft: Makrolide, Fluorchinolone, Cephalosporine der 3. und 4. Generation sowie Glykopeptid-Antibiotika. Wegen der Gefahr der Resistenzentwicklung und der Resistenzübertragung von Tier auf Mensch sollte der Einsatz dieser Wirkstoffe in der Tierhaltung nur im Ausnahmefall stattfinden. Noch ist wenig darüber bekannt, in welchen Mengen, bei welchen Nutztierspezies und für welche Indikationen diese Wirkstoffe in der Veterinärmedizin eingesetzt werden.
Im Rahmen einer retrospektiven Studie wurden Daten zum Einsatz von Antibiotika aus dem Zeitraum 2008 bis 2011 von 75 konventionellen Schweinebetrieben

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ausgewertet. Die Datenerfassung erfolgte im Betrieb direkt durch den Landwirt. Der Antibiotikaeinsatz wurde in den Einheiten „Menge an Wirksubstanz in [mg]" und „Anzahl an Tagesdosen" gemessen, in Bezug zur Körpermasse gesetzt und je Alterskategorie (Saugferkel, Aufzuchtferkel, Mastschweine < 60 kg, Mastschweine > 60 kg, Sauen, Eber), Wirksubstanzklasse und Indikation dargestellt. Der Schwerpunkt wurde dabei speziell auf die HPCIAs gelegt.
Der Gesamt-Einsatz von HPCIAs in der Studienpopulation betrug 3,0 mg/kg/Jahr; 1,1 UDD_{kg}/kg/Jahr; 0,2 ADD_{kg}/kg/Jahr und 0,6 $PrDD_{kg}$/kg/Jahr. Dies entspricht – abhängig von den genannten Einheiten – Anteilen von 9 %, 22 %, 12 % und 22 % am Gesamt-Antibiotikaeinsatz. In Mastbetrieben wurde die höchste Menge an HPCIAs eingesetzt. Aufzuchtferkeln, Saugferkeln und Mastschweinen < 60 kg wurde der größte Anteil der HPCIAs ($nADD_{kg}$/Jahr) appliziert. Ihr Einsatz spielte auch bei Saugferkeln eine große Rolle (ungefähr 40 % des Gesamt-Antibiotikaeinsatzes bei Saugferkeln).
Von den HPCIAs kamen die Makrolide am häufigsten zum Einsatz. Sie wurden hauptsächlich bei Magen-/Darmerkrankungen verschrieben. Eine nicht unerhebliche Menge an Makroliden wurde für metaphylaktische und prophylaktische Maßnahmen eingesetzt.

Schlüsselwörter: Antibiotikaeinsatz, critically important antimicrobials, Antibiotikaresistenz, Schwein, Tagesdosis

Introduction

In Europe, around 25 000 cases of human death per year are due to infections with resistant or multi-resistant bacteria (ECDC/EMEA, 2009). Especially immunosuppressed, young and old people are particularly at risk to contract such severe bacterial infections. Trend analyses show that antimicrobial resistance increased in the last years (EFSA, 2009). These facts clearly underline that antimicrobial resistance is causing high healthcare costs and represents a serious threat to human and animal health.

The "One health" perspective indicates that animal health must be taken into account when interpreting human antimicrobial resistance data. An association between the prevalence of resistant bacteria in animals and their occurrence in humans was evaluated by several studies (Jensen, 1998; Leverstein-van Hall et al., 2011). The ways of transmission are manifold: Resistant bacteria were detected in meat (Kola et al., 2012; Egervärn et al., 2014) as well as in the air and the environment of pig farms (Friese et al., 2012). The distribution of antimicrobial substances from agriculture in the environment represents a risk factor for the development of antimicrobial resistance (Christian et al., 2003; Kümmerer, 2008).

Reasons for the development of resistant bacteria are thought to be manifold and complex. However, the use of antibacterial substances was identified as one main risk factor (van den Bogaard and Stobberingh, 2000; Goossens et al., 2005). Evidences for an association between the occurrence of resistant bacteria in humans and antimicrobial use in animal husbandry exist (Anderson et al., 2003; Angulo et al., 2004). As a consequence, the use of antibiotics in human as well as in veterinary medicine actually represents the focus of attention.

The broad emphasis of the problem with resistant bacteria stresses the need for antimicrobial resistance containment strategies. In autumn 2012, the European Commission published a containment action plan with twelve measures including recommendations about an appropriate antimicrobial use and the implementation of surveillance programs in human as well as in veterinary medicine (European Commission, 2011). The WHO list of the "Critically Important Antimicrobials for Human Medicine" specifies antimicrobial substances with high relevance for human disease treatments (Collignon et al., 2009; WHO, 2012).

Especially the knowledge about the consumption of the antimicrobial substances categorised as "highest priority critically important" (HPCIAs), including macrolides, fluoroquinolones, 3rd and 4th generation cephalosporins as well as glycopeptide antibacterials, is of particular importance. At present, there are only few therapeutic alternatives to these substances for the treatment of specific human diseases. Therefore, their use in veterinary medicine should be restricted to a minimum.

According to the WHO, macrolides select especially for macrolide-resistant *Campylobacter jejuni* in poultry, but also generally for *Campylobacter* spp. in animals. In addition, they are very important for the treatment of *Campylobacter* infections in children, because in these cases the quinolones are not advisable. The fluoroquinolones and the 3rd and 4th generation cephalosporins select for resistant *E. coli* and *Salmonella* spp. in animals and they represent almost the only available treatment possibility for severe *E. coli* and *Salmonella* spp. infections in humans. Glycopeptides play an essential role in the treatment of human enterococcal infections. They select for glycopeptide-resistant *Enterococcus* spp. in food producing animals (WHO, 2012).

In Austria all veterinary drugs are prescription-only medicines. The dispensary of drugs for topical and oral use by the farmer is generally allowed (Anonymous, 2010), whereas the application of drugs for systemic and intramammary use by the farmer is only allowed in the context of the Austrian Animal Health Service (Anonymous, 2009). The diagnosis as well as the name and quantity of drugs used have to be recorded according to official documentation rules (Anonymous, 2002, 2009) without specifying the documentation in electronic form. Within the frame of the Austrian Animal Health Service the dispensary of drugs containing substances belonging to the HPCIAs is only permitted in the case of a special medical requirement; the veterinarian has to justify their use by means of appropriate and objective diagnostic measures (Anonymous, 2010). On 15 April 2014, a new law obligating the electronic documentation of the distribution of antimicrobials in Austria for pharmaceutical companies, wholesalers, marketing-authorisation holders and veterinarians came into force (Anonymous, 2014).

The result is that till now, very little information about veterinary drug consumption in Austria exists. While in the poultry sector representative data about the dispensary of antimicrobials are collected in the context of the Austrian Poultry Health Service, similar systems are not implemented for pig and cattle production.

For the measurement of antimicrobial consumption in animal husbandry, several approaches for data recording are up to discussion. Analyses based on overall sales data allow a representation of antimicrobial consumption in weight of active substance, without giving information about the therapy indication and the animal species. For that reason, collecting information about drug consumption directly from the end-user is preferred.

In this study, on-farm drug application data were evaluated. The aims of the project were (1) to quantify the consumption of the HPCIAs in the study swine population using four different units of measurement; and (2) to determine the therapy indications and the swine age class for which the HPCIAs are prescribed.

Material and Methods

Data collection

This study was conducted in the context of an agriculturally oriented, public-private partnership project representing a cluster of two Austrian universities and nine industrial partners. One of the nine industrial partners was a Styrian meat production company contracting 76 conventional pig farms. The company has implemented a quality-assurance system with supervision along the food chain from the animal to the food product. In the context of this system, the farmers are obligated to electronically record their drug consumption. Information about the applied drug (name, drug authorisation number), the treatment duration, the pig age class (piglets, weaners, fattening pigs < 60 kg biomass; fattening pigs > 60 kg biomass, sows, boars), the therapy indication and the used drug quantity are entered into an online platform for each drug application. Automatic plausibility checks and drop-down lists facilitate data entry and help to reduce the occurrence of mistakes. For more details, please see Trauffler et al. (2014).

For this study, the named company officially released their data in the frame of a consortial agreement. Drug application records from January 2008 to December 2011 from 75 out of the 76 pig farms were analysed. The farms (49 farrow-to-finish (FtF), 21 fattening and five breeding farms) kept around 77 300 pigs, a number which represents about 3% of the Austrian swine population. The farms were supervised by 19 veterinarians. Mean herd size was 941 pigs (FtF farms), 747 pigs (fattening farms) and 3100 pigs (breeding farms), respectively. Because the data were placed at disposal in the context of this research project, no sample size estimation was performed. One farm was excluded because the records of drug consumption of this farm were incomplete. All data were anonymised before analysis.

Data were evaluated in Microsoft® Excel® (Version 14.4.2).

Data evaluation

Plausibility check of data

Before evaluations, data were checked in depth for nonsense data. Veterinarians´ drug dispensary records were additionally evaluated and served as plausibility control for the farmers´ recorded drug amounts. The methods for this plausibility proof have already been described by Trauffler et al. (2014).

TABLE 1: *Consumption of the "highest priority critically important antimicrobials" in 75 conventional pig farms from 2008 until 2011, per year, using four different units of measurement*

	"Highest Priority Critically Important Antimicrobials"					Other antimicrobial substances (n = 17 448 records)	Total (n = 31 684 records)
	Macrolides (n = 2724 records)	Fluoroquinolones (n = 4556 records)	3rd and 4th generation cephalosporins (n = 6956 records)	Glycopeptide antibacterials (n = 0 records)	Total		
mg/kg/year							
2008	4.57	0.09	0.09	0.00	4.75	32.62	37.37
2009	2.44	0.08	0.10	0.00	2.62	33.49	36.11
2010	2.35	0.08	0.12	0.00	2.54	23.59	26.13
2011	1.94	0.10	0.11	0.00	2.14	33.79	35.94
Average	2.83	0.08	0.10	0.00	3.01	30.87	33.89
%	8.34	0.25	0.30	0.00	8.89	91.11	100.00
$nUDD_{kg}$/kg/year[1]							
2008	1.51	0.04	0.05	0.00	1.60	3.21	4.81
2009	0.98	0.04	0.05	0.00	1.08	4.22	5.30
2010	0.79	0.04	0.07	0.00	0.89	3.74	4.63
2011	0.62	0.04	0.07	0.00	0.74	4.03	4.77
Average	0.98	0.04	0.06	0.00	1.08	3.80	4.88
%	20.02	0.84	1.22	0.00	22.08	77.92	100.00
$nADD_{kg}$/kg/year[1]							
2008	0.21	0.05	0.04	0.00	0.30	1.95	2.25
2009	0.13	0.04	0.04	0.00	0.21	1.77	1.98
2010	0.12	0.04	0.05	0.00	0.21	1.56	1.77
2011	0.11	0.05	0.04	0.00	0.20	1.58	1.79
Average	0.14	0.05	0.04	0.00	0.23	1.71	1.95
%	7.35	2.44	2.15	0.00	11.94	88.06	100.00
$nPrDD_{kg}$/kg/year[1]							
2008	0.59	0.06	0.04	0.00	0.70	2.18	2.88
2009	0.45	0.05	0.04	0.00	0.55	2.13	2.68
2010	0.42	0.05	0.05	0.00	0.52	1.64	2.16
2011	0.35	0.06	0.04	0.00	0.45	1.87	2.32
Average	0.45	0.06	0.04	0.00	0.55	1.96	2.51
%	18.03	2.29	1.77	0.00	22.10	77.90	100.00

[1] Treatment frequency: nUDD (number of Used Daily Doses); nADD (number of Animal Daily Doses) or nPrDD (number of Product-related Daily Doses)

Units of measurement

Antimicrobial consumption was quantified using four different units: weight of active substance (mg), number of Used Daily Doses (nUDD), number of Animal Daily Doses (nADD), and number of Product-related Daily Doses (nPrDD). The Daily Doses, which represent the basis for the latter three units, were determined as follows:

– The Used Daily Dose per kg biomass (UDD_{kg}) was introduced by Timmerman et al. (2006) and is defined as the administered dose per day per kg biomass of a substance. It is based on real consumption data and can therefore differ between and within herds. In contrast to the definition of Timmerman et al. (2006), where median values are calculated when different dosages for a drug are applied, the UDD_{kg} in this study was calculated separately for each data entry, according to the formula:

$$\underset{(\text{mg/kg/day})}{UDD_{kg}} = \frac{\text{weight of active substance (mg)}}{\text{number of treated animals x standard weight (kg) x treatment duration (days)}}$$

As standard weight for the given pig age classes the figures defined by the Agrarmarkt Austria Marketing (ÖPUL, 2007): 75 kg for fattening pigs (1 fattening pig = 0.15 "livestock units") and 150 kg for sows and boars (1 sow/boar = 0.3 "livestock units") were used. For piglets an average weight of 8 kg; for weaners an average weight of 25 kg was defined.

– The Animal Daily Dose per kg biomass (ADD_{kg}) is defined as the maintenance dosage per day and per kg biomass for a drug for its main indication in one species (Jensen et al., 2004). In this study, the mean dosage per day and per kg biomass for the active substance(s) of each antibiotic product was defined according to the SPC (Summary of Product Characteristics). Subsequently, the median of all mean dosages was calculated for each substance or substance combination and fixed as the ADD_{kg} (Fuchs and Obritzhauser, 2010).

– The Product-related Daily Dose for one kg biomass ($PrDD_{kg}$) was first described by Fuchs and Obritzhauser (2010) (then called "Prescribed Daily Dose"). It is defined as 80% of the maximal dosage per day and per kg biomass for the active substance(s) according to the SPC. This Daily Dose respects different dosage recommendations for each single product, even if the active substance is the same.

The treatment frequency was assessed by dividing the weight of active substance(s) by the UDD, the ADD or the PrDD, representing the "number of UDDs" (nUDD), the "number of ADDs" (nADD) or the "number of PrDDs" (nPrDD) respectively. Antimicrobial consumption was evaluated per year. Except the antimicrobial consumption per pig age class, results were referred to the animal bodyweight (kg biomass annually produced). The antimicrobial use was evaluated in total, per farm-type and per farm. For that purpose, the total amount of the consumed antimicrobials per year (in total, per farm-type or per farm) was divided by the total biomass produced in kg (in total, per farm-type or per farm, respectively).

The treatment frequency calculated in this study describes the mean number of treatment days per animal or per population in one year. It is approximately comparable with the Dutch unit DD/ay or ADDD/Y (number of daily dosages per animal year; animal defined daily dosages per year) (MARAN, 2009; Bos et al., 2013), the Danish ADD (Defined Animal Daily Dose) (DANMAP, 2011) and the German nDD_{ay} (number of daily doses per animal year) (Merle et al., 2012).

Use of the "Highest Priority Critically Important Antimicrobials"

For the evaluations, only antimicrobial treatments for oral and parenteral application including premixes for medicated feeding stuff were considered (36 757 records). The active substances were classified according to the ATCvet classification system (WHO Collaborating Centre for Drug Statistics Methodology, 2013). In conformity with the WHO list, which declares macrolides, fluoroquinolones, 3rd and 4th generation cephalosporins and glycopeptide antibacterials as HPCIAs, the active substances in this study were accordingly categorised: macrolides (QJ01FA), fluoroquinolones (QJ01MA), 3rd and 4th generation cephalosporins (QJ01DD and QJ01DE), glycopeptide antibacterials (QJ01XA) and "other antibacterials".

The total antimicrobial consumption was broken down to these five categories and their active substances, and evaluated per pig age class. For the macrolides, the consumption was further broken down to the therapy indications.

TABLE 2: *Consumption of the "highest priority critically important antimicrobials" in 75 conventional pig farms from 2008 until 2011, per year, at farm-type level ($nADD_{kg}$/kg/year[1])*

	$nADD_{kg}$/kg/year[1]					
	"Highest Priority Critically Important Antimicrobials"				Other antimicrobial substances (n = 17 448 records)	Total (n = 31 684 records)
	Macrolides (n = 2724 records)	Fluoroquinolones (n = 4556 records)	3rd and 4th generation cephalosporins (n = 6956 records)	Glycopeptide antibacterials (n = 0 records)		
FtF farms[2] (n = 49)						
2008	0.09	0.05	0.04	0.00	1.30	1.48
2009	0.09	0.05	0.04	0.00	1.31	1.48
2010	0.08	0.05	0.04	0.00	1.16	1.33
2011	0.09	0.05	0.03	0.00	1.05	1.22
Average	0.09	0.05	0.04	0.00	1.21	1.38
%	6.28	3.58	2.68	0.00	87.46	100.00
Fattening farms (n = 21)						
2008	0.51	0.04	0.02	0.00	3.18	3.75
2009	0.22	0.03	0.02	0.00	1.78	2.04
2010	0.19	0.02	0.03	0.00	1.24	1.49
2011	0.14	0.02	0.04	0.00	1.18	1.38
Average	0.27	0.03	0.03	0.00	1.84	2.17
%	12.25	1.33	1.33	0.00	85.09	100.00
Breeding farms (n = 5)						
2008	0.31	0.08	0.11	0.00	3.36	3.86
2009	0.19	0.07	0.08	0.00	4.96	5.30
2010	0.23	0.07	0.10	0.00	4.99	5.40
2011	0.18	0.10	0.15	0.00	6.42	6.84
Average	0.23	0.08	0.11	0.00	4.93	5.35
%	4.28	1.53	2.02	0.00	92.17	100.00

[1] Treatment frequency: number of Animal Daily Doses

[2] FtF farms: Farrow-to-finish farms

Results

Plausibility check of data

Plausibility proof of data revealed some inconsistencies and inaccurate information. Accordance between applied and dispensed drug amounts was shown in 57% of records (n = 20 926). In some cases, the farmers applied less (22% of records; n = 8074) or – unrealistically – more (10% of records; n = 3602) drugs than the veterinarian dispensed to them; 11% of data (n = 4232) could not be evaluated because of missing information. Some implausible records as well as all data with application amounts exceeding the dispensary amounts were eliminated; finally 86% of data (31 684 records) remained evaluable. For that reason, all results representing antimicrobial consumption were extrapolated to 100% in order to avoid an underestimation. For more details, please see Trauffler et al. (2014).

Use of the "Highest Priority Critically Important Antimicrobials"

The antimicrobial consumption in total and per farm-type has already been presented in a previous study (Trauffler et al., 2014). In total, 33.9 mg/kg/year; 4.9 UDD_{kg}/kg/year; 1.9 ADD_{kg}/kg/year; and 2.5 $PrDD_{kg}$/kg/year were used (average values). The main portion of number of doses was applied orally (86% of $nADD_{kg}$/kg/year) and in the context of group-treatments (Trauffler et al., 2014).

Table 1 illustrates the consumption of the HPCIAs proportional to the total antimicrobial consumption. They were used at proportions of 7.4% (macrolides), 2.4% (fluoroquinolones), 2.2% (3rd and 4th generation cephalosporins) and 0.0% (glycopeptid antibacterials) of total antimicrobial consumption (in $nADD_{kg}$/kg/year). The absolute values for macrolides, which made the largest contribution of all HPCIAs, were 2.8 mg/kg/year, 1.0 UDD_{kg}/kg/year, 0.1 ADD_{kg}/kg/year, 0.5 $PrDD_{kg}$/kg/year. In Table 2, the use of these substances per farm-type is shown. Fattening farms had the highest consumption of HPCIAs, whereof fluoroquinolones and 3rd and 4th generation cephalosporins were only used at very low proportions.

Table 3 provides an overview of the different active substances applied, represented as a percentage of the total antimicrobial consumption ($nADD_{kg}$/kg/year). In addition, the number of different drug preparations that were used, is stated. The main part of the HPCIAs used was due to treatments with tylosin (6.4% of total consumption).

The consumption of the HPCIAs per pig age class is illustrated in Figure 1, represented as absolute values (top of the figure) and as a relative proportion to the total antimicrobial consumption per age class (bottom of the figure) (unit $nADD_{kg}$/year). As can be seen from the figure, 11 877 640 ADD_{kg}/year were applied to weaners, which represents 51% of the total annually administered ADD_{kg}. The absolute consumption of the HPCIAs was the highest in weaners, piglets and fattening pigs <60 kg. When illustrated as relative proportions,

TABLE 3: *Antimicrobial consumption in 75 conventional pig farms ($nADD_{kg}$/kg/year[1]), substances classified according to their ATCvet Code and the WHO´s list of the "highest priority critically important antimicrobials"*

ATCvet Code	Active substance	Number of drug preparations used in this study	$nADD_{kg}$/kg/year[1]	
			Average	%
Macrolides				
QJ01FA90	Tylosin	8	0.12	6.40
QJ01FA91	Tilmicosin	1	0.00	0.15
QJ01FA94	Tulathromycin	1	0.02	0.85
Fluoroquinolones				
QJ01MA90	Enrofloxacin	8	0.01	0.31
QJ01MA92	Danofloxacin	1	0.03	1.42
QJ01MA93	Marbofloxacin	3	0.01	0.70
3rd and 4th generation cephalosporins				
QJ01DD90	Ceftiofur	4	0.02	0.99
QJ01DE90	Cefquinome	1	0.02	1.15
Glycopeptide antibacterials				
/		0	0.00	0.00
Other antimicrobial substances				
QA07AA01	Neomycin	1	0.00	0.00
QA07AA10	Colistin	7	0.32	16.24
QA07AA91	Gentamicin	3	0.00	0.02
QJ01AA02	Doxycycline	4	0.11	5.63
QJ01AA03	Chlortetracycline	2	0.02	0.78
QJ01AA06	Oxytetracycline	18	0.32	16.53
QJ01AA56	Oxytetracycline, combinations	1	0.03	1.72
QJ01BA90	Florfenicol	3	0.01	0.37
QJ01CA01	Ampicillin	3	0.00	0.09
QJ01CA04	Amoxicillin	12	0.37	19.08
QJ01CE09	Procaine Benzylpenicillin	3	0.01	0.34
QJ01EW03	Sulfadimidine and Trimethoprim	1	0.00	0.10
QJ01EW10	Sulfadiazine and Trimethoprim	5	0.04	2.18
QJ01EW11	Sulfamethoxazole and Trimethoprim	3	0.02	0.80
QJ01EW13	Sulfadoxine and Trimethoprim	1	0.00	0.08
QJ01GA90	Dihydrostreptomycin	1	0.00	0.03
QJ01GB03	Gentamicin	1	0.00	0.01
QJ01GB05	Neomycin	2	0.02	0.94
QJ01RA01	Penicillins, combinations with other antibacterials	5	0.03	1.63
QJ01RA94	Lincosamides, combinations with other antibacterials	5	0.40	20.42
QJ01XQ01	Tiamulin	7	0.02	0.98
QJ01XQ02	Valnemulin	1	0.00	0.08
Total			1.95	100.00

[1] Treatment frequency: number of Animal Daily Doses

it appears that HPCIAs played an important role in the therapies of piglets (approximately 40% of the total antimicrobial consumption in piglets).

Therapy indications for the use of macrolides are presented in Table 4 ($nADD_{kg}$/kg/year). Diseases of the digestive tract were the most frequently indicated for the use of macrolides in all the three farm-types (48% FtF farms, 71% fattening farms, 87% breeding farms). In FtF farms, respiratory tract diseases and metaphylactic/prophylactic measures came in second and third position (22% and 12%, respectively). In fattening farms, metaphylactic/prophylactic measures followed the digestive tract diseases with 22% of $nADD_{kg}$/kg/year. Focusing on the digestive tract diseases, it appears that in 63% of $nADD_{kg}$/kg/year only "diarrhoea" has been indicated by the farmer, followed by the "porcine proliferative enteropathy" (37%), whereof the porcine intestinal adenomatosis played the major role.

Discussion

Till now, little knowledge exists about the veterinary use of these as "critically important with highest priority" declared substances. In the European report "European Surveillance of Veterinary Antimicrobial Consumption" (ESVAC), sales figures of HPCIAs in 25 member states are well presented (EMA, 2013a). However, there are only few studies measuring their consumption per animal species (Menéndez González et al., 2010; Callens et al., 2012; DANMAP, 2012; Moreno, 2012; Persoons et al., 2012) and at diagnosis-level (Jensen et al., 2011; Obritzhauser et al., 2013).

The information about the species in which HPCIAs are used and the underlying therapy indication is of particular importance when implementing effective containment strategies and can only be obtained when data are collected at farm-level. Therefore, the involvement of the end-user (farmer) in the collection of drug application data, which was achieved in this study, is internationally targeted. The results of the plausibility check of these data – published in a previous work (Trauffler et al., 2014) – showed that further improvements are necessary in order to guarantee the reliability of the data. This conclusion is in accordance with the study of Menéndez González et al. (2010).

Measuring and interpreting drug consumption data on an international level postulates the adoption of standardised units of measurement. One of the four units of measurement used in this study is based on the indicator "Animal Daily Dose", which was introduced by Jensen et al. (2004). A more current denotation for this indicator is DDDA (Defined Daily Dose Animal) and represents the unit in which dose data for ESVAC should be reported in the future (EMA, 2013b). Dosage recommendations between countries or regions can widely diverge, because of differences in national resistance situation (ECDC, 2013). Though, to date, ADDs are determined at national level, which complicates a comparison of antimicrobial consumption analyses between different countries.

The total usage of macrolides, fluoroquinolones, 3rd and 4th generation cephalosporins and glycopeptide antibacterials in the study population was 3.0 mg/kg/year; 1.1 UDD_{kg}/kg/year; 0.2 ADD_{kg}/kg/year and 0.6 $PrDD_{kg}$/kg/year. This represents about 9%, 22%, 12% and 22% of the total antimicrobial consumption, respectively. In the ESVAC report (EMA, 2013a) a use of HPCIAs in Austria of about 11% of the total antibiotic sales is noticed, which depicts a moderate consumption compared to the other countries. However, as demonstrated in this study, the proportion is higher when expressed in nUDD and nPrDD, which underlines the need for the expression of antimicrobial consumption in treatment frequency. Especially when measuring the consumption of antimicrobial substances with high therapeutic potency such as the HPCIAs, the amount of active substance is not an adequate unit for relating the consumption data to resistance data.

The consumption of the named antimicrobial substances varies significantly depending on the unit of measurement. The results range from 9% to 22% of total consumption, which is a wide range when considering the importance of the topic. This fact indicates that the choice for a specific unit of measurement may influence the outcomes and has also been described by Chauvin et al. (2008). Other studies also demonstrated that the consumption of the HPCIAs might change with the unit (Regula et al., 2009; Menéndez González et al., 2010). Reasons for the high discrepancy between the different units of measurement in this study are high divergences in the dosage recommendations according to the SPC in Austria (explaining the discrepancy between ADD and PrDD) as well as a high number of underdosages (explaining the discrepancy between UDD and the other measure units), which was broadly evaluated separately per active substance in our previous work (Trauffler et al., 2014).

A reduction in the use of HPCIAs from 2008 to 2009 can be determined in this data. This is associated

TABLE 4: *Therapy indications for macrolide treatments in 75 conventional pig farms ($nADD_{kg}$/kg/year[1])*

Therapy indication	$nADD_{kg}$/kg/year[1]					
	FtF farms[2] (n = 49)		Fattening farms (n = 21)		Breeding farms (n = 5)	
	Average	%	Average	%	Average	%
Cannibalism	0.00	0.50	0.00	0.07	0.00	0.00
Chirurgical intervention	0.00	0.04	0.00	0.00	0.00	0.00
Digestive tract diseases	0.04	47.94	0.19	71.39	0.20	87.04
General infection	0.00	2.25	0.00	0.03	0.00	0.00
Gynaecological diseases	0.00	0.04	0.00	0.00	0.00	0.00
Infection/Inflammation	0.00	0.06	0.00	0.00	0.00	0.14
Infections with involvement of several organ systems	0.00	2.56	0.00	0.33	0.00	0.00
Injuries	0.00	0.45	0.00	0.20	0.00	0.00
Implausible indications	0.01	7.25	0.00	0.00	0.01	4.06
Mastitis, Metritis, Agalactia	0.00	0.02	0.00	0.00	0.00	0.07
Metaphylactic/Prophylactic measures	0.01	11.61	0.06	22.12	0.01	5.79
Orthopaedic diseases	0.00	2.35	0.00	0.48	0.00	0.10
Other diseases	0.00	2.73	0.00	0.00	0.00	0.00
Respiratory tract diseases	0.02	22.20	0.01	5.38	0.01	2.80
Total	0.09	100.00	0.27	100.00	0.23	100.00

[1] Treatment frequency: number of Animal Daily Doses
[2] FtF farms: Farrow-to-finish farms

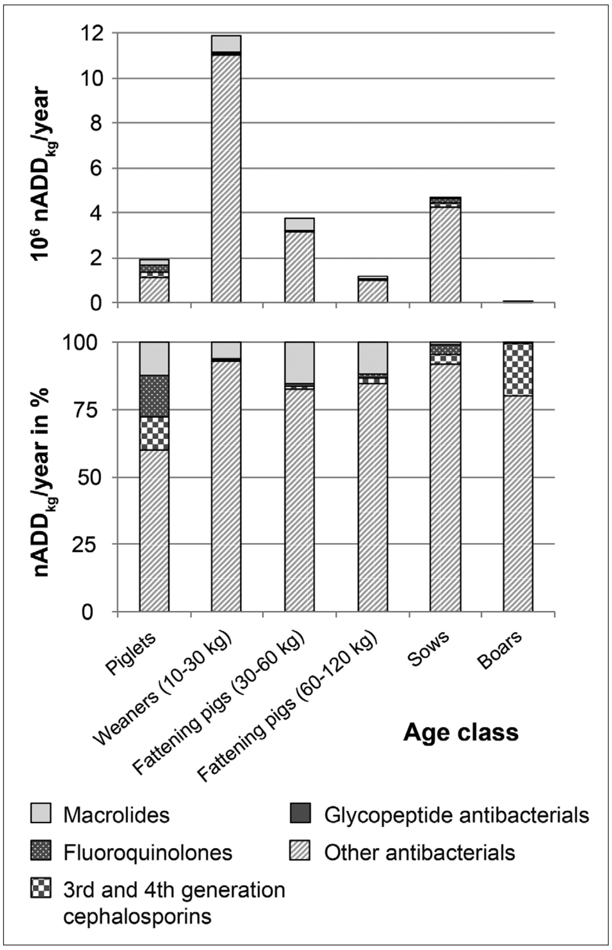

FIGURE 1: *Absolute and relative antimicrobial consumption in 75 conventional pig farms ($nADD_{kg}$/year[1]), by pig age class and categorised according to the WHO´s list of the "highest priority critically important antimicrobials".*

[1] Treatment frequency: number of Animal Daily Doses.

with an absolute reduction of the total antimicrobial consumption and might be the result of management measures taken at farm-level. For instance, the vaccination rate against the porcine circovirus type 2 in the 75 pig farms rose up from 2008 until 2011 and might have influenced the antimicrobial consumption (Raith et al., 2014, unpublished data). Alban et al. (2013) also found a decrease in antimicrobial consumption simultaneously to an increase in the general vaccination rate in Denmark after the introduction of the yellow card scheme. In addition, public pressure may have motivated the veterinarians to use less antibiotics.

Out of the HPCIAs, macrolides were most often used, whereas fluoroquinolones and 3rd and 4th generation cephalosporins were used at lower proportions. Similar outcomes were found in other studies (Jensen et al., 2011; DANMAP, 2012; van Rennings et al., 2013 [VetCAb]). In the ESVAC report, analogous distributions are indicated for 2011 for most countries (generally 8% macrolides, 1.6% fluoroquinolones and 0.2% 3rd and 4th generation cephalosporins), though the proportion of the usage of fluoroquinolones was higher in some member states (EMA, 2013a).

The consumption of the HPCIAs ($nADD_{kg}$/year) was the highest in weaners, in piglets and in young fattening pigs, as shown in figure 1. For the implementation of strategies for reducing the use of these substances, focusing on these two age classes may therefore be most effective. Represented as a relative proportion to the antimicrobial consumption per age class, it is striking that about 40% of the antibacterial treatments in piglets are related to the HPCIAs, whereof macrolides, fluoroquinolones and 3rd and 4th generation cephalosporins are almost equally distributed. Jensen et al. (2011) also estimated that in Denmark about one third of the piglets were treated with cephalosporins in 2007. In contrast to these outcomes, Merle et al. (2014) stated that fluoroquinolones and cephalosporins were used in only negligible portions in piglets (both 1.1% of total consumption in nUDD) in 47 farms from Lower Saxony (Germany).

Macrolides were mainly used for the therapy of digestive tract diseases (all farm-types), for respiratory tract diseases and for metaphylactic/prophylactic measures (FtF and fattening pig farms). Callens et al. (2012) also reported that for metaphylactic and prophylactic treatments Belgian pigs were often treated with antimicrobials belonging to the WHO list. When focusing on the digestive tract diseases, "diarrhoea" and "porcine proliferative enteropathy" were most often diagnosed. This detailed information concerning the use of macrolides may give a helpful advice when planning effective reduction strategies. It must be emphasised that information about the therapy indication could be entered freely into a text field by the farmer, so that these categories can overlap among themselves (Trauffler et al., 2014). Future updates of the data recording software will include automatic alignment between the entered indication and the indication specified in the SPC (Trauffler et al., 2014).

The WHO lists the macrolides as HPCIAs because they select for *Campylobacter* spp. in animals and are considered to be important for the treatment of *Campylobacter* infections in children. However, risk assessments investigating the consequences of the use of macrolides in veterinary medicine showed a very low risk for public health (Hurd et al., 2004; Alban et al., 2008; Hurd and Malladi, 2008). Alban et al. (2008) indicate that out of 186 human cases of campylobacteriosis caused by macrolide-resistant strains only seven cases could be explained by veterinary use of macrolides in Danish pigs. In addition, they mention that diseases due to *Campylobacter* are self-limiting and an increased risk of invasiveness or death in macrolide-resistant *Campylobacter* is mostly associated to the age of the patients (older people) and to severe coexistent diseases (Helms et al., 2005). Thus, it is questionable whether the macrolides really should be listed as "highest priority critically important".

Attention must be drawn to the fact that the results of this work are not representative for Austria. First, the sampling frame of 75 pig farms, representing about 3% of the Austrian pig production, is too small. Second, the evaluation of data from one meat production company might bias the results, because of internal vaccination regimes, farm-specific measures or other reasons.

Conclusion

The consumption of HPCIAs in the 75 Austrian pig farms was moderate. Out of these substances macrolides were most often used and the main reason for their prescription were digestive tract diseases. The use of HPCIAs varies significantly depending on the unit of measurement. This fact underlines that the choice for a specific unit of measurement is crucial.

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References

Alban L, Nielsen EO, Dahl J (2008): A human health risk assessment for macrolide-resistant *Campylobacter* associated with the use of macrolides in Danish pig production. Prev Vet Med 83: 115–129.

Alban L, Dahl J, Andreasen M, Petersen JV, Sandberg M (2013): Possible impact of the "yellow card" antimicrobial scheme on meat inspection lesions in Danish finisher pigs. Prev Vet Med 108: 334–341.

Anderson AD, Nelson JM, Rossiter S, Angulo FJ (2003): public health consequences of use of antimicrobial agents in food animals in the United States. Microb Drug Resist 9: 373–379.

Angulo FJ, Nargund VN, Chiller TC (2004): Evidence of an association between use of anti-microbial agents in food animals and anti-microbial resistance among bacteria isolated from humans and the human health consequences of such resistance. J Vet Med B Infect Dis Vet Public Health 51: 374–379.

Anonymous (2002): Tierarzneimittelkontrollgesetz – TAKG, Bundesgesetzblatt I Nr. 28/2002, Austria. www.ris.bka.gv.at.

Anonymous (2009): Verordnung des Bundesministers für Gesundheit über die Anerkennung und den Betrieb von Tiergesundheitsdiensten (Tiergesundheitsdienst-Verordnung 2009 – TGD-VO 2009), Bundesgesetzblatt II Nr. 434/2009, Austria. www.ris.bka.gv.at.

Anonymous (2010): Verordnung des Bundesministers für Gesundheit über die Anwendung von Veterinär-Arzneispezialitäten unter Einbindung des Tierhalters (Veterinär-Arzneispezialitäten-Anwendungsverordnung 2010), Bundesgesetzblatt II Nr. 259/2010, Austria. www.ris.bka.gv.at.

Anonymous (2014): Verordnung des Bundesministers für Gesundheit, mit der ein System zur Überwachung des Vertriebs und Verbrauchs von Antibiotika im Veterinärbereich eingerichtet wird (Veterinär-Antibiotika-MengenströmeVO), Bundesgesetzblatt II Nr. 83/2014, Austria. www.ris.bka.gv.at.

Bos ME, Taverne FJ, van Geijlswijk IM, Mouton JW, Mevius DJ, Heederik DJ; Netherlands Veterinary Medicines Authority SDa (2013): Consumption of antimicrobials in pigs, veal calves, and broilers in the Netherlands: quantitative results of nationwide collection of data in 2011. PLoS One 8(10): e77525.

Callens B, Persoons D, Maes D, Laanen M, Postma M, Boyen F, Haesebrouck F, Butaye P, Catry B, Dewulf J (2012): Prophylactic and metaphylactic antimicrobial use in Belgian fattening pig herds. Prev Vet Med 106: 53–62.

Chauvin C, Querrec M, Perot A, Guillemot D, Sanders P (2008): Impact of antimicrobial drug usage measures on the identification of heavy users, patterns of usage of the different antimicrobial classes and time-trends evolution. J Vet Pharmacol Ther 31: 301–311.

Christian T, Schneider RJ, Färber HA, Skutlarek D, Meyer MT, Goldbach HE (2003): Determination of Antibiotic Residues in Manure, Soil, and Surface Waters. Acta Hydrochim Hydrobiol 31: 36–44.

Collignon P, Powers JH, Chiller TM, Aidara-Kane A, Aarestrup FM (2009): World Health Organization ranking of antimicrobials according to their importance in human medicine: a critical step for developing risk management strategies for the use of antimicrobials in food production animals. Clin Infect Dis 49: 132–141.

DANMAP (2011): Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. ISSN 1600-2032.

DANMAP (2012): Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. ISSN 1600-2032.

ECDC (2013): Antimicrobial resistance surveillance in Europe 2012. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm, Sweden. ISBN 978-92-9193-511-6.

ECDC/EMEA (2009): The bacterial challenge: time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents. EMEA/576176/2009. ISBN 978-92-9193-193-4. Stockholm, Sweden.

EFSA (2009): Joint Opinion on antimicrobial resistance (AMR) focused on zoonotic infections. EFSA J 7: 1372. Question No. EFSA-Q-2008-781. EMEA/CVMP/447259/2009.

Egervärn M, Börjesson S, Byfors S, Finn M, Kaipe C, Englund S, Lindblad M (2014): *Escherichia coli* with extended-spectrum beta-lactamases or transferable AmpC beta-lactamases and *Salmonella* on meat imported into Sweden. Int J Food Microbiol 171: 8–14.

EMA (2013a): European Surveillance of Veterinary Antimicrobial Consumption. "Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011". EMA/236501/2013.

EMA (2013b): Revised ESVAC reflection paper on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals. London, United Kingdom. EMA/286416/2012-Rev.

European Commission (2011): Communication from the Commission to the European Parliament and the Council: Action plan against the rising threats from Antimicrobial Resistance. COM, 748.

Friese A, Schulz J, Hoehle L, Fetsch A, Tenhagen BA, Hartung J, Roesler U (2012): Occurrence of MRSA in air and housing environment of pig barns. Vet Microbiol 158: 129–135.

Fuchs K, Obritzhauser W (2010): Modelling the consumption of antimicrobials in Austrian cattle, pigs and poultry production. AGES, Final report. (Methodenvergleich zur Erfassung von Antibiotikamengenströmen im Veterinärbereich in Österreich. Forschungsendbericht der AGES), in German.

Goossens H, Ferech M, Vander Stichele R, Elseviers M (2005): Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 365: 579–587.

Helms M, Simonsen J, Olsen KEP, Mølbak K (2005): Adverse health events associated with antimicrobial drug resistance in *Campylobacter* species: a registry-based cohort study. J Infect Dis 191: 1050–1055.

Hurd HS, Malladi S (2008): A stochastic assessment of the public health risks of the use of macrolide antibiotics in food animals. Risk Anal 28: 695–710.

Hurd HS, Doores S, Hayes D, Mathew A, Maurer J, Silley P, Singer RS, Jones RN (2004): Public health consequences of macrolide use in food animals: a deterministic risk assessment. J Food Prot 67: 980–992.

Jensen LB (1998): differences in the occurrence of two base pair variants of Tn1546 from vancomycin-resistant enterococci from humans, pigs, and poultry. Antimicrob Agents Chemother 42: 2463–2464.

Jensen VF, Jacobsen E, Bager F (2004): Veterinary antimicrobial-usage statistics based on standardized measures of dosage. Prev Vet Med 64: 201–215.

Jensen VF, Emborg HD, Aarestrup FM (2011): Indications and patterns of therapeutic use of antimicrobial agents in the Danish pig production from 2002 to 2008. J Vet Pharmacol Ther 35: 33–46.

Kola A, Kohler C, Pfeifer Y, Schwab F, Kühn K, Schulz K, Balau V, Breitbach K, Bast A, Witte W, Gastmeier P, Steinmetz I (2012): High prevalence of extended-spectrum-β-lactamase-producing Enterobacteriaceae in organic and conventional retail chicken meat, Germany. J Antimicrob Chemother 67: 2631–2634.

Kümmerer K (2008): Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks. 3rd ed. Springer, Heidelberg, Germany. ISBN 978-3-540-74664-5.

Leverstein-van Hall MA, Dierikx CM, Cohen Stuart J, Voets GM, van den Munckhof MP, van Essen-Zandbergen A, Platteel T, Fluit AC, van de Sande-Bruinsma N, Scharinga J, Bonten MJM, Mevius DJ (2011): Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. Clin Microbiol Infect 17: 873–880.

MARAN (2009): Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2009. http://www.wageningenur.nl/nl/Expertises-Dienstverlening/Onderzoeksinstituten/Central-Veterinary-Institute/Publicaties-CVI/MARAN-Rapporten.htm.

Menéndez González S, Steiner A, Gassner B, Regula G (2010): Antimicrobial use in Swiss dairy farms: Quantification and evaluation of data quality. Prev Vet Med 95: 50–63.

Merle R, Hajek P, Käsbohrer A, Hegger-Gravenhorst C, Mollenhauer Y, Robanus M, Ungemach FR, Kreienbrock L (2012): Monitoring of antibiotic consumption in livestock: A German feasibility study. Prev Vet Med 104: 34–43.

Merle R, Robanus M, Hegger-Gravenhorst C, Mollenhauer Y, Hajek P, Käsbohrer A, Honscha W, Kreienbrock L (2014): Feasibility study of veterinary antibiotic consumption in Germany – comparison of ADDs and UDDs by animal production type, antimicrobial class and indication. BMC Vet Res 10: 7.

Moreno MA (2012): Survey of quantitative antimicrobial consumption in two different pig finishing systems. Vet Rec 171: 325.

Obritzhauser W, Kopacka I, Fuchs K (2013): Monitoring the use of antibiotics in dairy cattle in Austria. Proceedings of the European Buiatrics Forum 2013. Marseille, 27–29 November 2013, 89.

ÖPUL (2007): Anhänge zur Sonderrichtlinie des BMLFUW für das Österreichische Programm zur Förderung einer umweltgerechten, extensiven und den natürlichen Lebensraum schützenden Landwirtschaft. GZ BMLFUW-LE.1.1.8/0014-II/8/2010.

Persoons D, Dewulf J, Smet A, Herman L, Heyndrickx M, Martel A, Catry B, Butaye P, Haesebrouck F (2012): Antimicrobial use in Belgian broiler production. Prev Vet Med 105: 320–325.

Regula G, Torriani K, Gassner B, Stucki F, Müntener CR (2009): Prescription patterns of antimicrobials in veterinary practices in Switzerland. J Antimicrob Chemother 63: 805–811.

Timmerman T, Dewulf J, Catry B, Feyen B, Opsomer G, de Kruif A, Maes D (2006): Quantification and evaluation of antimicrobial drug use in group treatments for fattening pigs in Belgium. Prev Vet Med 74: 251–263.

Helms M, Simonsen J, Olsen K, Köfer J (2014): Antimicrobial drug use in Austrian pig farms: Plausibility check of electronic on-farm records and estimation of consumption. Vet Rec, accepted, in press. doi: 10.1136/vr.102520.

Van den Bogaard AE, Stobberingh EE (2000): Epidemiology of resistance to antibiotics. Links between animals and humans. Int J Antimicrob Agents 14: 327–335.

Van Rennings L, Von Münchhausen C, Honscha W, Ottilie H, Käsbohrer A, Kreienbrock L (2013): Repräsentative Verbrauchsmengenerfassung von Antibiotika in der Nutztierhaltung – Kurzbericht über die Ergebnisse der Studie „VetCAb-Pilot“. Fachinformation (Stand: 9. Juli 2013). Tierärztliche Hochschule Hannover/Universität Leipzig/Bundesinstitut für Risikobewertung. http://www.vetcab.de/.

WHO (2012): Critically Important Antimicrobials for Human Medicine – 3rd revision 2011. ISBN 978-92-4-150448-5.

WHO Collaborating Centre for Drug Statistics Methodology (2013): Guidelines for ATCvet classification 2013. Oslo, Norway. ISBN 978-82-8082-527-8.

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