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Associations of Swiss national reporting system's antimicrobial use data and management practices in dairy cows on tie stall farms

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ABSTRACT

Antimicrobial use (AMU) in Switzerland is above target and requires reduction especially in dairy cattle. Measuring AMU is pivotal to identify starting points for AMU reduction and so are studies investigating its potential drivers in dairy farms worldwide. However, although AMU in dairy farms is high, studies estimating AMU specifically in tie stall farms are scarce. Tie stalls are a common housing system and their prevalence among dairy farms accounts to approximatively 73%, 41% and 40% in Canada, the US and Switzerland, respectively. The objectives of this cross-sectional, retrospective observational study were to estimate AMU using the newly established Swiss national reporting system for AMU in livestock and to identify associated factors on Swiss tie stall dairy farms. We calculated the treatment incidence (TI) by using the European Medicines Agency's methodology and their Defined Daily and Defined Course Dose (DDD/DCD) standards. Data on factors potentially associated with AMU were obtained through personal interviews with farm managers on 221 farms. Retrospectively, during a 1-year period, data on a total of 7,619 treatments were extracted from the national database. Associations between management factors and TI were analyzed using a generalized linear model with gamma distribution. The mean overall TI was 5.46 DDD/cow-year (±standard deviation: 4.10 DDD/cow-year). Intramammary treatment during lactation accounted for highest TI (3.24; ± 3.16 DDD/cow-year), whereas dry-cow therapy accounted for lowest TI (0.44; ± 0.49 DCD/cow-year). Five of the investigated management factors were significantly associated with TI. Organic production (estimate −2.16; 95% confidence interval [95 CI] −3.62, −0.70) and herd size (estimate −0.81; 95 CI −1.23, −0.39) were negatively associated with TI. Specific cow breeds (Brown Swiss and Holstein Friesian: estimate 1.56; 95 CI 0.45, 2.68; estimate 1.42; 95 CI 0.03, 2.82, respectively; reference: other breeds) and the use of hygienic powders on the lying area (estimate 1.10; 95 CI 0.04, 2.17) were positively associated with TI. In conclusion, the Swiss national reporting system is a valuable tool for AMU estimation. Several herd characteristics and management factors were associated with AMU in tie stall farms. Further studies focusing on factors associated with AMU and which are amenable to intervention will help improve stewardship programs and subsequently reduce AMU in dairy cows.

Key words: tie stalls, management, dairy cows, antimicrobial use, national reporting system

INTRODUCTION

Antimicrobial use (**AMU**) in dairy cows and other livestock contributes to the emergence and spread of antimicrobial resistance (**AMR**), which is a major threat for human and animal health (Loo et al., 2019; Abdelfattah et al., 2021; CDC, 2022). To tackle this transboundary crisis, the World Health Organization (WHO) adopted a global action plan on AMR in 2015 (WHO, 2015). Together with the World Organization for Animal Health (WOAH) and the Food and Agriculture Organization (FAO) they conform the so known tripartite organizations and assist countries with their national action plans on AMR, which include improvements in the digital recording and reporting of AMU (OIE, 2018; Umair et al., 2021; Doyle et al., 2022).

In developed countries, approximatively 50–80% of total AMU is used in livestock farming (Cully M., 2014), and most is used in poultry, swine, and dairy cattle (Cuong et al., 2018). In the US, approximately 80% is used in food-producing animals (Van Boeckel et al., 2015). Relative to its dairy cattle population, Switzerland is among the highest users of antimicrobials in dairy cattle, notably concerning intramammary products (ESVAC, 2021). Accuracy in measuring and reporting AMU is crucial to identify potential drivers

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of AMU and subsequently implement efficient AMU reduction strategies (Ferreira, 2017). Several countries have therefore implemented reporting systems for the quantification of antimicrobial drug consumption (AACTING, 2021; Government of Canada, 2021; Dutch Working Party on Antibiotic Policy (SWAB), 2023). In the US, there are requirements for drug manufacturers to report sales data to the Food and Drug Administration (FDA), but farm-level AMU reporting directives are currently lacking (FDA, 2018; Schrag et al., 2020). In Switzerland, a national reporting system for AMU, entitled "Informationssystem für den Antibiotikaverbrauch in der Veterinärmedizin" (IS ABV, english name: "Information System of Antimicrobials in Veterinary Medicine"), was launched in the frame of the National Strategy on Antibiotic Resistance (StAR) in 2019 (BLV, 2023). There are substantial variations in AMU quantification methodologies (Ferreira, 2017; Umair et al., 2021) posing a challenge for direct comparisons among farms and countries. Efforts are made in the European Union to harmonize recording and reporting metrics (Ferreira, 2017). The Defined Daily Dose (**DDD**) and Defined Course Dose (**DCD**) methodology has been suggested by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project launched by the European Medicines Agency (EMA) (EMA, 2013). Defined daily doses are available for pigs, cattle, and poultry (EMA, 2016), and are necessary to estimate the treatment incidence (**TI**) from sales or prescription data. The doses are defined as follows: i) the DDD is the assumed average dose per kg animal per species per day, and ii) the DCD is the assumed average dose per kg animal per species per treatment course (EMA, 2015).

Reducing AMU has not only been in the scope of the governments and international organizations, but also of the scientific community. Several studies have focused on identifying drivers of AMU in dairy cattle. Results show that on farm level, potential risk factors relate to farm characteristics such as herd size (Krogh et al., 2020; Lardé et al., 2021), milk yield (Saini et al., 2012; Gussmann et al., 2018) and somatic cell count (SCC) (Gussmann et al., 2018). Management-related associations with AMU were found for calf-rearing practices and include nutritional aspects, housing and flooring type, cleaning habits and biosecurity (Holstege et al., 2018; Mallioris et al., 2022; Uyama et al., 2022). Other important influencing factors are socio-economic and behavioral aspects like veterinary advice, the producer's personal experience, awareness of AMR, external societal pressure as well as clinical signs and animal welfare, drug attributes like the withholding period and economic aspects, among others (McDougall et al., 2017; Ekakoro et al., 2018; Doyle et al., 2022; Farrell et al., 2023;). At the animal level, identified risk factors are breed in veal calf production (Lava et al., 2016), and sex (Diana et al., 2021). More generally, breed differences in susceptibility to disease are recognized (Kelm et al., 2001) and as such might correlate with AMU.

However, the association between AMU and dairy cow management practices in Swiss dairy farms remains largely unclear and may provide further insights for AMU reduction.

Tie stalls remain a widespread housing system accounting for approximatively 73%, 41% and 40% of Canadian, American and Swiss dairy farms, respectively (USDA, 2018; CDIC, 2020; Swiss Federal Statistical Office, 2016, as cited by Bernhard et al., 2020). Studies investigating drivers of AMU specifically in tie stalls are scarce, but hint to differences between housing systems (Spycher et al., 2002; Van Aken et al., 2022).

The objectives of this study were to estimate AMU in dairy cows on Swiss tie stall farms one year before farm enrolment, using data from the recently launched national reporting system, and to identify management-related factors associated with AMU in dairy cows in tie stall farms. We hypothesized that herd characteristics and management are associated with the antimicrobial TI.

MATERIALS AND METHODS

Study Design and Ethic Statement

A cross-sectional, retrospective observational study was conducted in the frame of a larger investigation on AMU and AMR in Swiss tie stall farms. Ethical approval for animal experimentation was obtained from all cantons (political districts) of Switzerland (n = 26, authorization no. BE76/2021).

Farm Recruitment

Eligible farmers needed to be milk producers and house lactating cows in tie stall barns, with each cow on an individual stand. To recruit farmers, newspaper articles were published in the agricultural press between October 2021 and March 2022. In addition, a short notice was released in specific cattle magazines (CH-braunvieh, Holstein news Switzerland and Swissherdbook). Invitation letters for participation were sent through the Swiss tie stall association to its members alongside a short publication on the respective official webpage. Furthermore, farmers were recruited via 11 agricultural schools located in the cantons of Argovia, Bern, Basel-Country, Fribourg, Grisons, Lucerne, St. Gallen, Solothurn, Thurgovia and Zurich. Registration for study participation was either done through signing up on a project-specific webpage or by contacting the first author by telephone or email. All farmers participated voluntarily and were not remunerated.

Data Collection

Questionnaire. A questionnaire on general farm characteristics, herd management and health management practices was developed in German, then checked for accuracy and relevance with farmers (n = 2). For French-speaking farmers, the questionnaire was translated into French. One veterinarian (first author) conducted the questionnaire-based interview with the farmers during farm visits to assess farm management characteristics. Answers were recorded on paper, then entered into a Microsoft Access datasheet (version 2016, Microsoft Corporation, Redmond, WA, USA) and exported to Microsoft Excel (version 2016, Microsoft Corporation, Redmond, WA, USA) for further handling, subsequently.

AMU Data. Written informed consent was obtained from farmers and their respective veterinarians to request from the IS ABV their respective AMU data for research purposes. Veterinarians are obliged by law to submit information on prescriptions containing antimicrobials to a government-driven database via the 'IS ABV web tool' or automatically via the practitioners' accounting software. This data includes detailed information on animal species, production category (heifers, suckler cows, piglets, etc.), administration route, therapeutic product, dosage or number of units, concerned organ(s), and diagnosis, among others. Data is stored by the Food Safety and Veterinary Office FSVO for each practitioner and animal owner. However, data accessibility for research purposes is strictly limited to a subset of the original data and personal data of farmers and veterinarians may not be published. Therefore, the data set available for the present study does not contain the full information. Notably, commercial names of therapeutic products were not available for this study. Records of AMU of participating farms were obtained from the IS ABV (BLV, 2023).

Data Analyses.

Questionnaire Data Descriptive statistics of farm characteristics and management practices data was performed using NCSS® (version 22.0.3, NCSS, LLC, Kaysville, UT, USA) and Microsoft Excel (version 2016, Microsoft Corporation, Redmond, WA, USA). Categorical variables included for analysis were predominant dairy breed, production system (e.g., organic), vaccinations, culturing milk sample before mastitis treatment, presence and type of other livestock species, seasonal movement for summer grazing to mountain pastures, cow replacement strategy, main bedding type, and use of hygienic powders on the lying area (i.e., chalk). Numerical variables were total herd size (cows, heifers, calves and bull if present), annual average SCC, annual average farm-level milk yield, and average number of days of access to outdoor paddock per month during winter. The annual average SCC was calculated as the mean of the yield-adjusted herd average SCC of the 11 monthly test days before the visit. These tests are made in the frame of milk performance assessments, where all cows are evaluated at the individual level. Seasonal alpine pasturing was considered for either cows, heifers, or both. For the descriptive statistics of variables with multiple-choice options (i.e., vaccines), all answers were considered and presented as the proportion of responses for each category. Finally, the data was checked for implausible values (entry errors) and outliers. Such values in the questionnaire were removed from the data set.

AMU Data The following exclusion criteria were successively applied during the data cleaning process: Raw data set provided by IS ABV (total entries n = 34,765), data outlying the one year period prior farm visit (remaining entries n = 15,175); 'prescription type': prescriptions dispensed on stock, oral group therapy, non-oral group therapy (n = 11,973); 'species': pigs, sheep, goats, other (n = 11,851); 'production category': 'rearing calves', 'rearing heifers', 'veal calves', 'beef cattle', 'suckler cows', 'suckler calves', 'other (heifers)' (n = 7,714). Remaining records with no written consent from the farm veterinarian were excluded in the last step (n = 7,619). Only prescriptions containing antimicrobials one year before the date of farm visit and belonging to the categories 'dairy cows' and 'individual therapy' remained in the data set.

Treatment incidences for each treatment and administration route were calculated using the DDD methodology as suggested by EMA (EMA 2013; EMA 2016) and aggregated on farm level. For each farm, TI was expressed as corrected TI per animal-year, i.e., total TI of all treatments of all treated cows was divided by the number of all cows (treated and non-treated). Overall treatment incidence of treated cows, grouped per a) administration route and b) antimicrobial class is shown in supplementary Table S1 (data will be published after peer-review process).

For TI calculation, only treatments with therapeutic products containing antimicrobials were processed. Prescriptions for parenteral treatments containing treatments with 2 antimicrobial drugs were counted as 2 treatments. Where available, DDD values for combination products were used. First, treatments were attributed to administration routes (parenteral, intramammary and intrauterine). For parenteral administrations, the amount of used antimicrobials (i.e., active substances in mg) was extracted from IS ABV for each treatment. The formula used for calculation for the parenteral route (TI_{SYS}) is provided in formula 1. For intramammary and intrauterine routes, amounts of used antimicrobials were measured as number of injectors and of units of intrauterine products (i.e., tablets), respectively. Calculation of intramammary products for lactating and dry cows (TI_{IMM}, TI_{DRY}) was performed using a modified formula used by Pucken et al. (2021) and is provided in formula 2 and 3, respectively. For intrauterine products (TI_{IU}), calculation was performed with formula 4. Since data only include treatments within exactly one year before the date of farm visit, observation period was one year throughout. The unit of TI is "treatment days per cow-year" for all admistration routes and overall TI.

Formula 1)

$$TI_{SYS} = \frac{total\ amount\ of\ drug\ administered\left(mg\right)}{DDD\left(\frac{mg}{kg}\right) \times no.\ of\ cows\ present \times std.\ wt.\left(kg\right) \times obs.\ period\left(d\right)} \times 365\,\mathrm{d};$$

Formula 2)

$$TI_{DRY} = \frac{total\ no.\ of\ intramammary\ injectors\ during\ lactation}{DDD\left(\frac{UD}{teat}\right) \times no.\ of\ cows\ present \times obs.\ period\left(d\right)} \times 365\,\mathrm{d};$$

Formula 3)

$$TI_{DRY} = \frac{total\ no.\ of\ intramammary\ injectors\ for\ dry\ off}{DCD\left(\frac{UD}{udder}\right) \times no.\ of\ cows\ present \times obs.\ period\left(d\right)} \times 365\,\mathrm{d};$$

Formula 4)

$$TI_{IU} = \frac{total\ no.\ of\ intrauterine\ tablets}{DDD\left(\frac{IUP}{animal}\right) \times no.\ of\ cows\ present \times obs.\ period\left(d\right)} \times 365\ \mathrm{d}.$$

Values of DDD for animals were extracted from European recommendations for the production category 'dairy cows' and their respective administration routes (EMA, 2016). Regarding intramammary formulations for use during lactation, entries have been handled as 1 injector per cow per day. The unit of DDD is unit dose per teat (UD/teat). For dry cow therapy, the unit of the defined course dose (DCD) is unit dose per udder (UD/udder), corresponding to 4 injectors per cow. Missing official DCD values for dry-off products were set as 4 UD/udder. If the total amount of injectors prescribed for dry-off was less than 4, the given amount was corrected to 4 injectors, handling them as entry errors since selective dry cow therapy at the teat level is not a common practice in Switzerland. Cows are typically dried-off depending on their individual somatic cell count value obtained generally from a composite sample from all 4 quarters during the monthly milk performance assessment (Bucher and Bleul, 2019). The DCD and UD are reported in the results as DDD. For intrauterine treatments, the unit of the DDD is intrauterine product per animal (IUP/animal), assuming use of 1 intrauterine product per cow per day.

In the case of intramammary products for mastitis that could not be extracted from IS ABV in quantities of injectors but in ml, the UD/teat was defined following the dose recommendations from the Swiss Compendium of Veterinary Medicinal Products (Swiss Compendium of Veterinary Medicinal Products, 2023). This applied for Gentamicin/Procaine penicillin, for which the attributed DDD value was 1 UD/teat per 25 mL, since 25 mL are necessary to treat 1 affected quarter.

The number of cows on each farm is the total number of adult dairy cows (lactating and dry cows) as recorded through the questionnaire. The standard weight (std. wt.) applied and defined by EMA for adult dairy cows was 500 kg (EMA, 2013).

Statistical Analyses

A generalized linear model (GLM) with gamma distribution was constructed to identify potential risk factors of the overall TI, which showed a right skewed distribution. Statistical analysis was performed using R version 4.2.0 (https://www.r-project.org/). To ensure compliance with the model's requirements and compare different models and link functions, we transformed the outcome by adding constant value of 1 to each observation. A gamma distribution was fitted to the transformed outcome variable with the estimated parameters of shape = 2.53 and rate = 0.39 (Figure S1, data will be published after peer review process). The goodness of fit was evaluated using the Kolmogorov-Smirnov test against a gamma distribution, which yielded a P-value $= 0.58$, showing that the chosen gamma distribution provided a good fit to the distribution of the overall TI. The distribution was fitted using the package fitdistrplus (Delignette-Muller and Dutang, 2015).

Herd size, dairy breed (Brown Swiss, Holstein Friesian, Swiss Fleckvieh, Simmental, Jersey, other), annual average farm-level milk yield [L], hygienic powder (yes, no), vaccinations (yes, no), other livestock (yes, no), livestock type (none, pig, poultry, goat, sheep, other), main bedding (straw bed, rubber mat, other), production system (conventional, organic, IP- Suisse), annual average SCC [cells/ml], average days on outdoor paddock (winter), summer grazing (yes, no) and cow replacement strategy (own calf rearing, external calf acquisition) were chosen as independent variables. Annual average SCC had 27 missing values (NA = 27), the annual average farm-level milk yield had 2 missing values (NA = 2) and the average days outside had one missing value (NA = 1). The latter 2 were obtained through the farmers' estimation when conducting the questionnaire. After imputation using the median, missing values were replaced. Herd size, annual average farm-level milk yield, and annual average SCC were normalized with a z-transformation. Due to the limited sample sizes in certain breeds, we combined all breeds except Brown Swiss and Holstein Friesian cattle into a single group. Similarly, we grouped less common 'livestock type' values, resulting in the following categories: none, pig, poultry, and other/mix. Numerical variables were tested for collinearity using the Spearman rank correlation test and none exhibited a correlation higher than $|0.75|$. Independent variables were assessed for univariable association with the dependent variable and only those exhibiting a $P < 0.20$ were included in the full generalized linear model. Interaction between variables were not considered because of the moderate number of samples within groups. The model was built with backward elimination, where variables with P-values >0.05 were removed if a likelihood ratio test after removal did not yield significance. For the final model we employed a generalized linear model (GLM) with gamma distribution and utilized the identity link function since it had a superior AIC/BIC score compared with the log link function. The residuals were analyzed using the DHARMa package (Hartig, 2022) with 1000 simulations and were found to be normally distributed (Komlogorov-Sminorv test $P > 0.05$). There was no dispersion of the fitted and simulated residuals (DHARMa dispersion test $P > 0.05$) and no outliers were detected. The variance inflation factor (VIF) values were calculated and ranged from 1.08 to 1.10, indicating low multicollinearity in the model.

RESULTS

Descriptive Statistics

Herds Characteristics and Management Practices. A total of 280 Swiss dairy farms were visited between November 2021 and January 2023. Data of 58 farms (21%) were excluded from analyses due to missing consent from the farm veterinarian to obtain IS ABV prescription data, resulting in missing AMU data. One farm was excluded due to an extremely unlikely value in the annual average SCC. Farms included in the analyses (n = 221) were located in 20 different cantons across Switzerland (Figure 1). Table 1 and Table 2 provide an overview of the descriptive results regarding herds characteristics and management practices, respectively.

AMU Data. For final analysis, a total of 5,424 prescriptions containing a total of 7,619 treatments were available for the 221 enrolled farms. Number of prescriptions and number of farms using the respective antimicrobial drugs are indicated alongside estimates of treatment incidences (Table 3). A total of 37 different antimicrobial drugs (including combinations) were reported, and their use ranged from high (procaine penicillin: 25.1% of prescriptions and on 94.1% of all farms) to low (tulathromycin: 0.03% used only on 1 farm; Table 3).

Mean herd level TI was 5.46 DDD/cow-year (±4.10; range: 0.02–17.98 DDD/cow-year). Treatment incidences attributed to each administration route and antimicrobial class are presented in Table 4. Overall, the TI was highest for intramammary formulations during lactation (TI_{IMM} mean: 3.24; ± 3.16; range: 0–14.89 DDD/cow-year) and penicillins (mean: 2.31; ± 1.99; range: 0–9.56 DDD/cow-year) and was lowest for dry-off formulations (TI_{DRY} mean: 0.44; ± 0.49; range: 0–2.14 DDD/cow-year) and phenicols (mean: 0.002; ± 0.01; range: 0–0.13 DDD/cow-year) (Table 4).

Regression Statistical Analysis. A total of 5 herd factors were significantly associated with the TI in the final model (Table 5). Farm level milk yield showed a univariate association with TI but was not retained in the final model. Organic production and herd size were negatively associated with TI (estimate −2.16, $P = 0.004$; −0.81, $P < 0.001$, respectively). Predominant breeds (Brown Swiss and Holstein Friesian) were associated with increased TI compared with other breeds (estimate 1.56, $P = 0.007$ and 1.42, $P = 0.046$, respectively). The use of hygienic powders on the lying area (estimate 1.10, $P = 0.043$) was positively associated with TI.

Table 1. Herds characteristics of 221 Swiss tie stall dairy farms participating in a study to assess risk factors for antimicrobial use

Variable	Farms (n) (%)
Production system	
Conventional	129/221 (58)
IP-Suisse	72/221 (33)
Organic	20/221 (9)
Dairy breed	
Brown Swiss	112/221 (51)
Holstein Friesian	51/221 (23)
Other	58/221 (26)
Other livestock	
None	76/221 (34)
Poultry	29/221 (13)
Pig	17/221 (8)
Other/mix	99/221 (45)
Herd size	
Mean	23
SD	9.91
Min-Max	6–60
Annual farm-level milk yield [L]	
Mean	154,988
SD	82,406
Min-Max	40,000–480,000
Annual average SCC [cells/ml]	
Mean	144,229
SD	85,180
Min-Max	17,000–675,000

DISCUSSION

We identified 5 herd factors in tie stall farms that showed a significant association with TI. To our knowledge, this study is the first to use AMU data from

Table 2. Management practices of 221 Swiss tie stall dairy farms participating in a study to assess risk factors for antimicrobial use

Variable	Farms (n) (%)
Milk sample for pathogen detection before treatment	
Yes	187/221 (85)
No	34/221 (15)
Vaccines	
Yes	61/221 (28)
1	44/58 (76)
^{3} 2 (range)	14/58 (24; 2–4)
No	160/221 (72)
Vaccine type	
Calf management (diarrhea, respiratory diseases)	28/58 (48)
Lungworm disease	14/58 (24)
Pinkeye	10/58 (17)
Blackleg disease	9/58 (16)
Ringworm disease	7/58 (12)
Mastitis	3/58 (5)
Digital dermatitis	1/58 (2)
Cow replacement strategy	
Own calf rearing	183/221 (83)
External calf acquisition	38/221 (17)
Bedding	
Rubber mats	158/221 (71)
Strawbeds	51/221 (23)
Other	12/221 (5)
Hygienic powder	
Yes	149/221 (67)
No	72/221 (33)
Summer grazing	
Yes	165/221 (75)
No	56/221 (25)
Monthly access to outdoor paddock [days]	
Mean	15.6
SD	5.31
Range	2.5–30

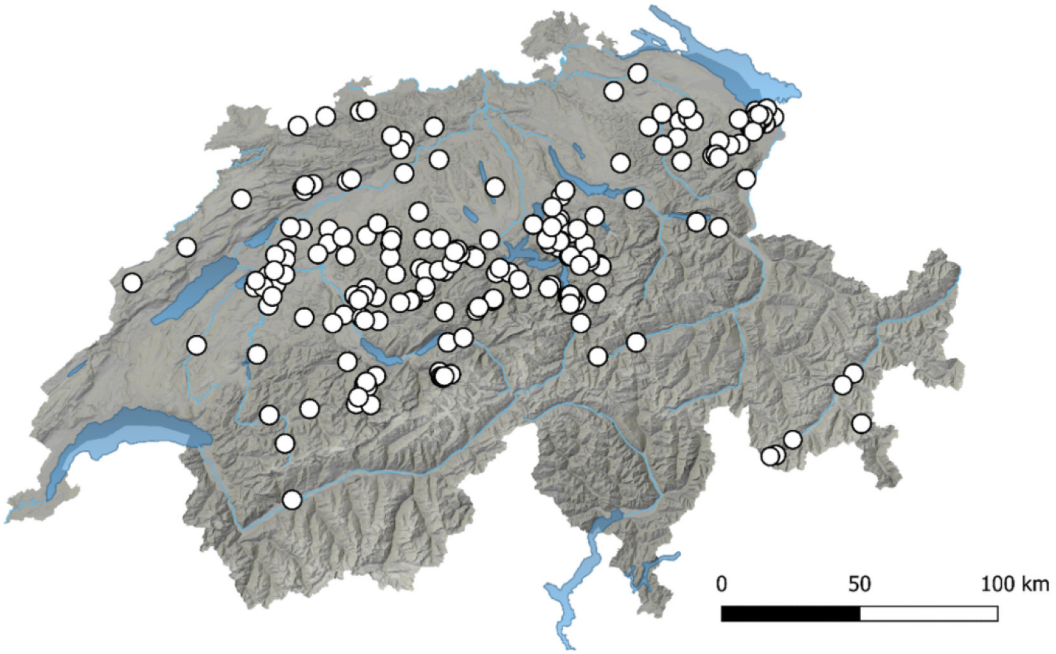

Figure 1. Location of the 221 included study farms (white dots) across 20 different cantons of Switzerland.

Table 3. Number prescriptions, number of farms, and estimates of treatment incidence ([TI], mean, standard deviation [SD], median and range) using defined daily doses (DDD) per cow-year of 7,619 antimicrobial treatments on 221 Swiss dairy farms from 2020 to 2022 (EMA, 2016)

			TI			
Antimicrobial class	Prescriptions (n)	Farms (n)	Mean		Median	Range
Antimicrobial drug	(%)[1]	(%)[2]	(DDD/cow-year)	SD	(DDD/cow-year)	(DDD/cow-year)
Penicillins						
Procaine penicillin	1913 (25.11)	208 (94.12)	3.41	4.02	2.00	0.20–56
Cloxacillin	490 (6.43)	126 (57.01)	1.39	1.06	1.00	1–12
Penethamate	372 (4.88)	111 (50.23)	4.22	3.87	3.15	0.16–28.36
Amoxicillin	265 (3.49)	106 (48.96)	7.29	6.93	6.00	0.20–64
Penicillin G	49 (0.64)	30 (13.58)	2.93	6.74	0.86	0.09–34.29
Benzathine benzylpenicillin	45 (0.59)	22 (9.95)	1.91	1.33	1.00	1–6.21
Nafcilline	43 (0.56)	19 (8.6)	1.12	0.50	1.00	1–4
Aminoglycosides						
Gentamicin	656 (8.61)	157 (71.04)	4.02	3.61	3.00	0.20–40
Neomycin	567 (7.44)	131 (59.28)	2.25	2.45	1.00	1–16
Kanamycin	274 (3.6)	107 (47.06)	7.93	5.68	5.00	1–40
Dihydrostreptomycin	248 (3.26)	100 (45.25)	1.55	0.93	1.37	0.25–7
Spectinomycin (Lincomycin combined)	4 (0.05)	3 (1.36)	0.04	0.01	0.04	0.03–0.04
Tetracyclines						
Tetracycline	548 (7.19)	157 (71.04)	4.38	2.17	4.00	1–20
Oxytetracycline	511 (6.71)	146 (66.06)	2.52	1.63	2.15	0.18–15.38
Doxycycline	3 (0.04)	3 (1.36)	4.70	3.99	7.00	0.09–7
Cephalosporines						
1st Generation						
Cephapirin	345 (4.53)	115 (52.04)	1.17	0.66	1.00	1–8
Cephalexin	265 (3.48)	104 (47.06)	8.08	5.72	5.00	1–40
3rd Generation[a]						
Ceftiofur	86 (1.13)	32 (14.48)	3.78	2.26	3.50	1.20–11.50
Cefoperazone	57 (0.75)	25 (11.31)	6.58	6.20	5.00	1–36
Ceftiofur LA	17 (0.22)	13 (5.88)	9.09	2.57	10.00	0.60–12
4th Generation[a]						
Cefquinome	76 (1.00)	33 (14.93)	4.20	2.88	4.00	0.93–18
Sulfonamides						
Sulfadoxine (Trimethoprim combined)	192 (2.52)	84 (38.01)	1.54	0.72	1.43	0.03–5.71
Sulfamethoxazole (Trimethoprim combined)	44 (0.58)	15 (6.79)	1.55	0.70	1.33	0.40–5.33
Sulfaguanidine	36 (0.47)	30 (13.57)	0.45	0.33	0.31	0–1.18
Sulfamidine	31 (0.41)	23 (10.41)	0.30	0.24	0.15	0.08–0.87
Sulfamethoxypyridazine	13 (0.17)	9 (4.07)	0.46	0.08	0.47	0.31–0.59
Diaminopyrimidines						
Trimethoprim (Sulfonamides combined)	236 (3.10)	97 (43.89)	1.56	0.73	1.43	0.03–5.71
Fluoroquinolones[a]						
Marbofloxacin	70 (0.92)	25 (11.31)	1.64	0.91	1.41	0.28–5
Danofloxacin	37 (0.49)	12 (5.43)	2.27	2.80	1.14	0.38–11.75
Enrofloxacin	22 (0.29)	12 (5.43)	1.15	0.99	0.95	0,07–3.81
Macrolides[a]						
Tylosin	48 (0.63)	24 (10.86)	1.48	0.94	1.08	0.62–4.46
Spiramycin	21 (0.28)	14 (6.33)	2.00	1.81	0.89	0.18–5
Tulathromycin	2 (0.03)	1 (0.45)	5.00	1.67	5.00	3.33–6.67
Lincosamides						
Lincomycin	24 (0.32)	14 (6.33)	6.46	3.64	5.50	1–16
Lincomycin (Spectinomycin combined)	4 (0.05)	3 (1.36)	0.03	0	0.03	0.02–0.03
Phenicols						
Florfenicol	5 (0.07)	5 (2.26)	2.28	1.81	2.31	0.46–4.62

[a] Highest priority critically important antimicrobials (HPCIAs) based on the importance to human medicine according to the classification of the World Health Organization (WHO, 2018).

[1] Proportion within prescriptions.

[2] Proportion within farms.

the newly established Swiss national antimicrobial prescription reporting system IS ABV.

Estimating AMU

The mean estimated TI of 5.46 DDD/cow-year in the participating farms is in line with results from other studies on AMU quantification in dairy herds. In the

Table 4. Herd-level estimates of treatment incidence [TI] in defined daily doses (DDD) per cow-year (mean, standard deviation [SD]) for each administration route and antimicrobial class on 221 Swiss dairy farms within a 1-year period between 2020 and 2022

	TI			
	Mean		Median	Range
	(DDD/cow-year)	SD	(DDD/cow-year)	(DDD/cow-year)
Administration route				
Parenteral	1.21	1.07	0.95	0–5.94
IMM during lactation	3.24	3.16	2.14	0–14.89
Dry-off	0.44	0.49	0.31	0–2.14
Intrauterine	0.57	0.61	0.40	0–3.83
Total	5.46	4.10	4.30	0.02–17.98
Antimicrobial class				
Aminoglycosides	1.37	1.37	0.89	0–7.22
Diaminopyrimidines	0.08	0.14	0	0–1.06
Fluoroquinolones	0.04	0.15	0	0–1.52
Lincosamides	0.03	0.12	0	0–0.90
Macrolides	0.02	0.07	0	0–0.59
Penicillins	2.31	1.99	1.81	0–9.56
Phenicols	0.00	0.01	0	0–0.13
Sulfonamides	0.08	0.14	0	0–1.05
Tetracyclines	0.76	0.76	0.56	0–5.92
1st generation cephalosporines	0.54	0.88	0.18	0–5.83
3rd generation cephalosporines	0.15	0.39	0	0–2.92
4th generation cephalosporines	0.06	0.22	0	0–1.75

Netherlands, Kuipers et al. (2016) reported an average Animal Defined Daily Dose (ADDD) of 5.86 DDD/cow-year. Reported ADDD values for dairy herds in Wisconsin, USA and in Canada were 5.43 (Pol and Ruegg; 2007) and 5.24 (Saini et al., 2012), respectively. A higher TI was reported in Belgium (7.58 DDD/cow-year) (Stevens et al., 2016; results from the latter 2 studies were adjusted from 1000 cow-days to cow-year). Slightly lower TI was reported for British dairy farms, where the mean estimated DDDvet/cow-year was 4.60 (Hyde et al., 2017). The latter study did not include dry cow therapy in the DDDvet calculation, possibly contributing to the lower result. However, direct comparisons between these results are hindered by discrepancies in data collection methodologies, different metrics used to estimate AMU data and different standard weights for dairy cows between countries. For instance, Kuipers et al. (2016) screened veterinary sales invoices, while Saini et al. (2012) and Stevens et al. (2016) collected data by analyzing empty drug containers stored on farms. Pol and Ruegg (2007) extracted information on AMU from survey responses, while Hyde et al. (2017) used mixed methodologies by using data from electronic farm records and veterinary

Table 5. Results of the final generalized linear model with gamma distribution showing associations between herd characteristics and management practices on farm level and the treatment incidence (TI, measured in DDD/cow-year), standard error [SE], probability [Pr] and confidence interval [CI], based on data collected in 221 Swiss dairies within a 1-year period

Predictor	Estimate	SE[1]	t-value	Pr(>|t|)	CI (2.5/97.5%)	
Intercept	4.91	0.58	8.44	<0.001	3.77	6.06
Production system						
Organic	−2.16	0.74	−2.91	0.004	−3.62	−0.70
IP-Suisse	−0.34	0.57	−0.59	0.556	−1.45	0.78
Conventional	Referent					
Herd size	−0.81	0.21	−3.80	<0.001	−1.23	−0.39
Dairy breed						
Brown Swiss	1.56	0.57	2.74	0.007	0.45	2.68
Holstein Friesian	1.42	0.71	2.00	0.046	0.03	2.82
Other	Referent					
Hygienic powder						
Yes	1.10	0.54	2.03	0.043	0.04	2.17
No	Referent					

[1] Residual degrees of freedom = 214.

sales data. Different data sources vary in their availability, level of detail and record methodology between and within farms and veterinary practices. As stated by Pucken et al. (2021), which compared 3 different data sources, "none of the methods was able to collect the integral antimicrobial consumption in participating farms." Different methods for AMU quantification present an additional challenge for comparisons since not all studies estimated TI based on EMA standards. Saini et al. (2012) and Stevens et al. (2016), for instance, based their calculations on the respective national compendium for veterinary products, while Pol and Ruegg (2007) determined DDD according to approved dosing and daily treatment frequency of antimicrobials outlined in the FDA Center for Veterinary Medicine Green Book. Only the scientists from the British study employed ESVAC/EMA standards (Hyde et al., 2017). Differences in the used standard weights is another source of inter-study variation. In the Netherlands, Belgium and Canada, an average cow live weight of 600 kg was assumed for calculations (Saini et al., 2012; Kuipers et al., 2016; Stevens et al., 2016), while the average cow weight in Wisconsin was set slightly higher (680 kg; Pol and Ruegg, 2007). The lowest standard cow weight was used in the UK (425 kg; Hyde et al., 2017). Using a lower standard weight than the actual weight for which antimicrobial dosage was calculated might overestimate the TI on farms, and vice versa. The defined standard weight for dairy cows assumed by EMA might have been lower compared with the Swiss herd average (Menéndez-González et al., 2010), resulting in potential overestimation of the TI in our study.

Since 2019, Swiss veterinarians have been obliged to submit all records of prescriptions containing antimicrobials to the IS ABV. We attempted to minimize bias resulting from the concurrent use of multiple record methodologies by using IS ABV data only. Nevertheless, possible limitations of IS ABV may be attributable to entry errors from veterinarians. We also showed that EMA's quantification methodology may be applied to data from the IS ABV.

Antimicrobial Classes

Among the 7,619 treatments obtained from the 221 farms, penicillins (41.7% of treatments, TI: 2.31 DDD/cow-year) followed by aminoglycosides (23%, 1.37 DDD/cow-year) and tetracyclines (13.9%, 0.76 DDD/cow-year) were used most commonly. In this regard, the results of this study were similar to those of a previous nationwide study in dairy farms in Switzerland, where penicillins (46%), aminoglycosides (13%) and tetracyclines (10%) were among the most consumed antimicrobials, based on weight of active substances data collected from farm treatment records (Menéndez-González et al., 2010). The similarity between these results suggests that the Swiss national reporting system reports AMU accurately. The latest published IS ABV annual report (IS ABV, 2022) shows that penicillins (35.5%), followed by sulfonamides (25.9%), tetracyclines (20.9%) and aminoglycosides (9%) were prescribed most in cattle. These results are not directly comparable to ours because they also encompass other types of cattle (i.e., veal calves and beef cattle). For the latter production types, it is known that other antimicrobials like tetracyclines and macrolides are among the most commonly used (Lava et al., 2016; Becker et al., 2021; Diana et al., 2021). At the Canadian national level, a higher TI of cephalosporines (1st and 3rd generation; 1.11 ADD/cow-year) was reported, followed by penicillins (0.93 ADD/cow-year), linco- spectinomycin (0.85 ADD/cow-year), penicillin combinations (0.80 ADD/cow-year) and tetracyclines (0.67 ADD/cow-year) (Saini et al., 2012). In a Belgian study, 4th-generation cephalosporines had the highest TI (1.82 DDDA/cow-year), followed by penicillins (1.35 DDDA/cow-year) and 3rd-generation cephalosporines (1.08 DDDA/cow-year), with tetracyclines representing a relatively low incidence (0.17 DDDA/cow-year) (Stevens et al., 2016). In comparison, our estimated TI of 0.75 DDD/cow-year for cephalosporins (1st, 3rd and 4th generation) was relatively low. This could be attributed to national guidelines established by StAR, to use 3rd and 4th generation cephalosporines only in exceptional cases, after conducting an antibiogram and where no alternative non-critical antimicrobial is predicted to be efficacious (BLV, 2022). Overall, highest priority critically important antimicrobials (3rd and 4th-generation cephalosporins, fluoroquinolones, and macrolides) accounted for a total of only 5.7% of all treatments in dairy cows (TI: 0.27 DDD/cow-year), which indicates an overall responsible use in Swiss dairy farms. However, as stated above, discrepancies in data collection methodologies, standard weights, and standard daily doses used may lead to results which are difficult to compare. To improve surveillance and stewardship programs, harmonizing guidelines to record and report AMU in veterinary medicine should be considered.

Administration Routes

In the present study, the mean estimated TI was highest for intramammary products during lactation ($TI_{IMM} = 3.24, \pm 3.16$) and lowest for dry-off products ($TI_{DRY} = 0.44, \pm 0.49$; Table 4).These findings may suggest that the use of antimicrobials in Swiss dairy cows in tie stalls is predominantly associated with mastitis during lactation, and that antimicrobials for dry-cow therapy were used at a lower frequency. However, this is affected by the metrics used, and using the number of intramammary injectors or the mass of active substance might have resulted in a different ranking of AMU estimates. Switzerland ranks as the highest antimicrobial user for intramammary products among all European countries (ESVAC, 2021). In contrast, concerning dry-off treatment, dispensing antimicrobials for prophylactic purposes on stock is no longer permitted in Switzerland (Veterinary Medicines Ordinance, 2016), therefore dry-off injectors may only be applied as individual therapy after thorough diagnostic investigation (e.g., milk culture or SCC) to justify treatment (BLV, 2022). This is due to new legal requirements established in 2016 (Veterinary Medicines Ordinance, 2016). Altogether, this might explain the overall low TI for dry-off therapies found in our study.

The high estimated $\mathrm{TI}_{\mathrm{IMM}}$ suggests that future research and national guidelines should focus on improving udder health and related antimicrobial stewardship specifically during lactation. A reduction of AMU could be achieved by implementing udder-specific health strategies like teat cleaning before milking, among others (Gerber et al., 2021). Mastitis vaccines, in use on a small number of farms in the present study, should not be regarded as the definitive solution, since they do not affect the incidence of clinical or subclinical mastitis per se, but mitigate the course of the infection (Bradley et al., 2015). We suggest to implement a combination of improved teat hygiene and vaccination if deemed appropriate as part of a herd-specific udder-health management plan. Similar to our study, in the US, Pol and Ruegg (2007) reported a higher AMU rate for clinical mastitis (2.02 DDD/cow-year) than for dry-cow therapy (1.56 DDD/cow-year), as also observed on Canadian dairy farms (Saini et al., 2012). In other studies, lower TI for mastitis and higher TI for dry-cow therapy were reported. Kuipers et al. (2016) found a mean ADDD per cow-year for mastitis treatments of 1.45 and for dry-cow therapy 2.57. It is important to note that latter authors also included the parenteral route for mastitis treatments, but those accounted only for 5% of TI. Stevens et al. (2016) reported a TI for intramammary treatment for (sub)clinical mastitis and dry-off of 2.30 and 2.51, respectively. However, direct comparisons between results regarding udder-specific TI should be approached with prudence, since there are variations in the assigned defined daily doses especially for dry-cow therapy. Specifically, in a Canadian study (Saini et al., 2012) one DDD was designated for blanket dry-cow therapy, whereas in studies from the Netherlands (Kuipers et al.; 2016), Belgium (Stevens et al.; 2016) and Switzerland (Pucken et al., 2021) 4 daily doses were assigned. Furthermore, other countries will likely experience long-lasting reduction of AMU attributed to dry-cow therapy due to the new European Union directive 2019/6 of veterinary medicinal products, which prohibits the systematic administration of dry-cow injectors in the herd since January 28th of 2022 (EU, 2018).

Management-related Associations

In the present study, the predominant breed in the herd was one of the factors associated with AMU. Furthermore, mastitis was the major reason for AMU. It is well established that genetic factors and selective breeding of dairy cows significantly influence the susceptibility or resistance to mastitis (Weigel and Shook, 2018). This genetic predisposition is more pronounced in purebred or crossbred high-yielding cattle, particularly Holstein Friesian cattle, in contrast to breeds that exhibit a moderate milk yield (Shaheen et al., 2016). In the US, Holstein Friesian cattle have experienced a substantial increase in milk production, with Brown Swiss emerging as the breed with the closest productivity levels (Dechow et al., 2007). Further, Jersey cattle had a lower incidence rate of clinical mastitis than Holstein Friesian cattle (Washburn et al., 2002). This might explain the higher TI seen in herds mainly composed of Brown Swiss and Holstein Friesian when compared with the other breeds.

Herds in organic production showed a lower TI when compared with conventional herds. Other studies revealed similar findings. For instance, Krogh et al. (2020) found the TI for cows on conventional farms to be between 2.2 and 2.9 times higher, depending on herd size, when compared with organic herds. In Switzerland, cows in organic production must not be treated with antimicrobials > 3 times per year, and critically important drugs are not allowed for initial treatments (BioSuisse, 2016). Our results suggest that restricting antimicrobial use by governmental regulations may be an effective way to tackle AMU on dairy farms. However, decision-making on treatments is influenced by diverse factors. Variations in treatment strategies on dairy farms are not only related to farm conditions – including the production type – but also to interactions between farmers and veterinarians (Poizat et al., 2017; Ekakoro et al., 2018; Doyle et al., 2022).

We found that herd size was negatively associated with TI, which was unexpected when comparing to other studies, in which a higher herd size was a risk factor for higher AMU (Krogh et al., 2020; Lardé et al., 2021). However, it is important to note that it was not possible to determine the housing system in those 2 studies, thus making direct comparisons difficult. In another study, no association between herd size and housing system with the overall AMU was seen (Saini et al., 2012). Among tie stall farms, those with a housing capacity for larger numbers of animals may have been constructed more recently, providing modern infrastructure and potentially facilitating better health management practices. Larger farms may rather be managed by professionals than smaller farms. This may explain why larger herds in our study showed an overall lower TI when compared with smaller ones. The observation of potential better management in larger herds was reported in the swine industry (Gardner et al., 2002; Van der Wolf et al., 2001; Laanen et al., 2013). The findings of our study suggest that future research could emphasize on small-scale dairy companies to investigate further possible starting points for AMU reduction on these farms.

Consistent vaccination could be considered as an efficient strategy for disease control, potentially decreasing AMU in livestock farming (Hosain et al., 2021). However, it was not associated with AMU in the present study. The high proportion of the total TI attributable to TI_{IMM} and TI_{DRY}, on which vaccination may have a limited impact, may have contributed to this finding. Another possible explanation is the fact that the most common vaccination type was aimed at preventing calf diseases, therefore minimally impacting AMU in lactating cows.

The use of hygienic powders (i.e., chalk) on the lying area was a frequent management practice (67%) and was associated with an increase in TI. This unexpected finding is probably a reverse causality, as farmers experiencing higher TI due to udder health issues may use hygienic powders in an attempt to improve bedding hygiene. The phenomenon of reverse causality was also reported in veal calf operations, where higher mortality was associated with better hygiene practices (Schnyder et al., 2019).

Study Limitations and Strengths

Selection bias of study participants may exist as farmers with good management practices and potentially low AMU could have had a higher likelihood of participating. Nearly one quarter of the farms had to be excluded due to missing consent of their veterinarian to analyze AMU data thus reducing sample size. We cannot exclude that high-users and/or users of above-average amounts of critically important antimicrobials are underrepresented in this study population. The selection bias attributable to the farm visits being conducted in German or French is likely minimal, considering that only 0.9% of dairy producers are located in the Italian-speaking canton of Ticino. Jersey dairy farms may have an underestimated TI through the calculation method with a standard weight. Also, TI estimation may be subjected to bias since antimicrobials prescribed on stock were excluded as they cannot be attributed to dairy cows with certainty or may not have been used within the time frame of this study. In general, the amount of active substances prescribed on stock was approximatively 30% for cattle in 2021 (IS ABV, 2022). On the other hand, by choosing this analytical procedure, we can assure to include antimicrobials administered to adult dairy cattle only. Another constraint might have emerged from the exclusive focus on significant effects within univariate associations, potentially resulting in biased estimates. Variations of herd size over time were not taken into account like in other studies (Saini et al., 2012; Stevens et al., 2016), resulting in potential minor deviations of the true TI at herd level. Similarly, management practices were those in place at the time of the visit and may have differed from those in place during the year before the visit and correlating with AMU. However, because our research was conducted as a cross-sectional study by visiting farms only once for the questionnaire, it was not possible to include this aspect into calculations. Commonly, cross-sectional studies may identify associations between factors and antimicrobial use, but do not define direct causality between predictors and the TI. However, establishing such associations might help to improve future AMU mitigating strategies.

CONCLUSIONS

We used digitally recorded data of the newly established mandatory Swiss national reporting system, which had not been available until recently. Thus, we reduced possible bias arising from AMU recording alternatives, such as on-farm paper treatment journals. Although several factors were already known to be associated with AMU on dairy farms, this study revealed some novel aspects specific to tie stall farms and their management conditions. Cows in tie stalls are administered a similar number of treatment days per year in comparison with other dairy cow husbandry systems based on previously published data, and critically important antimicrobials were used to a very limited extent. The Swiss national reporting system IS ABV should be highly recognized as a milestone for a nationwide unified AMU data collection methodology and will facilitate AMU comparisons among farms, years and countries for future research.

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