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Antimicrobial drug use on Austrian dairy farms with special consideration of the use of "highest priority critically important antimicrobials"

Antibiotikaeinsatz in österreichischen Milchrinderbetrieben mit Schwerpunkt auf den Einsatz von „highest priority critically important antimicrobials"

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Summary

The use of antibiotics in livestock production is coming under growing criticism. Beside overall antimicrobial use, specific substances listed by the WHO as "highest priority critically important antimicrobials" (HPCIAs) – these include fluoroquinolones, macrolides, 3rd and 4th generation cephalosporins, as well as glycopeptides – have been placed under specific restrictions and should only be applied in particular cases according to strict indication criteria.
In this study, the consumption of antimicrobial substances on Austrian dairy farms was evaluated quantitatively. The data covered 8027 prescription records on the use of antibiotics on 465 dairy farms. Eleven veterinary practices provided data from between four to 27 months during the period from 2008 to 2010 and the total consumption of antimicrobials was estimated. The amount of active substance(s) in grams used per livestock unit (g/LU) per year and the number of product-related daily doses used per livestock unit (n $PrDD_{LU}$/LU) per year were determined as units of measurement. These parameters were estimated by applying Monte Carlo simulation techniques, respecting variances in annual working days of the veterinary practices as well as variances in the proportion of non-treated populations.
Total antimicrobial consumption in the population-at-risk was determined to be 2.59 g/LU and 1.30 $PrDD_{LU}$/LU per year. HPCIAs were used at a proportion of 24.6% (0.31 $PrDD_{LU}$/LU) of the total consumption of antimicrobials for systemic and intramammary use. Of these, 3rd and 4th generation cephalosporins were most frequently administered, particularly for the treatment of mastitis and foot diseases. The total consumption of antimicrobials in Austrian dairy cattle production is negligible compared to their use in pig and poultry production systems. However, the use of HPCIAs, especially 3rd and 4th generation cephalosporins, should be minimised further.

Keywords: antimicrobial consumption, critically important antimicrobials, antimicrobial resistance, dairy cattle, daily dose

Zusammenfassung

Der Einsatz von Antibiotika bei lebensmittelliefernden Tieren ist in den letzten Jahren in zunehmendem Maße Gegenstand öffentlicher, politischer und auch wissenschaftlicher Diskussionen. Besonders die von der WHO als „highest priority critically important antimicrobials" (HPCIAs) eingestuften Makrolide, Fluorchinolone, Cephalosporine der 3. und 4. Generation und Glykopeptide sollten nur im Einzelfall und unter strenger Indikationsstellung eingesetzt werden.
Von 2008 bis 2010 wurde in elf Tierarztpraxen während eines Zeitraums von vier bis 27 Monaten eine Erhebung des Antibiotikaeinsatzes in 465 österreichischen Milchrinderbetrieben durchgeführt. Dabei wurden 8027 Datensätze über den Einsatz von Antibiotika erfasst. Als Maßzahlen für den Antibiotikaeinsatz wurden die Wirkstoffmenge in Gramm (g) und die Anzahl produktbezogener Tagesdosen (PrDD) berechnet und in Bezug zur gehaltenen Tiermenge (Großvieheinheit, GVE)

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gesetzt. Mithilfe einer Monte-Carlo-Simulation erfolgte die Schätzung der Zielparameter g/GVE pro Jahr und n $PrDD_{GVE}$/GVE und Jahr unter Berücksichtigung der unterschiedlichen Datenerfassungszeiträume und der nicht behandelten Population.
Demnach wurden bei Milchrindern in der untersuchten Population (population-at-risk) je Großvieheinheit und Jahr antimikrobielle Wirkstoffe in einer Menge von 2,59 g eingesetzt. Umgelegt auf die Anzahl produktbezogener Tagesdosen entsprach dies 1,30 $PrDD_{GVE}$/GVE und Jahr. Von den systemisch und intramammär eingesetzten Antibiotika entfielen 0,31 $PrDD_{GVE}$/GVE (24,6 %) auf HPCIAs, vor allem auf bei Eutererkrankungen und Klauenerkrankungen angewendete Cephalosporine der 3. und 4. Generation.
Die Antibiotikamenge, die beim Milchrind eingesetzt wird, ist im Vergleich zur Schweine- und Geflügelproduktion gering. Der Einsatz von HPCIAs, speziell von Cephalosporinen der 3. und 4. Generation, sollte aber minimiert werden.

Schlüsselwörter: Antibiotikaeinsatz, „critically important antimicrobials", Antibiotikaresistenz, Milchrind, Tagesdosis

Introduction

From a consumer´s perspective, the health risks which can potentially be caused by drug-resistant bacteria are of particular concern. A prerequisite to obtain information on the progression of resistance to antibiotics is the collection of data on the consumption of antibiotics. Point number 10 of the action plan against the rising threats from antimicrobial resistance published by the European Commission in 2011 determines the need to strengthen surveillance systems on antimicrobial resistance and antimicrobial consumption in veterinary medicine (European Commission, 2011). It is recommended that standardised data on the use of antimicrobials should be gathered, ideally stratified by animal species and production categories, as well as for different therapeutic indications. Consequently, the Austrian Agency for Health and Food Safety was assigned the task of developing methods with which the quantity of antimicrobials used in Austrian cattle, pig and poultry production could be determined and monitored.

Data collated as part of this project are presented in this article, focusing on dairy farms. First, the methodology for the assessment and statistical evaluation of antimicrobial quantification will be described. Subsequently, antimicrobial drug use in general, and stratified by therapeutic indication or diagnosis, will be illustrated. Finally, special focus will be given to active substances declared by the World Health Organization (WHO) as being the "highest priority critically important antimicrobials" (HPCIAs) (WHO, 2011). For fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and glycopeptides, no or limited alternatives exist for the treatment of serious infectious diseases in humans, in particular for diseases caused by bacteria that may be transmitted to people from non-human sources (WHO, 2011). These substances have therefore been classified as HPCIAs. One of the primary objectives of the WHO's HPCIA list is to support the implementation of risk management strategies aiming at restricting the use of these substances. However, it is known that 3rd and 4th generation cephalosporins, in particular, are often applied for the treatment of infections in dairy cattle due to their broad spectrum effects and their pharmacokinetic characteristics (Hornish and Kotarski, 2002).

The goals of this pilot project can be summarised as follows: (1) to develop an adequate method for measuring antimicrobial use in cattle, (2) to quantify antimicrobial drug use in a sample of Austrian dairy farms and (3) to focus on the frequency of use of substances declared by the WHO as "highest priority critically important antimicrobials" (HPCIAs).

Material and Methods

Data collection

In Austria, veterinarians are required by law to record any administration of veterinary drugs and their dispensing of such medications to farmers. It is compulsory to record the type and quantity of the drugs used, as well as the diagnosis made (Anonymous, 2009). Based on this legal requirement, an observational study was conducted to estimate antimicrobial use in dairy herds.

The database used in this study comprised a sample of administration/dispensing records from eleven Austrian veterinary practices, covering the use of antimicrobials in dairy cows, youngstock and calves on 465 dairy farms from January 2008 to March 2010. Data were either submitted electronically or collected in person from veterinary practices directly. Electronic data were submitted over a period of four to 27 months. An electronic data interface was provided to the participating veterinarians to enable a simple transfer of collected data into the study database. The data collected in person covered four months within one year. A more detailed description of the data collection process has already been published by Ferner et al. (2014).

Each data record included i) date of administration/dispensing of the antimicrobial substance, ii) ID number of the farm, iii) ID number of the veterinarian, iv) the number of animals treated, v) the ID numbers of the animals treated, vi) the diagnosis or treatment indication, vii) the marketing authorisation number of the drug used, and viii) the amount of medicinal products applied or dispensed (Ferner et al., 2014).

A total of 8027 records from 465 dairy herds were analysed to calculate the use of antibiotics in the dairy cattle population. The herds were all members of the official milk performance recording association in Austria.

TABLE 1: *Livestock unit (LU) coefficients as applied to various age categories in Austrian dairy cattle according to ÖPUL (2007)*

Cattle age category	Age	LU-coefficient
Calves	< 6 months	0.4
Youngstock	≥ 6 months – < 24 months	0.6
Cows	≥ 24 months	1

TABLE 2: *Correction factors to estimate the consumption of antibiotics*

Variable	Minimum (min)	Most likely value (mlv)	Maximum (max)
Veterinary practice working days per year (working $days_{vet, year}$)*	240	300	360
Proportion of dairy population treated (% n $LU_{treated}$)**	65	80	95

* expert opinion

** proportion of the treated population on the total population at risk calculated for the veterinary practices participating in the study

Estimating the consumption of antibiotics

Units of measurement

Antimicrobial consumption was expressed in the following units of measurement.

As numerators, the following units were used:

(1) The amount of active substance used in grams (g). Amounts of drugs given in international units were converted into grams (EMA, 2013).

(2) The product-related daily dose (PrDD) for each veterinary pharmaceutical product. The maximum dose recommended by the manufacturer was adjusted after consultation with veterinary pharmacologists by a factor of 0.8, correcting for the fact that the maximum dose indicated is more often used than the minimum or the mean dose, but not used for every treatment. The PrDD was related to one livestock unit ($PrDD_{LU}$) by multiplying the $PrDD_{kg}$ by 500. For intramammary preparations, the PrDD was defined as the dose in mg of one tube.

As denominator the livestock unit (LU) was used:

(3) The LU is commonly used for the quantification of livestock in Austria. One LU is consistent with approximately 500 kilograms liveweight. To convert the number of cattle per age group into the number of livestock units (n LU), the LU coefficients defined by Agrarmarkt Austria Marketing (AMA) were used (ÖPUL, 2007) (Tab. 1). This indicator was subsequently used to correlate antimicrobial consumption to the animal's liveweight.

By means of these indicators, the following units of measurement could be determined:

(4) g/LU where g = amount of active substance in grams and LU = livestock unit.

(5) n $PrDD_{LU}$/LU where $PrDD_{LU}$ = product-related daily dose related to one LU and LU = livestock unit.

Method of estimating antimicrobial consumption

Due to the fact that recorded data of the study herds did not cover the entire study period, as well as the fact that the total population at risk was not included in the study, corrections for the quantification of antimicrobial consumption were essential.

First, the data in the eleven veterinary practices were collected over different time periods and therefore included a varying number of working days of the individual practices (working $days_{vet}$). Consequently, the number of PrDDs used per year per veterinary practice (n $PrDD_{vet, year}$) was calculated according to the following formula:

$$n\ PrDD_{vet,\ year} = n\ PrDD_{vet} * (working\ days_{vet,\ year} / working\ days_{vet})$$

where n $PrDD_{vet}$ = number of PrDDs recorded by the individual veterinary practice, working $days_{vet, year}$ = approximate annual number of working days of an Austrian veterinarian dealing with dairy cattle (Tab. 2, expert opinion) and working $days_{vet}$ = number of working days, in which data were recorded by the individual practice.

Second, in order to determine the total population-at-risk (n $LU_{pop-risk}$), the proportion of the untreated population had to be estimated. For each herd, in which at least one treatment was administered within the analysed period, the number of LUs per herd was determined on the basis of the official census for cattle from 2009 (n $LU_{treated}$). To correct for herds with no treatments (untreated population), the following procedure was applied: All farms which were members of the Austrian animal health service are legally obliged to name a supporting veterinarian. The farms contracted to the participating veterinarians were known. For these farms the numbers of LUs were determined and summed up, irrespective of any treatment. This figure was correlated to the total number of LUs of contracted herds in which at least one treatment was administered to calculate a factor for correcting the treated population into the total population-at-risk ($factor_{pop-risk}$). The population-at-risk was defined as the total number of LUs produced (total cattle population including the no treatment population) under the care of the veterinarians participating in the study in the year 2009: n $LU_{pop-risk}$. Consequently, the $factor_{pop-risk}$ for correcting the quantity of antimicrobials annually used in the total population-at-risk could be calculated according to the following formulae:

$$\%\ n\ LU_{treated} = (n\ LU_{treated,\ contracted\ herds} / n\ LU_{total,\ contracted\ herds}) * 100$$

where n $LU_{treated}$ is the number of LUs of the treated population, n $LU_{treated, contracted herds}$ is the total number of LUs of contracted herds in which at least one treatment was administered and n $LU_{total, contracted herds}$ is the total number of LUs of contracted herds irrespective of any treatment.

$$factor_{pop-risk} = 100 / \%\ n\ LU_{treated}$$

where % n $LU_{treated}$ is the treated population as a percentage of the total population.

$$n\ LU_{pop-risk} = n\ LU_{treated} * factor_{pop-risk}$$

where n $LU_{pop-risk}$ is the total population at risk and n $LU_{treated}$ is the treated population.

$$n\ PrDD_{LU,\ year} / LU_{year,\ pop-risk} = n\ PrDD_{year} / (n\ LU_{treated} * factor_{pop-risk})$$

where n $PrDD_{LU, year}/LU_{year, pop-risk}$ is the number of PrDDs used in the total population-at-risk per livestock unit per year, n PrDDyear is the number of product related doses used per year, n $LU_{treated}$ is the treated population and $factor_{pop-risk}$ is the factor for correcting the treated population into the total population-at-risk.

The consumption-estimating process began with a spot test of treatments with antibiotics, followed by calculating the amount of drugs used per veterinarian per year. The amount of active substance and the number of $PrDD_{LU}$ used were divided by the number of LUs produced by the treated herds (n $LU_{treated}$) and were finally corrected by the proportion of untreated herds ($factor_{pop-risk}$) in order to estimate the consumption of antimicrobials per year and per LU (n $PrDD_{LU,\ year}/LU_{year,\ pop-risk}$) in the total population-at-risk.

In order to accurately estimate the variance of the working days (working $days_{vet,\ year}$) and of the proportion of treated herds (n $LU_{treated}$), minimum values (min), maximum values (max) and most likely values (mlv) for these two approximated variables were used to construct a Beta-Pert probability distribution (Tab. 2).

The variance of the number of PrDD per LU (n $PrDD_{LU,\ year}$ / $LU_{year,\ pop-risk}$) was quantified by calculating the lower and upper quartiles by Monte Carlo simulation techniques (Binder, 1984) using 9999 replications.

Antimicrobial substances

Active substances used in this study were categorised according to the Anatomical Therapeutic Chemical classification system for veterinary medicinal products (ATCvet classification system) (WHO, 2013). Antimicrobial consumption was evaluated for systemic (QJ01), intramammary (QJ51) and intrauterine (QG51) use. In total, 46 different active substances and 84 different veterinary medicinal products were included in this dataset.

"Highest priority critically important antimicrobials"

Special focus was given to antimicrobials classified as "highest priority critically important" by the WHO expert group (WHO, 2011). These substances include fluoroquinolones (QJ01MA), 3rd and 4th generation cephalosporins (QJ01DD/QJ51DD and QJ01DE/QJ51DE), macrolides (QJ01FA/QJ51FA) and glycopeptides (QJ01XA). In this study, particular focus was placed on the consumption of these substances and the therapeutic indications for the use of HPCIAs in the dairy population examined.

Indications of use

Diagnoses and therapeutic indications were reported by the participating veterinarians according to the official Austrian code for diagnoses in cattle (Egger-Danner et al., 2012). A total of 64 clinical diagnoses are listed in this code to ensure that a standardised diagnosis can be reported during a veterinarian's visit. The codes of diagnoses are allocated to ten groups: calf diseases, diseases of the digestive tract, metabolic diseases, diseases of the reproductive organs, udder diseases, foot diseases, diseases of the respiratory tract, cardiovascular diseases, systemic diseases and a "not otherwise specified" (NOS) symptom complex associated with fever, reduced appetite or weight loss. Particular attention was paid to these diagnoses when interpreting the total antimicrobial consumption, as well as the consumption of HPCIAs.

TABLE 3: *Antimicrobial consumption in Austrian dairy cattle herds: amount of active substances and number of $PrDD_{LU}$ used in the study population; g/LU per year and $nPrDD_{LU}$/LU per year in the population at risk*

		Study population		Population at risk	
ATCvet group	**Active substance**	**Amount of active substances (g)**	**$nPDD_{LU}$**	**$g/LU_{pop-risk}$ per year***	**$nPrDD_{LU}/LU_{pop-risk}$ per year***
QG	Antimicrobial agents for intrauterine use	873.50	735 .63	0.05	0.03
QJ01	Antimicrobial agents for systemic use	40 330.36	10 646.10	1.63	0.45
QJ51	Antimicrobial agents for intramammary use	16 461.52	15 096.19	0.91	0.82
Total		57 665.38	26 477,92	2.59	1.30

* results estimated by Monte Carlo simulation technique

Results

Population-at-risk

The number of cattle kept in treated herds equated to 17 267 $LU_{treated}$. Taking the proportion of the assumed untreated population into account, the most likely value (mlv) of the total annual population-at-risk was 21 584 $LU_{pop-risk}$ (mlv) ranging from 18 176 $LU_{pop-risk}$ (min) to 26 565 $LU_{pop-risk}$ (max).

Total consumption of antibiotics

In total, 57 665 grams of active antimicrobial substances were used for treatment in dairy cattle herds during the observation period (Tab. 3). The vast majority of antimicrobials was administered systemically (40 330 g), with intramammary amounts being lower (16 462 g). Expressed in the number of daily doses, this equates to 26 478 $PrDD_{LU}$ for antimicrobial treatment in total, while the share of agents for systemic and intramammary use was 10 646 and 15 096 product related doses ($PrDD_{LU}$), respectively (Tab. 3).

Relating the amount of antimicrobials used to one year and the total population-at-risk, a median annual consumption of 2.59 $g/LU_{pop-risk}$ was calculated using Monte Carlo simulation techniques. Relating the number of product related daily doses to one year and the total population-at-risk, a median annual usage of 1.30 $PrDD_{LU}/LU_{pop-risk}$ was calculated. The majority of the doses were assigned to antibiotics for intramammary (0.82 $PrDD_{LU}/LU_{pop-risk}$) or systemic use (0.45 $PrDD_{LU}/LU_{pop-risk}$) (Tab. 3).

Within the group of antibacterials administered for systemic use, the calculation of the median number of $PrDD_{LU}/LU_{pop-risk}$ per year showed that, with the exception of antibacterial combination products (QJ01R; 0.20 $PrDD_{LU}/LU_{pop-risk}$), cephalosporins (QJ01D; 0.07 $PrDD_{LU}/LU_{pop-risk}$) were most frequently applied or prescribed. Within the antibiotics for intramammary use, antimicrobial substances most often belonged to the penicillin group of beta-lactam antibacterials (QJ51C; 0.39 $PrDD_{LU}/LU_{pop-risk}$) (Tab. 4).

The indications for antimicrobial treatments in dairy herds are shown in Table 5. The most frequently recorded indications requiring antimicrobial treatment systemi-

TABLE 4: *Consumption of antibiotics for systemic and intramammary use in dairy cattle ($g/LU_{pop\text{-}risk}$ per year, n $PrDD_{LU}/LU_{pop\text{-}risk}$ per year). Results estimated by Monte Carlo simulation technique*

		Percentiles											
		Active substance in $g/LU_{pop\text{-}risk}$ per year						n $PrDD_{LU}/LU_{pop\text{-}risk}$ per year					
ATCvet group	Active substance	Min	2.5^{th}	50^{th} (median)	97.5^{th}	Max	% (50^{th})	Min	2.5^{th}	50^{th} (median)	97.5^{th}	Max	% (50^{th})
Antimicrobials for systemic use													
QJ01A	Tetracyclines	0.08	0.10	**0.13**	0.16	0.19	7.97	0.01	0.01	**0.01**	0.01	0.02	2.82
QJ01B	Amphenicoles	0.01	0.01	**0.02**	0.02	0.02	0.99	0.00	0.00	**0.00**	0.00	0.00	0.28
QJ01C	Beta-Lactam Antibacterials, Penicillins	0.19	0.22	**0.29**	0.36	0.41	17.57	0.03	0.04	**0.04**	0.05	0.06	9.94
QJ01D	Other Beta-Lactam Antibacterials	0.02	0.03	**0.04**	0.05	0.05	2.31	0.05	0.06	**0.07**	0.08	0.10	16.42
QJ01E	Sulfonamides and Trimethoprim	0.28	0.33	**0.44**	0.56	0.62	26.83	0.01	0.02	**0.02**	0.02	0.03	4.82
QJ01F	Macrolides, Lincosamides and Streptogramins	0.12	0.14	**0.19**	0.24	0.27	11.47	0.03	0.04	**0.05**	0.05	0.07	10.37
QJ01G	Aminoglycoside Antibacterials	0.01	0.01	**0.01**	0.02	0.02	0.82	0.00	0.00	**0.00**	0.00	0.00	0.76
QJ01M	Quinolones and Quinoxaline Antibacterials	0.03	0.03	**0.04**	0.06	0.06	2.70	0.03	0.04	**0.05**	0.06	0.07	10.80
QJ01R	Combinations of Antibacterials	0.31	0.36	**0.48**	0.61	0.68	29.35	0.13	0.17	**0.20**	0.23	0.28	43.80
QJ01X	Other Antibacterials	0.00	0.00	**0.00**	0.00	0.00	0.00	0.00	0.00	**0.00**	0.00	0.00	0.00
Total systemic use		1.06	1.23	**1.63**	2.08	2.33	100.00	0.29	0.38	**0.45**	0.52	0.64	100.00
Antimicrobials for intramammary use													
QJ51A	Tetracyclines	0.00	0.00	**0.00**	0.00	0.00	0.00	0.00	0.00	**0.00**	0.00	0.00	0.00
QJ51B	Amphenicols	0.00	0.00	**0.00**	0.00	0.00	0.00	0.00	0.00	**0.00**	0.00	0.00	0.00
QJ51C	Beta-Lactam Antibacterials, Penicillins	0.45	0.53	**0.70**	0.87	0.99	76.33	0.26	0.34	**0.39**	0.44	0.56	47.70
QJ51D	Other Beta-Lactam Antibacterials	0.01	0.01	**0.02**	0.02	0.02	1.80	0.09	0.12	**0.14**	0.16	0.20	17.43
QJ51E	Sulfonamides and Trimethoprim	0.00	0.00	**0.00**	0.00	0.00	0.00	0.00	0.00	**0.00**	0.00	0.00	0.00
QJ51F	Macrolides, Lincosamides and Streptogramins	0.00	0.00	**0.00**	0.00	0.00	0.01	0.00	0.00	**0.00**	0.00	0.00	0.20
QJ51G	Aminoglycoside Antibacterials	0.00	0.00	**0.00**	0.00	0.00	0.00	0.00	0.00	**0.00**	0.00	0.00	0.00
QJ51R	Combinations of Antibacterials	0.13	0.15	**0.20**	0.25	0.28	21.84	0.18	0.25	**0.28**	0.32	0.40	34.46
QJ51X	Other Antibacterials	0.00	0.00	**0.00**	0.00	0.00	0.02	0.00	0.00	**0.00**	0.00	0.00	0.21
Total intramammary use		0.59	0.70	**0.91**	1.14	1.30	100.00	0.53	0.71	**0.82**	0.93	1.17	100.00
Total		1.66	1.93	**2.54**	3.23	3.63		0.83	1.10	**1.27**	1.45	1.81	

cally were referred to collectively as udder diseases, diseases of the respiratory tract, and systemic diseases. The majority of antibiotics (72.1%; 0.91 $PrDD_{LU}/LU_{pop\text{-}risk}$) was used to treat diseases ranked under the collective term "udder diseases".

Consumption of "highest priority critically important antibiotics"

The use of HPCIAs in Austrian dairy cattle is presented in Table 5 and illustrated in Figure 1 and Figure 2. HPCIAs for systemic and intramammary use made up a total of 0.31 $PrDD_{LU}/LU_{pop\text{-}risk}$ per year, which corresponds to 24.6% of all prescribed dosages of antimicrobials for systemic or intramammary use (1.27 $PrDD_{LU}/LU_{pop\text{-}risk}$). Approximately 70% (0.22 $PrDD_{LU}/LU_{pop\text{-}risk}$) of the total consumption of HPCIAs comprised 3rd and 4th generation cephalosporins, while fluoroquinolones and macrolides were less frequently used. The majority of cephalosporins (0.14 $PrDD_{LU}/LU_{pop\text{-}risk}$) were applied for "udder diseases" in the form of intramammary preparations.

Within the HPCIAs, approximately 54% of the PrDDs were used systemically and 46% were administered via the intramammary route. HPCIAs were most often used to treat "udder diseases" (0.22 $PrDD_{LU}/LU_{pop\text{-}risk}$; 69.3% of total HPCIA consumption) (Tab. 5). Of all HPCIAs, 3rd and 4th generation cephalosporins were predominantly used in "udder diseases" (intramammary administration, 0.14 $PrDD_{LU}/LU_{pop\text{-}risk}$) and in foot diseases (systemic, 0.04 $PrDD_{LU}/LU_{pop\text{-}risk}$), with both categories together corresponding to 88% of the total use of cephalosporins (Fig. 2).

Discussion

This is the first study describing the amount of antimicrobials used in Austrian dairy cattle herds at an on-farm level with special consideration of the "highest priority critically important" antimicrobial substances. Besides information regarding the amount of antimicrobials prescribed, data also included the clinical diagnosis, allowing an assessment of antimicrobial use relating to therapeutic indication.

Database

Crucial factors in quantifying antimicrobial consumption in animals are data reliability, traceability and accuracy. In this study, drug administration and dispensing records of the participating veterinary practitioners were used to quantify antimicrobial consumption in dairy cows, youngstock and calves on Austrian dairy farms. In Austria, farm veterinarians are legally required to document the administration and dispensing of veterinary medicinal products (Anonymous, 2002; Anonymous, 2009). It can therefore be assumed that the recorded amounts of antimicrobial products, which were either directly administered by the veterinarian or distributed to the farmer for use in food-producing animals, are close to the real dimensions of antimicrobial consumption and that underreporting was negligible.

Using prescription records as a data source for the determination of antimicrobial consumption is standard practice in other countries, e. g. Denmark (DANMAP, 2013). In contrast to the present study, data in Denmark originate predominantly from pharmacies (Stege et al.,

FIGURE 1: *Use of the "highest priority critically important antimicrobials" (HPCIAs) in Austrian dairy cattle. Consumption of antimicrobials expressed in number of product-related daily doses per livestock unit per year (n* $\mathrm{PrDD_{LU}}/LU_{pop\text{-}risk}$*).*

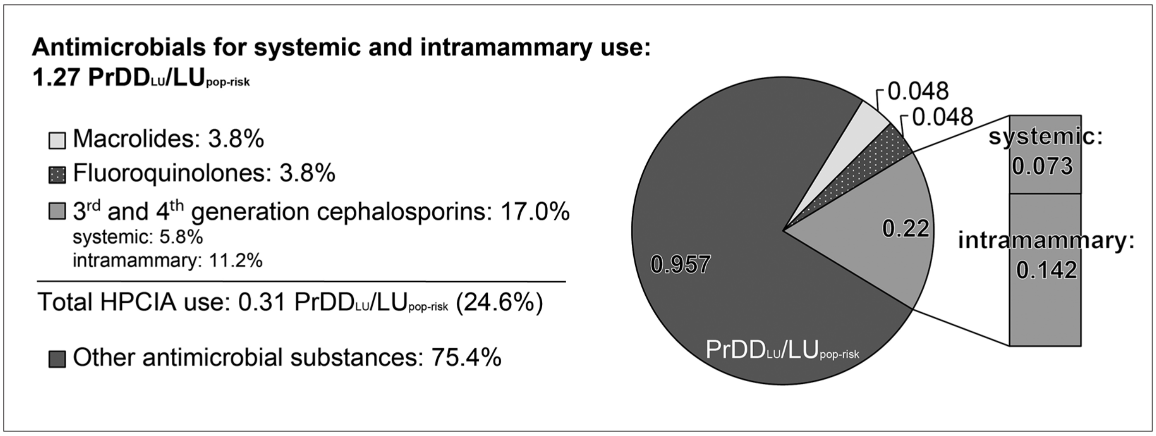
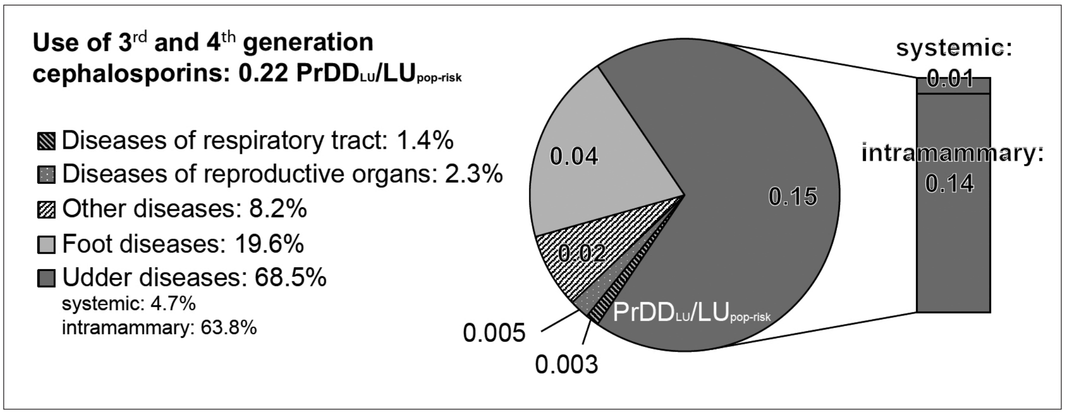


FIGURE 2: *Indications for the use of 3rd and 4th generation cephalosporins in Austrian dairy cattle as recorded by veterinary practitioners. Results are expressed in number of product-related daily doses per livestock unit per year (n* $\mathrm{PrDD_{LU}}/LU_{pop\text{-}risk}$*).*



2003). From 2004 onwards, the antibiotic use per animal species has been monitored in a stratified sample of farms, as well as in large-scale animal production in the Netherlands (MARAN, 2014). Since 2011, the SDa (the Netherlands Veterinary Medicines Authority) has published reports using consumption data from all farms in the largest sectors of food-producing animals (SDa, 2014). These data are recorded by veterinarians. Furthermore, the antimicrobial consumption has been evaluated by means of a series of questionnaires (Brunton et al., 2012; De Briyne et al., 2013; Gibbons et al., 2013). By using this method, the dispensing habits of the veterinarian (De Briyne et al., 2013; Gibbons et al., 2013), the administration habits of the farmer, and the routine practices of using antibiotics with respect to resistance development (Brunton et al., 2012) can be assessed; however the exact amounts of antibiotic substances used cannot be calculated. Menéndez González et al. (2010) used farmers' records for the quantification of antimicrobial consumption. Data were validated against records provided by veterinarians and it was highlighted that the implementation of a user-friendly electronic data collection system enabled centralized data acquisition and improved data traceability, completeness and quality. Electronic data collection systems, however, are not a safeguard for secure and correct data, which in turn implies the need for plausibility checks to assess the correctness of dosages, number of treated animals, animal´s liveweight and therapeutic indications (Regula et al., 2009, Trauffler et al., 2014a). In countries where farmers or farm workers themselves administer most antibiotics, antimicrobial consumption can easily be quantified by collecting empty packages or vials of medicinal products (Saini et al., 2012; Redding et al., 2014). In the predominantly small Austrian dairy herds medicines are most often administered directly by veterinarians themselves. To this end, data collection from these veterinary practitioners should be more reliable than from countries where medication administration is carried out by laypeople.

Units of measurement of antimicrobial use

Using the marketing authorisation number and the exact amount of the drug used or dispensed, the data collected enabled the calculation of the total amount of antimicrobial substances used. The target unit of measurement for antimicrobial use in this study was the number of PrDD related to the population-at-risk per year. Antimicrobial consumption expressed in terms of the number of daily doses of antibiotics is more appropriate for the interpretation of therapy frequency than presenting the total amount of active substance (Chauvin et al., 2001). The PrDD is equivalent to the product-related daily dose described by Trauffler et al. (2014a). A distinction between the dosages for different indications could not be made. In this study, the $\mathrm{PrDD_{kg}}$ was multiplied by the factor 500 in order to relate to one livestock unit (LU) as defined in Austria according to ÖPUL (2007). This conversion corresponds to the approach of Grave et al. (1999), who used the DDDcow (500 kg) as a unit of measurement for the number of doses of antimicrobials used for mastitis therapy in dairy cows.

The denominator "livestock unit" was used as the animal unit for the population-at-risk. Comparable to the

TABLE 5: *Consumption of antibiotics for systemic and intramammary use in dairy cattle (n $PrDD_{LU}/LU_{pop\text{-}risk}$ per year) subject to HPCIAs and reported diagnoses/indications of use. Median values estimated by Monte Carlo simulation technique*

		Diagnosis/indication of use										
ATCvet group	**Active substance**	**NOS**	**calf diseases**	**diseases diges-tive tract**	**meta-bolic diseases**	**diseases repro-ductive organs**	**udder diseases**	**foot diseases**	**diseases respi-ratory tract**	**cardio-vascular diseases**	**syste-mic diseases**	**total**
Antimicrobials for systemic use		0.06	0.01	0.01	0.00	0.02	0.11	0.06	0.10	0.00	0.08	0.45
QJ01D	3rd and 4th generation cephalosporins	0.01	0.00	0.00	0.00	0.00	0.01	0.04	0.00	0.00	0.00	0.07
QJ01F	macrolides	0.00	0.00	0.00	0.00	0.00	0.04	0.00	0.00	0.00	0.00	0.05
QJ01M	fluoroquinolones	0.01	0.00	0.01	0.00	0.00	0.02	0.00	0.01	0.00	0.00	0.05
Other antibiotics for systemic use		0.04	0.01	0.01	0.00	0.01	0.04	0.01	0.09	0.00	0.08	0.28
Antimicrobials for intramammary use		0.01	0.00	0.00	0.00	0.01	0.80	0.00	0.00	0.00	0.00	0.82
QJ51D	3rd and 4th generation cephalosporins	0.00	0.00	0.00	0.00	0.00	0.14	0.00	0.00	0.00	0.00	0.14
QJ51F	macrolides	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other antibiotics for intramammary use		0.00	0.00	0.00	0.00	0.01	0.66	0.00	0.00	0.00	0.00	0.68
Total		0.07	0.01	0.01	0.00	0.03	0.91	0.06	0.10	0.00	0.08	1.27
% Total		5.3	0.7	1.0	0.0	2.2	72.1	4.5	7.8	0.1	6.2	100.0
Total HPCIA		0.02	0.00	0.01	0.00	0.01	0.22	0.04	0.01	0.00	0.00	0.31
% HPCIA		7.9	0.2	2.1	0.0	2.1	69.3	13.6	4.4	0.4	0.0	100.0

* not otherwise specified

N. B.: data have been rounded to 2 decimal places.

population corrected unit (PCU) used for estimating the weight of livestock by the European Medicines Agency in the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project, the LU is a technical unit of measurement (EMA, 2011). As it is based on an animal's standardised liveweight, it can serve as a reference tool to allow comparison between different production types and different animal species.

In national surveys for evaluating antimicrobial use, census data are usually applied in order to define the population-at-risk (Grave et al., 1999). The ESVAC project uses the PCU as an estimate of the livestock biomass produced by the European member states. The PCU is calculated by multiplying the number of livestock and the number of animals slaughtered by the average liveweight at treatment (EMA, 2011). In the present study, the annual animal population of one farm (including youngstock and calves) was determined from census data for cattle as the population-at-risk per year and was expressed in number of livestock units (n $LU_{pop\text{-}risk}$). Pol and Ruegg (2007) related the number of DDD (Defined Daily Doses) to the total number of lactating cows of the surveyed farms. Variations in the number of cattle during the observation period can lead to an over or underestimation of antimicrobial consumption. Menéndez González et al. (2010) used the unit "incidence density" (ID) and calculated the population-at-risk as the mean of the number of cows at the beginning and at the end of the study period, which also might lead to an over or underestimation of the real ID of antimicrobial treatments. Calculating the population-at-risk in this way is very similar to the method used by Saini et al. (2012), who defined the average total number of adult cattle per farm as the reference population.

As data collection covered varying time frames and only the treated population was known, corrections for the calculation of the number of PrDD related to the population-at-risk per year were necessary to avoid an overestimation of antimicrobial consumption. Minimum, maximum and most likely values were defined for the number of working days and the proportion of the treated population in order to create a realistic framework for the quantification of the variance of antimicrobial amount estimates and the number of PrDD per LU (n $PrDD_{LU}/LU_{pop\text{-}risk}$) per year by Monte Carlo simulation techniques.

It is important to note that it is difficult to compare antimicrobial consumption between different countries while the units of measurement, as well as the calculation methods, are not internationally standardised. Varying calculations of population size (to which antimicrobial usage is directly related) as well as varying approaches for the specification of the daily doses often prohibit direct comparisons. Other studies have also highlighted the fact that differing measurement units and their varying definitions might substantially influence the outcomes of the calculation of antimicrobial treatments (Chauvin et al., 2008; Regula et al., 2009; Menéndez González et al., 2010; Trauffler et al., 2014a).

Consumption of antimicrobials

In the present study, the estimated amount of antimicrobials administered (for intrauterine, systemic and intramammary use) was 2.59 g and 1.30 PrDD per $LU_{pop\text{-}risk}$ per year). The amount of antibacterials applied here was lower than the figures reported by Menéndez González et al. (2010) in Switzerland, who found 9.6 g per animal-year at risk in cows. Since farm structures in Switzerland are quite similar to those in Austria, reasons for this difference may be the application of different antimicrobial substances or the fact that the untreated population was not considered in the Swiss calculations.

In order to make a rough estimate of the treatment frequency related to 100 cow-years, the amount of antimicrobial use per LU can be multiplied by the factor 100, resulting in 48 $PrDD_{LU}$ per 100 $LU_{pop\text{-}risk}$ per year for antimicrobial agents for intrauterine and systemic use. The treatment incidence for dairy cows in Switzerland, as described by Menéndez González et al. (2010), revealed 47 doses per 100 cow-years at risk for antimicrobials for intrauterine and systemic use. This figure is, however, based on the used course dose, and consequently based on the amount of active substance that was used during the whole treatment duration and does not include antimicrobial use in youngstock and calves. Antimicrobials for intramammary use were determined to be 154 used unit doses per 100 cow-years at risk in the Swiss study; the corresponding figure in the present study was 82 PrDD per 100 $LU_{pop\text{-}risk}$. As explained before, this difference may be due to the fact that the figures in the current study were corrected to account for the estimated untreated population.

Pol and Ruegg (2007) estimated an overall exposure to antimicrobial drugs of 5.43 defined daily doses (DDD) per adult cow per year in conventional dairy herds. The so obtained levels of use were, however, only related to herds given at least one treatment. This needs to be considered when comparing the figure to the number of PrDD per $LU_{pop\text{-}risk}$ in the study at hand. Reviewing the usage of intramammary antimicrobial drugs only, 1.85 DDD per adult cow per year were estimated by Pol and Ruegg (2007) compared to 0.82 PrDD per $LU_{pop\text{-}risk}$ in this study.

When antimicrobial consumption is expressed in the veterinary unit "defined daily dose" (DDD), which is commonly used as an equivalent of the term "animal daily dose" (ADD), it is important to consider the definition of this unit. Pol and Ruegg (2007) used the maximum label-dosage, which refers to a standard animal with 680 kg liveweight as the denominator for the calculation of the number of DDD out of the total amount of active substance. In contrast, this study used 80% of the maximum label-dosage, which refers to 500 kg liveweight (1 LU), as the denominator to calculate the number of $PrDD_{LU}$ used. The "antimicrobial drug use rate" (ADUR) defined by Saini et al. (2012) is related to 1000 cow days and determines the ADD as the average on-label dosage of one dairy cow at 600 kg liveweight. In these Canadian dairy herds, the overall ADUR was 14.35 ADD per 1000 cow days, which equates to 5.2 ADD per cow per year. This figure is very close to the overall exposure to antimicrobial drugs in conventional dairy herds of 5.43 defined daily doses (DDD) per adult cow per year found by Pol and Ruegg (2007) and is approximately four times higher than the consumption of antibiotics estimated in the examined Austrian dairy herds (1.30 PrDD per $LU_{pop\text{-}risk}$ per year).

Indications of use of antibiotics in dairy cattle

The most important indications for using antibiotics in dairy herds were reported under the collective term "udder diseases" and for treatment at drying-off, with a total of 72.1% of all PrDDs prescribed (Tab. 5). This is in line with the results of a Swiss study (Menéndez González et al., 2010) in which dry-cow therapy (36%) and "udder diseases" (35%) were the most frequent indications for antimicrobial treatment. Pol and Ruegg (2007) estimated that 88% of all defined daily doses (DDD) of antibiotics per cow per year were used for clinical mastitis and dry-cow therapy. When considering systemic applications only, "udder diseases" contributed to 24.4% of the total antimicrobial consumption. Merle et al. (2014) found that "udder diseases" represented a similar proportion of antibiotic consumption with 24.8% of the total used for this indication.

In addition to treating udder disorders, antibiotics were also prescribed for the treatments of systemic diseases, respiratory diseases and foot diseases in dairy cattle herds (6.2%, 7.8%, and 4.5% of PrDDs respectively) (Tab. 5). The percentage of defined daily doses (DDD) per cow per year of the total use estimated by Pol and Ruegg (2007) for foot infections and respiratory diseases were comparable to the proportions of respiratory diseases and foot diseases determined in the present study. Considering total antibiotic use, De Briyne et al. (2014) indicated, from the results of a survey which was completed by 3004 veterinary practitioners from 25 European countries, that mastitis was the most commonly cited reason (40%) for antibiotic use in cattle. In addition, this pan-European study also mentioned respiratory diseases (22%) and diarrhoea (14%) as diseases that often required antibiotic treatment. In a study from Pennsylvania (USA), treatment of clinical mastitis, metritis and foot rot were the predominant disorders requiring treatment with antibiotics (Sawant, 2005).

For the present study, it is necessary to note that in 5.3% of the total number of PrDDs prescribed, fever, reduced appetite, weight loss or "not otherwise specified (NOS)" was recorded by the prescribing veterinarian. In 6.2% of the total number of PrDDs prescribed, general systemic infections were reported. With these not further specified diagnoses, it is unclear whether antibiotic therapy is carried out in accordance with prudent use guidelines. The estimation of antimicrobial consumption related to therapeutic indications provides the potential to reduce the use of antibiotics in accordance with responsible use guidelines.

Use of "highest priority critically important antimicrobials" in dairy cattle

In this study, special attention was paid to macrolides, fluoroquinolones and 3rd and 4th generation cephalosporins, which have been defined as "highest priority critically important antimicrobials" (HPCIAs) by the WHO (WHO, 2011). The use of HPCIAs poses the risk of developing resistance to these antimicrobials in bacteria, which may affect a high absolute number of people with extremely limited treatment options. Furthermore, HPCIA-resistant bacteria may emerge as infection sources for humans resulting from transmission of resistant bacteria or their resistance genes from animals to humans (WHO, 2011).

In the dairy cattle population studied here, 24.6% of the administered daily doses were related to antimicrobial substances declared as "highest priority critically important" (Fig. 1). This corresponds approximately to the use of these substances in Austrian pig herds (Trauffler et al., 2014b). In contrast to the use of HPCIAs in Austrian pigs, where the largest proportion of HPCIAs applied were macrolides, in Austrian dairy cattle mainly 3rd and 4th generation cephalosporins were used within the HPCIA-group (0.22 $PrDD/LU_{pop\text{-}risk}$).

For the treatment of "udder diseases" primarily 3rd and 4th generation cephalosporins were used (0.15 $PrDD/LU_{pop\text{-}risk}$) – preferably through intramammary administration (0.14 $PrDD/LU_{pop\text{-}risk}$) (Fig. 2). The use of 3rd and 4th generation cephalosporins for the treatment of locomotory infections was common (Fig. 2). The use of 3rd and 4th generation cephalosporins as first-choice antibiotics is contrary to the recommendations of the European Medicines Agency (EMA, 2012). Prescription of 3rd and 4th generation cephalosporins can, however, often be justified by their broad-spectrum effects and, when used systemically, their short withdrawal period for milk in dairy cows. Less than 50% of veterinarians in the pan-European study regularly performed sensitivity tests (De Briyne et al., 2013), although HPCIAs should, according to international prudent use guidelines, be reserved only for infections that respond poorly to other antibiotics and to which the sensitivity of the causal bacteria have been tested (BVA, 2009; Ungemach et al., 2006). Short withdrawal periods are an important economic factor for dairy farmers, because milking treated cows separately is time-consuming and discarding waste milk is cost-intensive. Analysing the responses of veterinarians from seven different countries who were questioned about factors influencing their prescribing behaviour, the mean score representing the importance of the withdrawal period as an economic factor was 2.8 on a 5 point scale (where 0 was unimportant and 4 was very important) (De Briyne et al., 2013). This factor therefore constitutes one of the most important drivers for choosing a certain antibiotic.

Saini et al. (2012) estimated a median antimicrobial drug use rate (doses per 1000 cows) for 3rd generation cephalosporins of 1.24 for Canadian dairy herds, corresponding to 0.45 doses per cow per day. In this Canadian study, macrolides and fluoroquinolones were also only used at low rates. In conventional dairy herds, Pol and Ruegg (2007) estimated a mean number of defined daily doses (DDD) per cow per year for the 3rd generation cephalosporin ceftiofur of 0.47, 0.33, 0.07 and 0.19 for the treatment of clinical mastitis, foot diseases, respiratory diseases and metritis respectively. For Swiss dairy farms, Menéndez González et al. (2010) calculated a treatment incidence for macrolides, fluoroquinolones and 3rd and 4th generation cephalosporins of 0.33 course doses per animal per year, which equated to 19.6% of all treatments with antimicrobials for intestinal, intrauterine and systemic use. This proportion is a little lower than the corresponding estimate for Austrian dairy herds (24.6%) in which 3rd and 4th generation cephalosporins containing intramammary tubes are included. On dairy farms in England and Wales, the 4th generation cephalosporin, cefquinome, was present in the second most frequently used intramammary tubes in milking cows (29% of first choice therapy) (Brunton et al, 2012). The macrolide tylosin (27.4% of farms), 3rd and 4th generation cephalosporins (19.1% of farms) and fluoroquinolones (5.5% of farms) were frequently used systemic antibiotics in England and Wales (Brunton et al., 2012).

In an European-wide survey, veterinarians specified the indications for which they most commonly prescribed antibiotics (De Briyne, 2014). HPCIAs were the most frequently cited therapy in cattle for respiratory diseases (45%), diarrhoea (29%) and locomotion disorders (31%). Preferences could be observed in prescribing habits between different countries, with no use of HPCIAs in Sweden, for example. Due to legal restrictions of use, sales figures of HPCIAs are very low in the Nordic countries: Denmark, Norway and Sweden (EMA, 2014). Following restrictions on the dispensing rights of veterinarians in Denmark, the consumption of 3rd and 4th generation cephalosporins in intramammary treatments for cattle significantly declined in this country between 2007 and 2013 (DANMAP, 2013). In the Netherlands, similar measures were taken: substances were classified according to their importance for human medicine into first, second and third choice substances. All critically important antimicrobials for human health were classified as third choice, which means that they can only be used on an individual basis after mandatory sensitivity testing for alternatives (Ministry of Economic Affairs, 2014). Results of the monitoring of the antibiotic use on a stratified sample of dairy farms in the Netherlands show a significant decrease in the use of 3rd and 4th generation cephalosporins (from 13% of daily doses used in 2009 to 1% of daily doses used in 2012) (MARAN, 2012) and remaining below 0.01 daily doses between 2012 and 2014 (MARAN, 2015). As already described above, Austrian veterinarians are required to justify the use of HPCIAs by objective diagnostic measures (Anonymous, 2010). However, as these measures are neither specified nor checked by the relevant authorities, their accurate implementation in veterinary practice is not clear. Benchmarking the use of antimicrobials with special attention to HPCIAs on both the farm level and the level of veterinary practices as seen in Denmark and the Netherlands could be helpful to further reduce the use of HPCIAs in dairy herds in Austria. Attention must be drawn to the fact that efforts to reduce the use of certain substances may be prevented by the limited availability of some distinct antibacterials licensed for mastitis therapy, such as the benzylpenicillin-prodrug penethamate.

Compared to other food producing species, the absolute number of PrDDs of HPCIAs administered or dispensed for the treatment of diseases in Austrian dairy cattle is very low. However, considering the use of 3rd and 4th generation cephalosporins particularly with respect to the efforts made by countries such as the Netherlands, Denmark or Sweden, it is vital that legal requirements should be enforced in order to comply with the international prudent use guidelines for HPCIAs.

Conclusion

The consumption of antibiotics in dairy cattle production is of minor importance compared to their use in pig and poultry production in Austria. However, the use of the highest priority critically important antimicrobials – especially the administration of 3rd and 4th generation cephalosporins – is not negligible and there are doubts that the use of these substances is always in line with the guidelines for the prudent use of antimicrobials. The documentation of antimicrobial use data along with diagnostic data provides valuable information on the indications for antibiotic treatment in dairy cattle production. It serves as a very important tool for further research on the impact of drug use on antimicrobial resistance and for implementing future measures to reduce the use of antibiotics.

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Conflict of interest

The authors confirm that no professional, financial or other personal relationships exist which could influence the presented contents or could give rise to doubts to their independence.

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