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Survey of drug use and its association with herd-level and farm-level characteristics on German dairy farms

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ABSTRACT

The use of veterinary drugs is of similar importance to that of human drugs in addressing health challenges. In this context, pharmaceuticals and their metabolites inevitably enter soil and water in unknown quantities. Therefore, this study collects and analyzes drug data from 2020 for 50 dairy farms located in Germany. The most frequently used substance group is antibiotics (40.13%), followed by antiphlogistics (18.86%), antiparasitics (13.09%), and hormones (9.29%). Treatment frequencies record the number of days per year on which an average animal on a farm was treated with a substance. The calculated values range from 0.94 to 21.69 d/yr and are distributed heterogeneously across farms. In this study, on average, a cow was treated on 6 d in 2020: 2.34 d with antibiotics, 1.07 d with antiphlogistics, 0.76 d with antiparasitics, and 0.41 d with hormones. In addition to individual farm management practices, other factors are related to treatment frequency. Farms with a veterinary care contract used more hormonal substances than farms without a care contract. In addition, higher milk yield coincides with more frequent treatments with antiphlogistic or hormonal substances. Other related factors include grazing, longevity, farm size, and use of a claw bath. Our study represents an important first step in describing the amounts and determinants of veterinary drugs used in livestock farming. Such insights on magnitudes and farm parameters are essential to estimate potential environmental effects and derive strategies to reduce veterinary drug use.

Key words: veterinary drugs, treatment frequency, substance monitoring, dairy farms

INTRODUCTION

Pharmaceuticals are an indispensable and fundamental part of public health. In particular, advancements in pharmaceutical therapy have enhanced the ability to effectively address health challenges, including various infectious diseases. In this context, not only is the use of human medicines is important, but also the use of veterinary medicines. The latter contribute not only to animal well-being, but also to food safety.

Various substances are used for the treatment and prevention of diseases. However, their detection in soils and waters has been raising concerns for years (Zuccato et al., 2006; Barra Caracciolo et al., 2015; Mesa et al., 2018; Maculewicz et al., 2022). These concerns encompass the effects of drugs and their metabolites on non-target organisms in the environment as well as the development of resistance. Antibiotic resistance is recognized by the World Health Organization as one of the top 10 threats to global health (World Health Organization, 2019). In addition to human pharmaceuticals, veterinary drugs also have a substantial effect on the emergence of resistance (Bártíková et al., 2016). Resistance to both antibiotics and antiparasitic agents is a growing concern in the therapy of livestock (Charlier et al., 2022). Furthermore, substances such as moxidectin, which are excreted in substantial quantities by cattle after treatment, exhibit lethal toxicity to numerous invertebrates (Mesa et al., 2018). Within the realm of anti-inflammatory agents, Parolini (2020) demonstrates, through various in vitro experiments, that a mixture of different compounds resembling those found in natural aquatic environments significantly heightens the toxicity to aquatic invertebrates in comparison to individual components. When hormonal agents find their way into the environment, their effect is primarily observed in vertebrates. Kidd et al. (2007) conducted a study in Canada revealing that estrogenic compounds in water bodies had such a profound influence on fish reproduction that they neared extinction. Furthermore,

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the use of anti-inflammatory drugs has been subject to critical discourse. Oaks et al. (2004) illustrated that the administration of diclofenac to cattle in Pakistan nearly eradicated vulture populations. In the European Union (**EU**), diclofenac is only approved for use in cattle in Estonia and Spain (European Medicines Agency, 2022), with the first vulture fatality attributed to diclofenac documented in 2020 (Herrero-Villar et al., 2021).

It is essential to note that all the aforementioned studies encompass only a limited perspective of the ecological consequences of the application of specific pharmaceuticals within particular regions. In Germany, veterinary drugs are used in livestock farming on cattle, pigs, and poultry. Consequently, pharmacologically active substances and their metabolites primarily enter soil and water through farm manure (Hamscher and Mohring, 2012; Hamscher and Bachour, 2018). To assess the actual environmental input of veterinary drugs, comprehensive data are required, differentiated by animal species and farm characteristics (Wöhler et al., 2020).

In the EU, the use of veterinary drugs is regulated by law. In addition to the EU-wide antibiotic minimization concept (European Union, 2022), national efforts are also underway in Germany to record and reduce the use of antibiotics in animal husbandry. Since 2014, certain fattening farms in Germany have therefore been required to report the quantities of antibiotics used to the competent authority every 6 mo (Federal Ministry of Food and Agriculture, 2021). This system will be further expanded in the upcoming years. Despite these efforts, limited data are available for Germany documenting the use of veterinary drugs in general (i.e., substances other than antibiotics). In Germany, veterinarians themselves are required by law to document all drugs applied and dispensed for livestock, not just antibiotics. However, this is usually only done locally in offices and on farms (Federal Ministry of Food and Agriculture, 2009, 2015). In contrast to fattening farms, dairy farms have not been required to report any drug data until 2023. The annually published pharmacological industry sales figures for antibiotics to veterinarians in Germany indicate the absolute quantity and the sales region (Federal Office of Consumer Protection and Food Safety, 2021). However, those figures do not include information on the actual use of antibiotics in specific animal species. In particular, the type of production system and the kind of species are important for assessing potential emissions into the environment (Wöhler et al., 2023).

Studies in Germany and the EU have mostly been limited to the use of antibiotics in farm animals for fattening, or have only included the application frequency of other drugs (Mitrenga et al., 2020; van der Laan et al., 2021). On the other hand, in human medicine, surveys which provide information beyond the pure use of antibiotics already exist (Ludwig et al., 2022). However, to assess the input and environmental effects of veterinary drug use, it is particularly important to know the application quantities (not only frequencies) of all substance groups (not only antibiotics) for all kinds of animal species, not only fattening animals (Bártíková et al., 2016).

Our study contributes to closing this research gap by recording all drugs used in 2020 in a first step via a nationwide survey on dairy farms. Based on the legally required documentation on the farms, drug use was evaluated with regard to both the quantity applied and the frequency of application. In addition, other farm parameters were collected to investigate their relationship on drug usage. From this, potential strategies for reducing the use of certain substance groups can be derived in further steps to minimize their environmental effects.

MATERIALS AND METHODS

The data in this study come from a nationwide survey on 50 dairy farms. We collected general farm data by a questionnaire and combined it with drug data from the application and dispensing receipts. For protection of data privacy, we collected and anonymized all data in 2021/22 for the entire year 2020. Institutional Review Board approval was not necessary because data collection was anonymous, precluding any identification of individuals, and did not involve animal experimentation.

The questionnaire listed in Supplemental Table S1 (http://dx.doi.org/10.22029/jlupub-18392) was filled out by the farm manager during the farm visit and was used to collect data about the farm, farm managers, animals, and the production parameters in the year 2020. It is based on the farm surveys by Alvåsen et al. (2018) and Dickhaus (2010). The standardized questionnaire used in this study meets the requirements for objectivity, reliability, and internal validity (Moosbrugger and Kelava, 2020). Its comprehensibility was tested on 2 test farms before the survey. To answer questions on animal numbers, farmers relied on the official animal database of the federal states (HI-Tier), and for performance data, they relied on documentation from the local control associations on the farms (Bavarian State Ministry of Food Agriculture and Forestry, 2023).

For the collection of pharmaceutical data, we retrieved existing data. According to the legal situation for the survey year 2020, veterinarians and farmers were required to document the application or prescription of pharmaceuticals by the Veterinary Home Pharmacy

Regulation (Federal Ministry of Food and Agriculture, 2009) and required to keep the receipts for 5 yr by the Regulation on the Application and Documentation of Veterinary Medicinal Products by Animal Keepers (Federal Ministry of Food and Agriculture, 2015). We accessed the supporting documents, handwritten or machine-generated on paper, onsite at the farms as part of the survey and supplemented the drug data on the receipts with manufacturer information regarding active substances and concentrations contained.

The entire survey took place on a selection of the approximately 54,000 dairy farms in Germany (Federal Statistical Office of Germany, 2022a). Some of the farm managers volunteered after calls in journals and via associations. We actively recruited others via lists of training farms. To assess the regional representativeness of our sample, we mapped the regional location of the 50 farms in our sample to official statistics on the regional frequency of dairy farms in Germany (Federal Statistical Office of Germany, 2021). The overall survey is not representative, so its external validity is not entirely ensured. However, it does provide a valuable reference point for Germany, as the means of our sample closely resemble those reported in German statistics for many variables (see Supplemental Tables S2A and S2B; http://dx.doi.org/10.22029/jlupub-18392).

First, we examined the collected drug data descriptively for the quantity applied and the application frequency, independently of the farm surveyed. Then, farm-specific treatment frequencies were calculated from the drug data. Equation 1 shows the treatment frequency, which is a metric introduced by the German legislature originally intended to solely depict the utilization of antibiotics in animal husbandry (Federal Ministry of Food and Agriculture, 2013):

$$T_j = \frac{\sum_{i=1}^{N}\left(X_{ij} \times D_{ij}\right)}{A_j}. \quad [1]$$

To calculate the general treatment frequency (T_j) per farm (j), we sum over all substances used (i). The number of animals treated with a substance (X_{ij}) is multiplied by the number of treatment days (D_{ij}). The application frequency in the numerator ($X_{ij} \times D_{ij}$) is an absolute value that indicates how often a substance is used. The sum over all substances used is then divided by the average number of animals kept per farm (A_j). The treatment frequency thus represents a farm-specific and relative value describing how often an animal is treated with any substance on average per year.

In our study, we not only calculated the treatment frequency for the substance group of antibiotics (**TAB**), but the overall treatment frequency (**TO**) and, in addition, separate treatment frequencies for the substance groups antiphlogistics (**TAPH**), antiparasitics (**TAP**), and hormones (**TH**).

As an example, a farmer has 50 animals, which received medications in the year 2020 as follows: 15 cows received 3 d of penicillin each, 10 cows received 1 d of tetracycline each, and 8 cows received 1 d of prostaglandin each. According to Equation 2, this results in a total therapy frequency of 1.26, specific to this farm. Additionally, therapy frequencies for certain groups of substances can be calculated. For animals on this farm, the therapy frequency is 1.1 for antibiotics (Equation 3) and 0.16 for hormones (Equation 4). In other words, on average, each animal on this farm received medication on 1.26 d in 2020, including 0.16 d with hormone treatment and 1.1 d with antibiotic treatment:

$$TO_j = \frac{15 \times 3 + 10 \times 1 + 8 \times 1}{50} = 1.26; \quad [2]$$

$$TAB_j = \frac{15 \times 3 + 10 \times 1}{50} = 1.1; \quad [3]$$

$$TH_j = \frac{8 \times 1}{50} = 0.16. \quad [4]$$

Using regression analysis, part of the variation in treatment frequencies can be explained by differences in farm characteristics. The selection of explanatory variables is based on a recent approach using machine learning. The least absolute shrinkage and selection operator (**LASSO**) method is a supervised machine learning algorithm that identifies the variables that are correlated with the variable being explained. Variables that have less influence or no influence at all are set to zero, and LASSO finds groups or correlations among the explanatory variables and removes all but one of the variables that measure the same effect. This means LASSO only selects the truly important ones from a plethora of variables to reduce overfitting by irrelevant variables (Tibshirani, 1996; Ranstam and Cook, 2018). Because LASSO still considered a multitude of farm characteristics to be important, and to avoid the issue of multiple testing, we selectively examined only a handful of parameters from those generated by LASSO, guided by the relevant literature (Heringstad et al., 2007; Koeck et al., 2014; Arnott et al., 2017; van der Laan et al., 2021).

We regressed the explanatory variables individually on treatment frequencies using ordinary least squares regression. The R^2 shows in percentage terms how much variation in treatment frequencies can be explained by variation in the parameters studied. The performed t-tests provide information on the significance of the estimated parameters for continuous variables. For binary dummy variables, the *t*-test indicates whether the means of the 2 groups differ significantly from each other. For categorial variables, we used ANOVA to compare multiple groups. For heterogeneous groups, the Games-Howell test indicates which groups are significantly different from each other (Ruxton and Beauchamp, 2008). In the results section, we present the direction, the relevance as an absolute value, and the significance of the effects.

RESULTS

A total of 50 dairy farms from 8 different federal states with a total of 13,565 cattle participated in the study. For later analysis, we divided them into smaller farms (farm size = 0) with less than 88 lactating cows and larger farms (farm size = 1) with more than 88 lactating cows based on the median. In addition, we subdivided the farms into the regions south (region = 0), middle (region = 1) and north (region = 2). Within these groups, 58% of farms are located in the southern region, followed by 26% the in northern region and 16% in the middle region, which roughly corresponds to the regional distribution of all dairy farms in Germany (Federal Statistical Office of Germany, 2021). Supplemental Table S3 (http://dx.doi.org/10.22029/jlupub-18392) provides more detailed information on the classification and distribution of farms across federal states.

For a better overview of farm characteristics in the sample, we present a farm with mean values as follows: The mean farm in our sample was built in 1996 and is managed by a 45-yr-old person with a title of master craftsman. On 150 ha, the managing person and their 3 workers take care of 270 cattle, 128 of which are lactating cows that give approximately 9,360 kg of milk per year. The alley ways of the freestalls are equipped with a slatted floor, and the cows from own breeding are milked in the milking parlor. In 2020, 204 drug receipts were issued for the mean farm. Of these, 40% of the drugs were applied directly by the veterinarian, 65% were dispensed to the farmer, and some technically belonged to both categories. Within the entire group of farms, 6% are certified organic, 74% have a veterinary care contract, and 26% use a claw bath. Supplemental Tables S3A and S3B show more detailed information on the individual variables.

In this survey, we were able to collect an overall active ingredient quantity of 956.47 kg, which can be classified into 26 active ingredient groups based on 91,126 individual applications. In terms of quantity, electrolytes with a share of 44.56% (426.52 kg) of the total quantity and carbohydrates with 35.16% (336.59 kg) were used the most on the dairy farms visited. According to EU Regulation 2019/06 in Europe (European Union, 2022), electrolytes and carbohydrates are also classified as drugs. These are, for example, glucose infusions for cattle with metabolic diseases. They are followed by antibiotics (9.37%, 89.71 kg) and antiphlogistics with (6.77%, 64.84 kg). If, on the other hand, the frequency of application is considered instead of the quantity applied, antibiotics are in the lead, as expected, with a share of 40.13% of all applications, as they usually must be applied for several days in a row. They are followed by antiphlogistics (18.86%), antiparasitics (13.09%), and hormones (9.29%), as they are mostly applied just once. Supplemental Table S4 (http://dx.doi.org/10.22029/jlupub-18392) shows all other substance groups and their share of quantity and frequency applied.

Antibiotics

Figure 1a shows the application quantities and Figure 1b shows the application frequencies of antibacterial substances, categorized by substance subgroups. Penicillins are the antibiotics used the most in terms of quantity (46.20%, 41.45 kg) and frequency (37.11%). Tetracyclines are important in terms of quantity (16.15%, 14.49 kg), but are used rather rarely, with 0.97% relative application frequency. In contrast, polyene antibiotics, aminoglycosides, first generation cephalosporins, β-lactamase inhibitors (usually combined with penicillins), and fourth generation cephalosporins are used relatively frequently compared with the quantity applied. The fourth generation cephalosporins in particular, which represent highest priority critically important antimicrobials, are used more frequently (2.08%) than tetracyclines, but have a minimal effect in terms of the quantity applied (0.31%, 0.28 kg).

Antiphlogistics

Figure 2 shows 3 substance subgroups for antiphlogistics. Non-steroidal anti-inflammatory drugs are the most relevant group, accounting for 99.86% (64.74 kg) of the quantity of antiphlogistics applied. Glucocorticoids are used relatively frequently (16.54%) among the antiphlogistics, but are of lesser importance in terms of their quantity applied (0.13%, 0.09 kg). Antihistamines are of little importance in terms of quantity (0.01%, 0.006 kg) and application frequency (0.15%).

Antiparasitics

In the group of antiparasitics, salicylic acid anilides (1.65%) are used very rarely along with benzimidazoles (1.04%). However, due to the high concentration required for oral application form, they have the great-

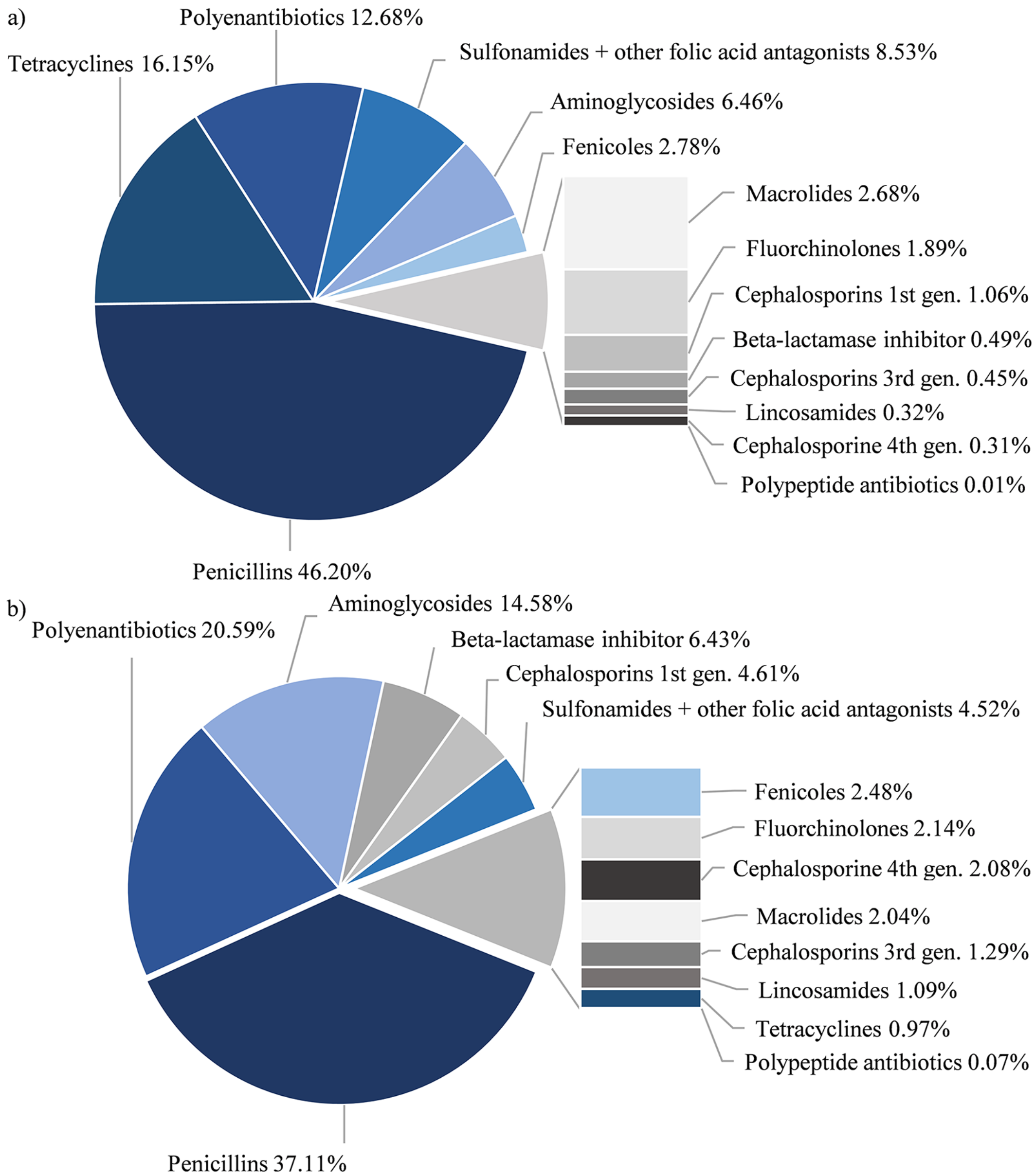

Figure 1. (a) Proportional application quantity and (b) proportional application frequency of the substance group antibiotics used on 50 dairy cow farms in Germany in 2020, categorized by antibiotic subgroups.

est importance in terms of quantity (33.58%, 1.5 kg; 21.65%, 0.97 kg), as shown in Figure 3. Anticoccidials are applied the most frequently with 52.6%. Because they are only used in calves at low concentrations, the quantitative importance is low (0.53%, 0.02 kg).

Hormones

Figure 4 shows the substance subgroups of hormones and their application quantity and frequency. Progestins are used very rarely (1.56%) as a local long-term preparation but have the greatest importance in terms of quantity (83.33%, 0.06 kg) due to their high concentration. Prostaglandin, GnRH, and oxytocin preparations are used relatively frequently (38.83%; 34.05%; 25.36%) in very low concentrations (15.87%, 0.01 kg; 0.39%, 0.0003 kg; 0.34%, 0.0003 kg).

Farm Characteristics

To examine the correlation of the farm characteristics with drug use in more detail, we used the treatment frequencies. Table 1 provides an overview of TO and the treatment frequency of each substance group (TAB,

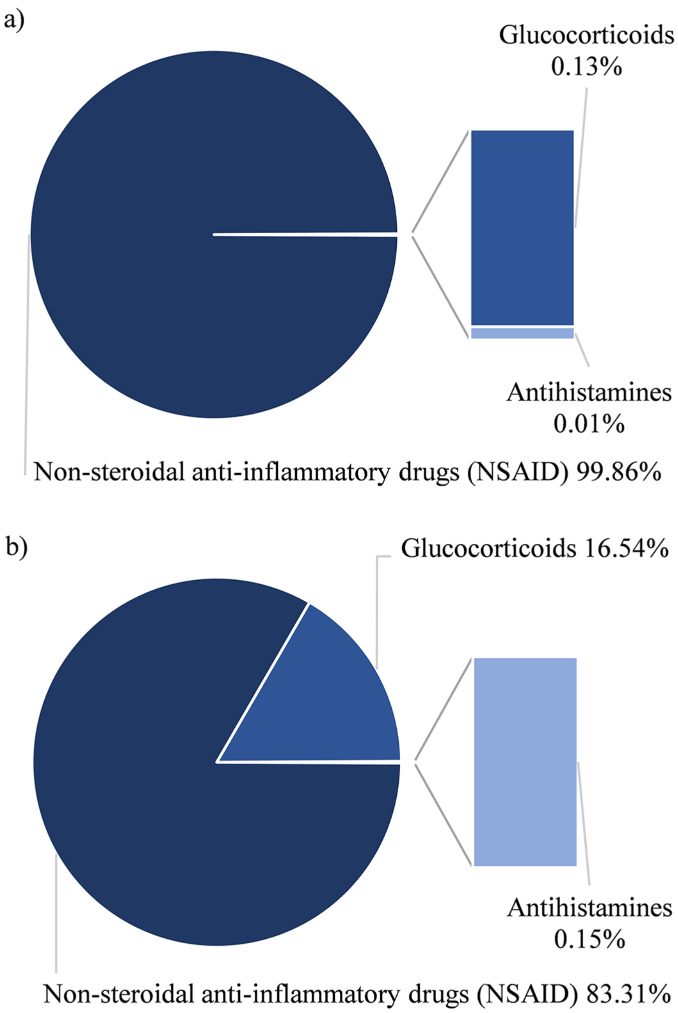

Figure 2. (a) Proportional application quantity and (b) proportional application frequency of the substance group antiphlogistics used on 50 dairy cow farms in Germany in 2020, categorized by antiphlogistic subgroups.

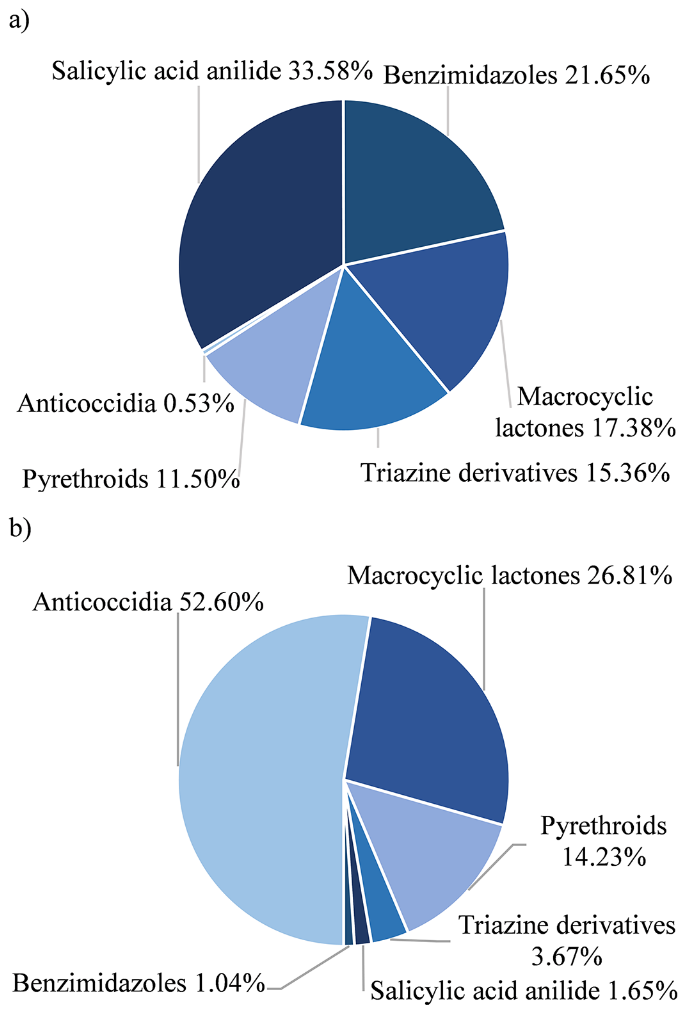

Figure 3. (a) Proportional application quantity and (b) proportional application frequency of the substance group antiparasitics used on 50 dairy cow farms in Germany in 2020, categorized by antiparasitic subgroups.

TAPH, TAP, and TH). The mean shows that an average cow in this survey is treated with a substance on approximately 6 d/yr: on 2.34 d with antibiotics, on 1.07 d with antiphlogistics, on 0.76 d with antiparasitics and on 0.41 d with hormones. Sixteen of 50 farms do not use any antiparasitics and 10 farms do not use any hormones. We found a wide range in TO from a minimum of 0.94 d to a maximum of 21.69 d in 2020.

Due to the large number of farm characteristics, not all of them were examined for their influence on treatment frequencies. Subsequently, we confine our focus to a subset of parameters whose effects are documented in the existing literature and have been further identified as pertinent through LASSO regression analysis with $\alpha = 1$, as the number of potential covariates exceeds the number of observations. The result of a 10-fold cross-validation, with the objective of minimizing the mean squared error, is $\lambda = 0.086$. Supplemental Table S5 (http://dx.doi.org/10.22029/jlupub-18392) displays all the variables that LASSO has deemed relevant but

Table 1. Summary statistics of treatment frequencies measured in days per year

Variable[1]	N[2]	Mean	SD	Minimum	Maximum
TO	50	5.82	3.79	0.94	21.69
TAB	50	2.34	1.59	0.25	8.72
TAPH	50	1.07	0.86	0.14	4.74
TAP	50	0.76	1.30	0.00	6.03
TH	50	0.41	0.518	0.00	2.15

[1]TO = overall treatment frequency; TAB = treatment frequency with antibiotics; TAPH = treatment frequency with antiphlogistics; TAP = treatment frequency with antiparasitics; TH = treatment frequency with hormones.
[2]N = number of dairy farms in study.

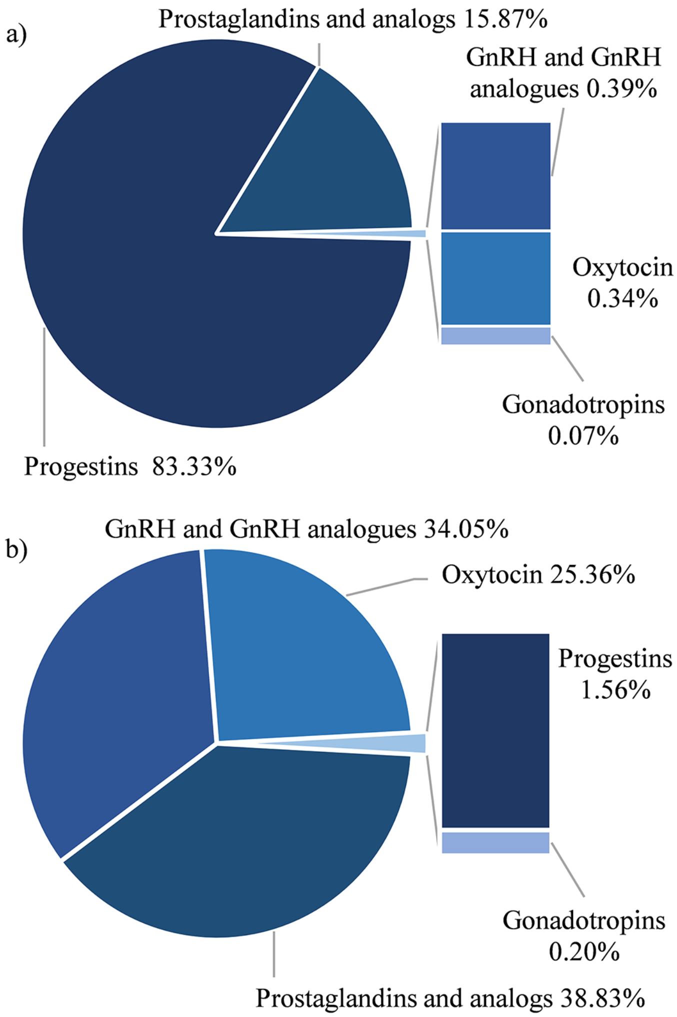

Figure 4. (a) Proportional application quantity and (b) proportional application frequency of the substance group hormones used on 50 dairy cow farms in Germany in 2020, categorized by hormone subgroups.

which, based on the literature, are not included in our regression analysis.

Table 2 shows the results of simple regressions of selected farm characteristics on respective treatment frequencies. Farm size in line 1 shows a significant ($P = 0.04$) correlation with TO. On average, large farms with a TO of 6.9 d/yr used drugs on roughly 2 more days than small farms (TO = 4.7 d). The treatment frequency of antibiotics (TAB = 0.77 d, $P = 0.088$) and antiparasitics (TAP = 0.7 d, $P = 0.057$) is higher for large farms. Large farms have a significantly ($P = 0.005$) higher TH by 0.4 d. Small farms used hormonal substances on average on 0.2 d and large farms on 0.6 d. A veterinary care contract in line 2 comes along with a 0.346 d higher TH ($P = 0.037$).

Milk yield in line 3 has an effect on all treatment frequencies in the simple regression. Thus, a 500 kg higher average annual milk yield correlates with an increase in TO by 0.5 d ($P = 0.007$). For TAB, treatment frequency increases by 0.1 d when average annual milk yield increases by 500 kg ($P = 0.067$). A similar effect is observed for TH ($P = 0.002$) and TAPH ($P = 0.046$). The effect size is lower with a 0.05 d increase in TH and TAPH for the same milk yield increase of 500kg.

According to line 4 in Table 2, the regional distribution of farms has an influence solely on use of hormones. We found a significant increase in TH by 0.3 d in the northern direction when compared with the south, center, and north regions ($P = 0.02$).

If farmers offer their cows outside grazing (line 5), this leads to a tendential reduction in treatment frequency. If grazing is offered, the treatment frequency is 0.46 d ($P = 0.07$) lower for antiphlogistics and 0.26 ($P = 0.08$) days lower for hormones.

A longer utilization period in line 6 comes along with a significantly reduced treatment frequency. Thus, TO decreases by 0.76 d when the average duration of use increases by one year ($P = 0.04$). This decrease is mainly driven by the associated decrease in treatment frequency of antibiotics (TAB = −0.312 d, $P = 0.04$) and hormones (TH = −0.14 d, $P = 0.006$).

Farms using a claw bath (line 7) showed 2.876 d higher TO ($P = 0.02$) and a 1.671 d significantly higher TAB ($P = 0.00$), as well as a 0.696 d higher TH ($P = 0.00$) as seen in line 7.

DISCUSSION

To the authors' knowledge, this study first describes the use of all substance groups applied on dairy farms in Germany. Previous studies, such as Hommerich et al. (2019) and Preine and Krömker (2022), focused exclusively on the use of antimicrobial substances.

On the 50 dairy farms in the study, antibiotics were the most frequently applied substance group, followed by antiphlogistics, antiparasitics, and hormones. The quantity applied in part differed greatly from the application frequency. By calculating treatment frequencies, it is possible to determine how many times per year an average animal on a farm was treated with a particular substance. For the overall treatment frequency, values ranged from 0.94 to 21.69 d/yr and were highly heterogeneous. On average, a cow in the study was treated on about 6 d, including 2.34 d with antibiotics, 1.07 d with antiphlogistics, 0.76 d with antiparasitics, and 0.41 d with hormones. In addition to individual farm management, other factors are also related to treatment frequency, such as a veterinary care contract, milk yield, grazing, longevity, farm size, and use of a claw bath.

The data from our study were obtained from a convenient sample, as participation in the study was

Table 2. Effects of farm-specific characteristics on dairy herd treatment frequencies; ordinary least square estimates

	Dependent variable[1,2]				
Explanatory variable	TO	TAB	TAPH	TAP	TH
Farm size	2.160**	0.769*	0.213	0.696*	0.399***
(0 = small; 1 = large)	(1.037)	(0.441)	(0.244)	(0.358)	(0.136)
	{4.739***}	{1.957***}	{0.965***}	{0.415}	{0.210**}
	[0.083]	[0.060]	[0.016]	[0.073]	[0.151]
Veterinary care contract	1.679	0.387	0.260	0.474	0.346**
(0 = no; 1 = yes)	(1.210)	(0.516)	(0.278)	(0.418)	(0.161)
	{4.577***}	{2.055***}	{0.879***}	{0.412}	{0.154}
	[0.039]	[0.012]	[0.018]	[0.026]	[0.087]
Milk yield	0.001***	0.0002*	0.0001**	0.0001	0.0001***
(annual average in kg)	(0.0003)	(0.0001)	(0.0001)	(0.0001)	(0.00004)
	{−1.379}	{0.299}	{−0.130}	{−0.431}	{−0.669*}
	[0.149]	[0.068]	[0.080]	[0.035]	[0.178]
Region	0.686	0.257	0.073	0.041	0.299***
(0 = south; 1 = middle; 2 = north)	(0.623)	(0.262)	(0.143)	(0.216)	(0.075)
	{4.667***}	{1.910***}	{0.949***}	{0.694*}	{−0.093}
	[0.025]	[0.020]	[0.005]	[0.001]	[0.251]
Grazing	−1.360	−0.478	−0.456*	0.430	−0.264*
(0 = no; 1 = yes)	(1.111)	(0.469)	(0.247)	(0.382)	(0.150)
	{6.309***}	{2.514***}	{1.235***}	{0.608**}	{0.505***}
	[0.030]	[0.021]	[0.066]	[0.026]	[0.061]
Longevity	−0.763**	−0.312**	−0.110	−0.111	−0.140***
(average period in years)	(0.368)	(0.155)	(0.086)	(0.131)	(0.049)
	{9.282***}	{3.759***}	{1.569***}	{1.266**}	{1.043***}
	[0.082]	[0.078]	[0.033]	[0.015]	[0.147]
Claw bath	2.876**	1.671***	0.361	0.161	0.696***
(0 = no; 1 = yes)	(1.163)	(0.459)	(0.275)	(0.423)	(0.136)
	{5.072***}	{1.907***}	{0.977***}	{0.721***}	{0.228***}
	[0.113]	[0.216]	[0.035]	[0.003]	[0.354]

[1]Coefficients of simple linear regression are listed in the first line for each variable. Standard errors are indicated in parentheses, constants in curly brackets, and R^2 in square brackets.

[2]TO = overall treatment frequency; TAB = treatment frequency with antibiotics; TAPH = treatment frequency with antiphlogistics; TAP = treatment frequency with antiparasitics; TH = treatment frequency with hormones.

*$P < 0.1$; **$P < 0.05$; ***$P < 0.01$.

voluntary. To better estimate the extent of voluntary response bias, we compared the characteristics of participating farms with all farms in Germany, displayed in Supplemental Tables S3A and S3B. By relying on voluntary participation following announcements in journals, we predominantly reached farmers who are self-motivated and proactive in seeking information. Additionally, through targeted phone calls to training farms, we were able to include a higher proportion of farms with younger (year of birth in study: 1974, in Germany [**DE**]: 1986) and better-educated (master craftsmen in study: 58%, DE = 37%) farm managers, as one must possess a master's title to be eligible for training apprentices. In our study, very small farms are underrepresented (area in study: 151 ha, DE = 101 ha; small farm size in study: 50%, DE = 60%), but we captured the regional distribution across Germany (see Supplemental Table S2 for details). Unfortunately, we cannot definitively state whether the values in our study statistically differ from those in Germany, and we therefore acknowledge a bias. We can only argue that very small farms, which are predominantly part-time operations in Germany, are becoming less common, and their effect on the quantities of pharmaceuticals used is minimal due to their small livestock numbers. Despite this minor bias, our unique data set provides added value because it combines pharmaceutical data with farm and animal characteristics for Germany for the first time.

The data quality in this study profits from the extraction of information exclusively from books, thereby ensuring the exclusion of subjective opinions or assessments. Farms in Germany are required by law to keep their veterinary drug records on the farm for 5 yr, which is why we were able to review all drugs prescribed and applied by a veterinarian on site in 2020 (Federal Ministry of Food and Agriculture, 2009). It is reasonable to assume that every drug sold by a veterinarian to a farm is documented and that we can rely on the stated quantities, given the stringent controls in place in Germany. A questionnaire used to collect different farm parameters in addition to the data about drug use was completed by the farm manager or herd manager. For animal numbers and performance measures, we relied on the official animal database of the federal states (HI-Tier) and on the local control associations for the farms (Bavarian State Ministry of Food Agriculture and Forestry, 2023).

The official regulatory treatment frequency is determined per 6-mo period (Federal Ministry of Food and Agriculture, 2021) and the number of animals kept enters the formula on the exact day matching the application period. However, animal number recording to the exact date is prone to error (Hemme et al., 2017). The associated data were not available to us due to data protection rights, which is why the treatment frequency in this study was calculated on an annual basis using the average number of animals kept over the entire year from the HI-Tier database.

On average, a cow in our study has a treatment frequency for antibiotics of 2.34 d. This is comparable to the survey by Hommerich et al. (2019), in which the treatment frequency for antibiotics on 474 farms averaged 2.1 d from 2011 to 2015. Despite the smaller sample size compared with that of the aforementioned papers, we are able to contribute meaningful results which are comparable to other studies and rely on high-quality data.

The use of antibiotics is heavily discussed. Nevertheless, particularly in cows on dairy farms, limited data are available on the actual quantities applied per species and year so far. Our data show that in terms of quantity, penicillins and tetracyclines are the antibiotic groups used the most in cows on dairy farms. The same is shown by Hajek et al. (2010), van Rennings et al. (2014), and the German sales surveys according to the regulation on the database-supported information system on medicinal products of the German Institute of Medical Documentation and Information (DIMDI-AMV; Federal Office of Consumer Protection and Food Safety, 2021). However, the first 2 studies include beef cattle in addition to cows on dairy farms. The sales survey includes all antibiotics sold to veterinarians in Germany, irrespective of animal species, and thus does not show animal species-specific consumption. The study of van Rennings et al. (2014), comparable to our study, found large differences between the application frequency and the application quantity of substance subgroups. Again, cephalosporins and aminoglycosides are used relatively frequently in comparison to the quantity applied. The difference between application quantity and frequency for tetracyclines seen in our study is not shown in the survey by van Rennings et al. (2014). This could be because fattening animals integrated therein are treated more frequently with tetracyclines (Mitrenga et al., 2020). Polyene antibiotics were used in fairly high quantities (12.7%) and frequencies (20.6%), and monensin is the only active substance approved in Germany as a veterinary drug for cows. In light of the EU's antibiotic reduction concept, its use for ketosis prophylaxis is viewed critically because it is not used to treat infections, but rather to influence the metabolic state.

For antiphlogistics and antiparasitics, our collected data are unique for Germany in this form, so no comparable data are available. Anti-inflammatory drugs (antiphlogistics) account for only 6.77% of the total quantity of administered agents, yet they play a significant role with an application frequency of 18.86%. Farmers and veterinarians are obliged under German animal welfare legislation to treat animals and alleviate pain, and in this context, anti-inflammatory drugs play a crucial role. It is well established that the early use of anti-inflammatory drugs reduces systemic inflammation (Schmitt et al., 2023), thereby contributing to antibiotic conservation. Quantitatively, glucocorticoids have a limited presence among anti-inflammatory drugs, as their high activity necessitates administration in very low concentrations. Nevertheless, they are frequently employed, comprising 16.54% of the total usage.

The use of antiparasitic agents is highly farm specific. Within our sample, 16 farms do not use antiparasitics at all. The most common application of antiparasitics is for young calves against *Cryptosporidia*. However, the largest quantity of active ingredients is used in cattle that have access to pasture. This is because the parasite pressure is significantly higher in grazing conditions (Vanderstichel et al., 2012) compared with pure confinement housing. Despite the lower quantity of active ingredients compared with other groups, the environmental effects of antiparasitics should not be underestimated.

Data on hormone use in German cows are not yet available. In the Netherlands, van der Laan et al. (2021) surveyed the application frequency of reproductive hormones on 760 farms. They show a frequency of hormone use (prostaglandin 62.9%; GnRH 33.1%; progesterone 4.0%) comparable to the one in our study (prostaglandin 38.83%; GnRH 34.05%; progesterone 1.56%). Progestins (progesterones) were used very rarely in both studies. However, our study shows that progestins are by far the most important in terms of quantity. Again, substantial differences exist between the application frequency and quantity of drugs.

Our regression results show that, among other characteristics, farm size and the overall treatment frequency, as well as the treatment frequency of hormones, are correlated. Accordingly, the large farms in our study use drugs such as hormones more frequently compared with smaller farms. Additionally, a veterinary care contract is associated with a change in hormone use. In the study by van der Laan et al. (2021) from the Netherlands, it also was shown that farms with a veterinary care contract used hormones more frequently. A possible explanation could be the more regular rectal examination of the animals on the farms (Derks et al., 2013), which results in a more frequent diagnosis of fertility disorder and an accompanying therapy with hormones. In addition, farms with veterinary care contracts often have higher performance levels. According to a study by Ries et al. (2022), they achieve higher performance levels as measured by milk yield than farms without a care contract. The increased focus on performance parameters could be a reason for more active fertility management as well. Among the farms that did not use hormones at all, the majority were smaller farms (<88 lactating cows). However, in the Netherlands, farm size was not correlated with hormone use according to van der Laan et al. (2021). Ries et al. (2022) showed that smaller farms were more likely to not have a veterinary care contract. In our study, we see a tendency that large farms are 20% more likely to have a care contract than small farms ($P = 0.1$). Thus, it seems reasonable to assume that the increased use of hormones is correlated with the existence of the veterinary care contract and the associated stronger veterinary monitoring with regard to fertility disorders, rather than by farm size, as initially posited.

As discussed in detail in many studies, milk yield and health traits are negatively correlated with breeding (Heringstad et al., 2007; Koeck et al., 2014). In our study, farms with high milk yield show a higher treatment frequency. The effect is large, with an increase in overall treatment frequency of 0.5 d per 500 kg more milk per year. In addition to overall treatment frequency, milk yield is also related to treatment frequencies of antiphlogistics, hormones and antibiotics. Conditions associated with high milk yield include mastitis, ketosis, lameness, ovarian cysts, and retained placenta (Simianer et al., 1991; Heringstad et al., 2007; Koeck et al., 2014). Mastitis, lameness, and retained placenta are usually treated with antibiotics and antiphlogistics, and ovarian cysts are most often treated with hormones (Taktaz et al., 2015), which is mirrored by the increased treatment frequencies. In general, estrus detection is essential for reproductive performance (Gordon, 2011). In a study of 267 lactating cows, Lopez et al. (2004) showed that increasing milk yield reduced the duration of estrus, making it less detectable. This could be an additional explanation for the more frequent use of hormones when milk yield increases. Because in our study large farms with more than 88 lactating cows showed a significantly higher milk yield ($P = 0.00$, mean = 8,187.2 kg vs. 10,533.8 kg), it can be suspected that farm size has an indirect influence on treatment frequency.

In this survey, the region has an influence on the treatment frequency of hormones. Farms from the southern region used hormones significantly less frequently than farms from northern regions. Southern Germany is mainly home to small traditional farms (Merle et al., 2012), which use a different fertility strategy. As mentioned before, small farms usually do not have a veterinary care contract and have a lower milk yield, which could explain our present findings.

Hygiene has a major influence on biosecurity and thus on the health of animals in the herd. Animals kept permanently indoors are dirtier than animals that have pasture access (Nielsen et al., 2011). In addition, animals with pasture access are less likely to be affected by lameness (Haskell et al., 2006; Olmos et al., 2009a), mastitis (Washburn et al., 2002), and uterine disease (Olmos et al., 2009b). Overall, grazing has a positive effect on animal health (Arnott et al., 2017). In our survey, farms with grazing options used antiphlogistics and hormones slightly less often than farms without that option. In contrast, a significant increase in the use of antiparasitics would have been expected on farms with grazing options, as animals are exposed to greater parasite pressure when grazing (Vanderstichel et al., 2012). We could not prove this with respect to all animals on a farm. However, when considering treatment frequency excluding applications to calves younger than 6 mo, which often do not have access to pasture, farms with pasture access tend to have a higher treatment frequency of 0.32 d for antiparasitics compared with farms without pasture access ($P = 0.03$). Calves have a strong influence on the treatment frequency of antiparasitics, as they are significantly more likely to receive antiparasitic treatment, and treatment frequency is not about the quantity applied, but the application frequency.

Farms with a longer utilization period treat their animals less often in this study. This is mainly related to the less frequent use of antibiotics and hormones. Older animals tend to fall ill more often (Gernand et al., 2012; Abebe et al., 2016), but are thus discarded more quickly. In Germany, cows are most often discarded due to fertility problems and udder diseases (Heise et al., 2016). It can be speculated that a longer life of milking cows could speak for a farm management with optimal general conditions for the animals, in a way that they are generally healthier, require less treatment, and grow older as well. However, in this study, only drug data were collected, which is why it is not possible to draw any direct conclusions about the overall health of animals studied.

In Germany, claw baths cannot be used for the therapy of claw diseases (European Union, 2022) because no products are available for therapeutic use. However, precautionary care measures to reduce germ pressure are possible. Therefore, one might assume that farms that use a claw bath for prevention would have a lower treatment frequency than farms that do not. Our results, however, present a contrasting picture: Farms with a claw bath have a 2.9 d higher overall treatment frequency ($P = 0.016$). The treatment frequencies with antibiotics and hormones with 1.7 d and 0.7 d are significantly higher than in farms without claw bath ($P = 0.00$). Studies on the efficacy of claw baths in cattle are limited (Jacobs et al., 2019). In addition, the design and management of the claw bath is critical to its success (Cook, 2017). In our study, the use of a claw bath is positively correlated with the amount of diagnosis concerning the musculoskeletal system ($P = 0.008$). Supplemental Table S6 (http://dx.doi.org/10.22029/jlupub-18392) provides an overview of the frequency of diagnoses recorded in our study, sorted by diagnosis group. Dobson et al. (2008) showed that lame cows had significantly reduced estrus behavior. In addition, lame cows are 3.5 times more likely to have delayed cyclicity (Garbarino et al., 2004) and lower ovulation rates (Melendez et al., 2018). Omontese et al. (2020) found a lower proportion of cyclic cows in cows with claw lesions compared with healthy cows. This could explain why farms with a claw bath used hormones more frequently than farms without a claw bath.

Wet and manure-soiled areas promote potential claw disease (Stanek, 2005) and negatively affect udder health (Dohmen et al., 2010), resulting in more frequent mastitis (Firth et al., 2019). Animals with claw problems lie down more than healthy animals (Ito et al., 2010). The increased ground contact of the udder when lying down results in poorer udder hygiene (DeVries et al., 2012), and thus may contribute to increased infection of the udder by environmental germs. Farms that used a claw bath were more likely to have a diagnosis of mastitis in our study ($P = 0.08$). This could explain why farms with a claw bath used antibiotics significantly more often than other farms.

Dairy livestock operations in central European countries such as Germany and the Netherlands are structured in a similar way, with a large number of family-run dairy operations that keep small- to medium-sized herds, depending on the region. On average, German farms keep about 72 dairy cows (Federal Statistical Office of Germany, 2022b), and Dutch farms keep about 110 dairy cows (Statistics Netherlands, 2022). Legal regulations on animal husbandry and the use of medicines are at a comparable level as well, despite country-specific laws through EU regulations. On the contrary, dairy livestock operations in the United States have a different structure, as a US farm keeps an average of 316 dairy cows (USDA, 2022). In addition, the legal framework is different compared with the European Union. For these reasons, our data can only be transferred very cautiously to countries with different agricultural and legal structures.

When looking at the substances applied, large differences between the application frequency and the application quantity of substance subgroups are noticeable. In Germany, treatment frequencies are used as a key figure in the field of antibiotic minimization to document the use of antibiotics in livestock farming. However, this indicator only represents the application frequency of drugs, but not the application quantity (van Rennings et al., 2013). In addition, our study shows an excerpt of multiple parameters which are related to the application frequency of veterinary drugs, but refrains from making assumptions about herd management, the different sensitivity of farmers to detect diseases, or the role of prophylaxis. Hence, to comprehensively capture and assess the utilization of veterinary drugs on farms, it is imperative to consider more than just a singular frequency-based application statistic.

CONCLUSIONS

Our study has shown that cows on dairy farms are treated with antibiotics and other substances with high environmental risk probability, such as antiphlogistics, antiparasitics, and hormones. However, our study shows that the treatment frequency per animal is very heterogeneously distributed between farms. In addition to individual farm management, factors such as the presence of a veterinary care contract, farm size, milk yield, grazing, longevity, and the use of a claw bath correlate with treatment frequency. With regard to the recording and minimization of environmental inputs by veterinary drugs, we see that the monitoring of a single substance group (antibiotics) is not sufficient and can only provide initial aspects for further regulation across all substance groups. A first enhancement would entail the centralized provision of comprehensive veterinary drug data across all animal species, given their current high-quality existence but limited local accessibility on farms. Further studies are needed to evaluate the specific release into the environment and consequences for the ecosystem.

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