

## Quantitative analysis of antimicrobial use on British dairy farms

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## Abstract

Antimicrobial resistance has been reported to represent a growing threat to both human and animal health, and concerns have been raised around levels of antimicrobial usage (AMU) within the livestock industry. To provide a benchmark for dairy cattle AMU and identify factors associated with high AMU, data from a convenience sample of 358 dairy farms were analysed using both mass-based and dose-based metrics following standard methodologies proposed by the European Surveillance of Veterinary Antimicrobial Consumption project. Metrics calculated were mass (mg) of antimicrobial active ingredient per population correction unit (mg/PCU), defined daily doses (DDDvet) and defined course doses (DCDvet). AMU on dairy farms ranged from 0.36 to 97.79 mg/PCU, with a median and mean of 15.97 and 20.62 mg/PCU, respectively. Dose-based analysis ranged from 0.05 to 20.29 DDDvet, with a median and mean of 4.03 and 4.60 DDDvet, respectively. Multivariable analysis highlighted that usage of antibiotics via oral and footbath routes increased the odds of a farm being in the top quartile (>27.9 mg/PCU) of antimicrobial users. While dairy cattle farm AMU appeared to be lower than UK livestock average, there were a selection of outlying farms with extremely high AMU, with the top 25 per cent of farms contributing greater than 50 per cent of AMU by mass. Identification of these high use farms may enable targeted AMU reduction strategies and facilitate a significant reduction in overall dairy cattle AMU.

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## Introduction

Antimicrobial resistance (AMR) has been reported to represent a growing threat to both human and animal health,<sup>1</sup> with the inappropriate use of antimicrobials in human and animal fields being considered responsible for the emergence of resistance in bacteria.<sup>2</sup> Concerns have been raised regarding the zoonotic transfer of resistant bacteria from livestock to human beings,<sup>3</sup> with potential routes of transfer including food products,<sup>4</sup> direct contact<sup>5</sup> and via environmental contamination.<sup>6</sup> There are however many knowledge gaps in livestock–human AMR transfer routes,<sup>7</sup> and links between on-farm antimicrobial usage (AMU) and the increased transfer of major foodborne drug-resistant organisms such as *Campylobacter* spp and *Salmonella* spp have not been found.<sup>8,9</sup>

Remarkably strong interactions between AMU and AMR in livestock have been described,<sup>10</sup> and UK Government-commissioned reports have called for a reduction in antimicrobial use within the livestock industry.<sup>11</sup> There are numerous metrics available to measure veterinary AMU, which have great impact on both the AMU figures obtained and consequent influence on AMU reduction policy,<sup>12</sup> and international recommendations have been provided for the most suitable metrics to monitor both human and veterinary AMU.<sup>13</sup> The UK Government has called for an AMU reduction target from 62 mg per population correction unit (mg/PCU) in 2013 to less than 50 mg/PCU as an average across all livestock sectors by 2018,<sup>14</sup> and total livestock AMU figures for the UK indicate this target has already been reached.<sup>15</sup> Farm-level AMU monitoring studies in dairy cattle have been conducted in several countries including the USA,<sup>16</sup> Canada,<sup>17</sup> New Zealand<sup>18</sup> and the Netherlands<sup>19</sup>; however, to date, no detailed farm-level AMU studies identifying factors associated with high AMU have been conducted in the UK dairy industry.

Therefore, this study aims to provide an evaluation of the levels of AMU in a convenience sample of British dairy farms over a 12-month period and to identify factors associated with high usage on these farms.

## Methods

### Sources of data

Data were collected from both veterinary practice records and electronic on-farm records between January 1, 2016 and December 31, 2016. A convenience sample of four farm animal veterinary practices in the south, midlands and north of England was identified after an expression of interest in AMU monitoring, and anonymised antimicrobial sales data were provided for all dairy farm clients between January 1, 2016 and December 31, 2016. Cow numbers were estimated for each farm using electronic cattle movement records (using the British Cattle Movement Service Cattle Tracing System, with animals being >24 months and female) for two practices or otherwise directly from farmer estimates of average adult dairy cow numbers. Farms

with any other livestock on farm (ie, sheep or beef enterprises) were excluded from the study to ensure antimicrobials purchased were solely for dairy cattle.

AMU records were obtained from a separate group of farms recording medicines usage electronically on farm, which were enrolled in regular milk recording with a laboratory based in the south of England (Quality Milk Management Services). Farmer-recorded electronic medicines records, cow numbers and veterinary practice ID were extracted from on-farm software.

Antimicrobial sales records were collected for 332 farms, with 40 farms being excluded due to the presence of a livestock enterprise other than dairy, resulting in a final data set of 292 farms. Electronically recorded AMU records were collected from 70 farms, with 4 farms being excluded due to data recording errors, resulting in a final data set of 66 farms. These two data sets were combined to provide a total of 358 farms, with antimicrobial data for 81,640 dairy cows ([Table 1](#)), representing ~3.6 per cent of total dairy farms and ~7.0 per cent of total dairy cows in England.<sup>20</sup> Farm size ranged from 21 to 2080, with a mean herd size of 228. The four practices supplying antimicrobial sales data were dominated by one practice providing information for 182 farms, with the other three practices supplying data for the remaining 110 farms ([Table 1](#)).

	<i>Practice 1</i>	<i>Practice 2</i>	<i>Practice 3</i>	<i>Practice 4</i>	<i>All Sales</i>	<i>All Use</i>	<i>All farms</i>
<i>Min</i>	70	37	21	25	21	50	21
<i>Max</i>	340	550	562	2080	2080	1290	2080
<i>Median</i>	160	120	199	179	171	183	172
<i>Mean</i>	178	160	199	252	223	249	228
<i>Total dairy cows</i>	3551	8807	6973	45892	65223	16417	81640
<i>Total dairy farms</i>	20	55	35	182	292	66	358

TABLE 1: Cow numbers per farm for four veterinary practices that provided antimicrobial sales data ('All Sales') and from a group of farms recording medicines usage electronically ('All Use')

### Calculation of AMU

Total mass (mg) of antimicrobial active ingredient per population correction unit (mg/PCU) was calculated using the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) standard methodology,<sup>21</sup> using a standardised adult dairy cow bodyweight of 425 kg. Youngstock and slaughtered animals were not included in the calculation of PCU, and topical sprays were not included in the calculation of antibiotic mass.

To facilitate comparison between different monitoring metrics, three separate metrics were calculated for both sales and usage data: mg/PCU, defined daily doses (DDDvet) and defined course doses (DCDvet). Critically important

antibiotics (CIAs) were defined as third-generation or fourth-generation cephalosporins and fluoroquinolones.<sup>22</sup>

DDDvet calculations followed standard ESVAC/European Medicines Agency (EMA) methodology<sup>21</sup> to provide an estimation of AMU while taking into account differences in dosing between antimicrobial products. Oral and parenteral antibiotic formulations were calculated per kilogram of animal (adult dairy cow weight being 425 kg), and intrauterine and lactating cow intramammary doses (IMM) were calculated per cow. Antibiotic dry cow therapy (DCT) was excluded from DDDvet calculations as per ESVAC/EMA methodology, as were topical antibiotic therapies (including antibiotic footbathing).

DCDvet calculations were performed similarly, calculating oral and parenteral doses per kilogram, intrauterine and lactating cow intramammary courses per cow, also including dry cow intramammary therapy, with four tubes per cow being equal to a single course.

Basic descriptive statistics (range, median, mean) were performed for all metrics calculated, and total mass of antimicrobials by route was also calculated and illustrated graphically. Calculations were repeated for CIAs. Total AMU/sales per farm were graphically illustrated for each practice to identify any patterns within practices. This was also repeated for CIAs. Basic descriptive statistics and graphical illustrations were conducted using Microsoft Excel 2016 and R V.3.4.0 statistical software.<sup>23</sup>

### Statistical analysis

To investigate factors that influenced farms being high antimicrobial users, multilevel logistic regression models were developed using MLwiN,<sup>24</sup> with farms in the top 25 per cent of antimicrobial users (>27.9 mg/PCU, >5.88 DDDvet or >2.32 DCDvet) as a binary outcome variable (highest 25 per cent or not). Categorical variables were created for herd size (small <136, medium 136–236, large >236), and a binary variable of route usage was created illustrating either 'used' or 'did not use' for each route category (parenteral, IMM, DCT, footbath, intrauterine, oral, pessary). Models were constructed using a backwards stepwise approach until variables that remained in the model were significant at  $P < 0.05$ , and model fit was checked using a modified Hosmer-Lemeshow method<sup>25</sup>. A multilevel structure was employed to allow for correlations between farms within veterinary practices, with veterinary practice being included as a random effect. Parameters were estimated using iterative generalised least squares. Final parameter estimates were generated using Markov Chain Monte Carlo (MCMC), with Gibbs sampling to avoid potential parameter bias.<sup>26</sup> A burn in chain of 500 iterations with a monitoring chain of 10,000 iterations was used, and MCMC chains were visually checked to ensure convergence. To estimate the proportional reduction in high AMU farms that would occur if significant risk factors were removed, population attributable fractions (PAFs) were calculated for significant model covariates.<sup>27</sup> PAFs and 95 per cent confidence

intervals were calculated directly from MCMC chains using R statistical software (R V.3.4.0 2017).

## Results

Antimicrobial sales to dairy farms ranged from 0.36 to 97.79 mg/PCU, with a median and mean of 17.25 and 22.11 mg/PCU, respectively. DDDvet for sales data ranged from 0.05 to 20.29 doses, with a median and mean of 4.22 and 4.84, respectively. DCDvet for sales data ranged from 0.01 to 6.74 courses, with a median and mean of 1.73 and 1.93, respectively.

Farmer-recorded AMU ranged from 1.20 to 48.48 mg/PCU, with a median and mean of 11.42 and 14.06 mg/PCU, respectively. DDDvet for usage data ranged from 0.14 to 16.09 doses, with a median and mean of 3.24 and 3.56, respectively, and DCDvet for usage data ranged from 0.33 to 5.33 courses, with a median and mean of 1.55 and 1.58, respectively.

Of all the farms included in this study, the median AMU was 15.97 mg/PCU, or 4.03 DDDvet and 1.69 DCDvet. The mean AMU from all the farms in the study was 20.62 mg/PCU, or 4.60 DDDvet and 1.86 DCDvet (Table 2).

*Source (Farm numbers)*

		<b>Practice 1 (20)</b>	<b>Practice 2 (55)</b>	<b>Practice 3 (35)</b>	<b>Practice 4 (182)</b>	<b>All Sales (292)</b>	<b>All Use (66)</b>	<b>All farms (358)</b>
<b>mg/PCU</b>	Min	7.84	0.36	5.02	0.55	0.36	1.20	0.36
	Max	85.92	97.79	96.47	70.76	97.79	48.48	97.79
	Median	19.86	18.62	32.41	15.55	17.25	11.42	15.97
	Mean	26.85	22.59	38.07	18.37	22.11	14.06	20.62
<b>DDDvet</b>	Min	0.90	0.07	0.97	0.05	0.05	0.14	0.05
	Max	17.23	18.59	12.78	20.29	20.29	16.09	20.29
	Median	6.39	5.01	4.89	3.71	4.22	3.24	4.03
	Mean	6.48	6.04	5.57	4.15	4.84	3.56	4.60
<b>DCDvet</b>	Min	0.26	0.02	0.31	0.01	0.01	0.33	0.01
	Max	6.62	6.74	4.45	6.63	6.74	5.33	6.74
	Median	2.35	2.23	1.81	1.57	1.73	1.55	1.69
	Mean	2.61	2.45	2.09	1.67	1.93	1.58	1.86

**TABLE 2:**

*Antimicrobial usage (mg/PCU, DDDvet, DCDvet) for four veterinary practices that provided antimicrobial sales data ('All Sales') and from a group of farms recording medicines usage electronically ('All Use')*

Antibiotic sales and usage largely consisted of injectable treatments, comprising 78.1 per cent of total antibiotic mass used or sold (Fig 1). Lactating cow intramammary treatments represented 6.5 per cent of antimicrobial active ingredient mass (mg), with DCT representing 6.0 per cent. Off-licence antibiotic footbath powders represented 4.5 per cent of total mg, and oral powders, intrauterine treatments and pessaries combined represented 5.0 per cent. Beta lactams made up the bulk of antimicrobials, totalling 42.8 per cent of mg, with aminoglycosides totalling 20.9 per cent. CIAs totalled 3.3 per cent of mg, with third-generation or fourth-generation cephalosporins and fluoroquinolones comprising 2.5 per cent and 0.8 per cent of mg, respectively, and representing a mean farm AMU of 4.7 per cent of mg/PCU ranging from 0 to 47.6 per cent. Due to the relatively lower dosing requirements of CIAs, CIAs represented a higher proportion of doses administered, ranging from 0 to 90.1 per cent DDDvet and from 0 to 89.0 per

cent DCDvet, representing a mean of 17.8 per cent DDDvet and 14.9 per cent DCDvet, respectively.

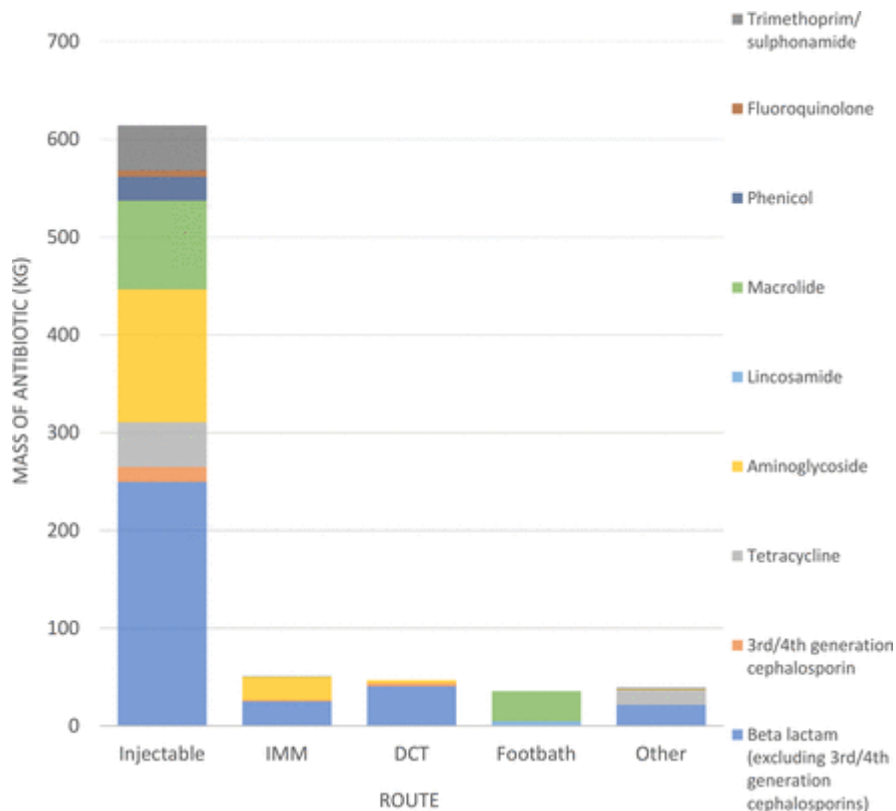


FIG 1: Total mass (kg) of antimicrobial classes from sales data to farms ( $n=292$ ) from four veterinary practices and for usage data from farms ( $n=66$ ) recording medicines usage electronically on farm. DCT, dry cow therapy; IMM, intramammary lactating cow therapy.

The majority of farms used/purchased antibiotic IMM and DCT products (345 (96 per cent) and 338 (94 per cent), respectively), and all farms used/purchased injectable antibiotic products. Farms also used/purchased the following products: intrauterine antibiotics (184 (51 per cent)), antibiotic pessaries (117 (33 per cent)), antibiotic footbaths (98 (27 per cent)) and oral antibiotics (18 (5 per cent)). Multivariable regression modelling illustrated that the use of oral and footbath antibiotics significantly increased the odds of a farm being in the top 25 per cent of antimicrobial users, measured by mg/PCU (Table 3). Other variables such as herd size and usage of other routes of antimicrobial administration (parenteral, IMM, DCT, intrauterine and pessary) did not remain in the model.



<i>Outcome variable</i>	<i>Explanatory variable (N)</i>	<i>Odds ratio</i>	<i>95%CI</i>	<i>P-value</i>	<i>Population attributable fraction (%)</i>	<i>95%CI</i>
<b>Top 25% AMU (mg/PCU) (n=90)</b>	<b>Oral antibiotics used (n=13)</b>	9.43	(2.76-32.27)	<0.001	8.4	(3.03-14.00)
	<b>Antibiotic footbath used (n=39)</b>	2.75	(1.46-5.17)	0.001	20.28	(8.99-33.02)

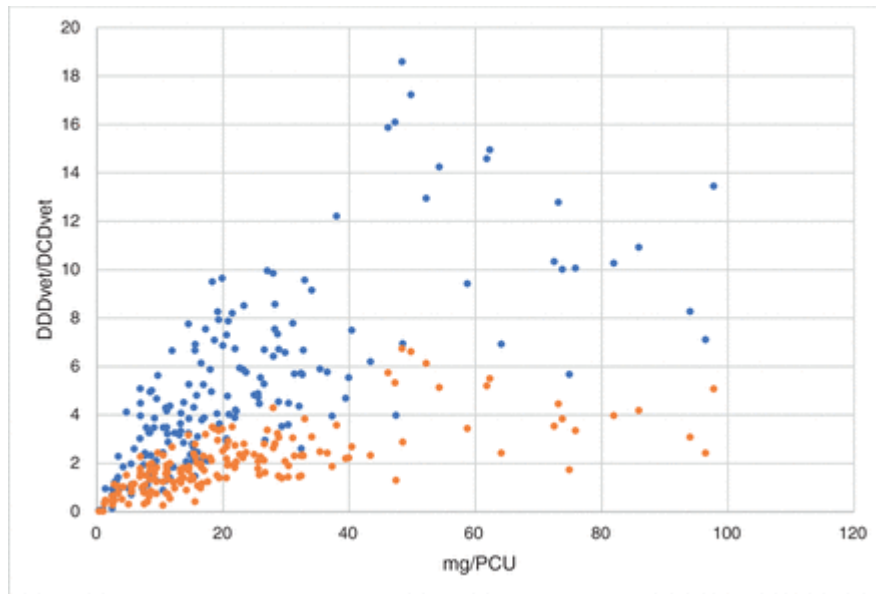
TABLE 3: Logistic regression model of factors affecting the odds of farms (n=358) being in the highest 25 per cent of antimicrobial users (as measured by mg/PCU)

## Discussion

Given that cattle represents 25 per cent of total livestock mass in the UK as estimated by PCU,<sup>15</sup> roughly equivalent to pig and poultry PCU combined, AMU within the cattle industry plays an important role in the UK's overall AMU. The results from this study indicate that AMU in dairy cattle is likely to be significantly lower than overall UK livestock AMU of 45 mg/PCU in 2016.<sup>15</sup> While a large proportion of dairy farms are likely to be relatively low in terms of AMU, in this data set there exists an outlying population of farms that exhibit a relatively high usage of antimicrobials, with the highest 25 per cent of antimicrobial users representing 52 per cent of the total mass (mg) of antimicrobials. Establishing monitoring methods and targets will be essential to identify high antimicrobial users, and an understanding of factors that influence relatively high AMU will allow targeted AMU reduction interventions.

Injectable preparations represented the majority of antimicrobial use/sales mass, with the remainder being predominantly IMM, DCT and footbath routes (Fig 1). Of injectable products 3.5 per cent by mass were CIAs, and injectable treatments largely comprised beta lactams (40.6 per cent) and aminoglycosides (22.1 per cent) by mass, representing the common usage of both penicillin-based antibiotics and penicillin streptomycin combinations. Differences between monitoring metrics resulted in important differences between proportions of AMU attributed to various routes of therapeutic application, which has the potential to influence national-level and farm-level protocols to reduce AMU. Mass-based AMU monitoring (ie, mg/PCU) appears heavily influenced by parenteral therapy, potentially incentivising the reduction of parenteral therapy as a priority with IMM treatments playing a small role in overall mg/PCU as previously reported.<sup>12</sup> Dose-based metrics (ie, DDDvet, DCDvet), however, highlight IMM therapies as major contributors to total AMU and may encourage reductions in IMM antimicrobials as a priority. While there is a degree of correlation between the monitoring methodologies, there are high AMU farms that would not be detected if a single monitoring metric was used (Fig 2), with high IMM and high footbath AMU being particularly poorly

represented when using mass-based or dose-based methodology, respectively. Given that monitoring methodologies will potentially incentivise reductions in specific treatment routes, it may be prudent to aim for AMU reductions as monitored by both mass-based and dose-based metrics.

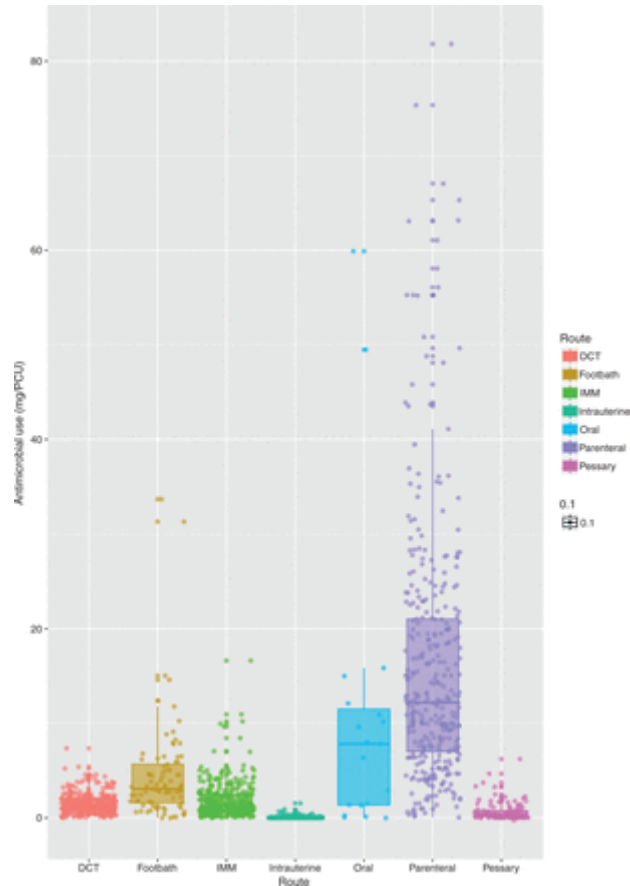


*FIG 2: Antimicrobial usage measured by mg/PCU compared with DDDvet (blue) and DCDvet (orange) from sales data to farms from four veterinary practices and for usage data from farms recording medicines usage electronically. The total number of farms is 358. DCDvet, defined course doses; DDDvet, defined daily doses; PCU, population correction unit.*

The reduction/cessation of usage of antibiotics critically important for human health has received great attention within the livestock industry.<sup>11</sup> The current study demonstrated that CIAs represent a mean of 4.7 per cent mg/PCU used on dairy farms, which is high compared with other species (1 per cent of all livestock mg/PCU in 2016<sup>15</sup>). When employing dose-based methodology, the mean farm CIA usage represented 17.8 per cent of DDDvet and 14.9 per cent of DCDvet, respectively, a difference largely due to generally lower dosing requirements of CIAs. Since pressure on the livestock industry to reduce CIA usage will continue to grow, the usage of CIAs on dairy farms will come under scrutiny. To reduce AMU across the livestock industry, it will be important to provide industry-specific targets both in terms of reducing overall usage and specific therapeutics such as CIAs.

Monitoring dairy farm AMU to identify high antimicrobial users would enable targeted interventions to facilitate the most effective reductions in overall AMU. The use of oral and footbath antibiotics on farms appears to increase the odds of farms being in the highest 25 per cent of antimicrobial users (mg/PCU), possibly indicating the effects of group medication protocols on increased AMU. This study also illustrated that while most dairy cattle farms do not employ these methods of medication, those that do can dramatically increase overall mass-based AMU (Fig 3). High levels of injectable antibiotic usage are also likely to be a significant driver of overall AMU as measured by

mg/PCU, but due to all farms using injectable products, injectable usage was not retained in the final multivariable model. Targeting the reduction of AMU among the minority of high antimicrobial users while maintaining high standards of health, welfare and production may be a fast and effective first step to reduce AMU at farm, practice and national levels.



*FIG 3: Antimicrobial usage (mg/PCU) by route from sales data to farms from four veterinary practices and for usage data from farms recording medicines usage electronically. Points represent antimicrobial usage (mg/PCU) for each farm by route, with box plots illustrating interquartile range and median. The total number of farms is 358. DCT, dry cow therapy; IMM, intramammary lactating cow; PCU, population correction unit.*

UK legislation requires medicines administered to livestock to be recorded on farm and the sales of all veterinary products to livestock businesses to be recorded by veterinary practices,<sup>28</sup> resulting in two readily available data sources for farm-level AMU monitoring. Farmer-recorded usage will potentially under-report actual usage on farm, as farmer-inputted medicines use has previously been shown to be an under-representation when compared with medicines sales.<sup>19,29</sup> This may in part be related to medicines being bought in bulk and not all being used (and therefore not recorded), alongside errors in updating medicines records. In contrast, practice sales records capture all antimicrobials sold to a farm, and therefore may over-report AMU due to antimicrobials not ultimately used. Since important differences in recording methodology and terminology exist between both farms and practices, standardisation of recording protocol will be essential in national monitoring

efforts, and caution should be taken when comparing farmer-recorded usage with antimicrobial sales figures.

AMU comparisons between monitoring studies can be challenging, with many factors influencing both the numerator (mg or doses) and the denominator (PCU) populations, depending on methodology used. The standard weight of an adult cow will have a significant bearing on denominator population, with studies using 'weight at time of treatment' such as 425 kg<sup>21</sup> potentially underestimating weight when compared with live cattle weights such as 600 kg<sup>17,19</sup> and 680 kg,<sup>16</sup> resulting in AMU overestimation. The inclusion/exclusion of youngstock also has bearing on the denominator population, and the inclusion of youngstock AMU in this study despite exclusion of youngstock PCU may slightly overestimate AMU as previously described,<sup>17,19</sup> although AMU for calves have previously been reported to likely represent a small proportion of total AMU on dairy farms.<sup>19</sup> DCT recording, however, can have a significant bearing on dose-based methodologies, and while DCT is excluded from DDDvet,<sup>21</sup> doses both per cow and per teat have been previously reported.<sup>17,19</sup> Antibiotic footbathing has a dramatic effect on mg/PCU, however is not accounted for when applying DDDvet or DCDvet methodologies. It is challenging to provide clear guidance as to the 'dosage' applied to each animal, and anecdotally ~100 g of antibiotic powder might be advised to treat around 100 cows via footbath. Using a dosage of 1 g of product per cow as a daily dose allows an estimation into the effect of footbathing on the dose-based metrics, which would increase mean farm AMU by over 10 per cent from 4.6 to 5.1 DDDvet.

ESVAC/EMA calculations based on live dairy cattle and slaughter weights have been largely designed to facilitate national/international monitoring, and are not intended for farm-level comparisons. Since the number of youngstock on dairy farms varies widely, it can be challenging to directly compare farms due to the variation in PCU not captured using ESVAC/EMA methodology. Cattle births, deaths and movements in the UK are reported to the British Cattle Movement Service.<sup>30</sup> Using this database, it should be possible to identify a relatively accurate estimation of PCU present on each holding by assigning weights to each age category, calculating number of days spent in each weight class and providing an overall estimation as to kg/year at risk. This methodology should reduce PCU estimation errors between dairy farms with variations in youngstock rearing and would also be applicable to the beef industry, where a wide range of farm management systems make farm-level AMU comparisons challenging.

The mean herd size (228) in this study was larger than average for dairy herds in England (145<sup>20</sup>), although herd size did not appear to be associated with AMU in this study. The study population is based on a convenience sample and cannot be assumed to be a sample entirely representative of British dairy farms. There is potential for selection bias, with veterinary practices contributing data having previously expressed their interest and proactive approach to AMU monitoring, and farms identified via milk recording records

already being engaged in electronic medicines recording. Despite this, there appears to be clear similarities between practices, with most farms in each practice representing a relatively low usage of antimicrobials, with a minority of farms comprising a major proportion of total AMU (Figs 4 and 5).

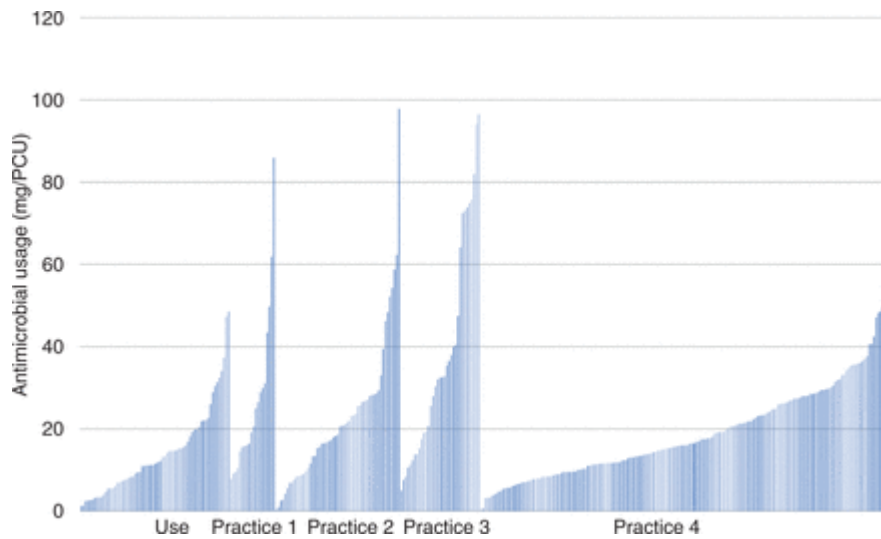


FIG 4: Antimicrobial usage (mg/PCU) from sales data to farms (n=292) from four veterinary practices and for usage data from farms (n=66) recording medicines usage electronically on farm. PCU, population correction unit.

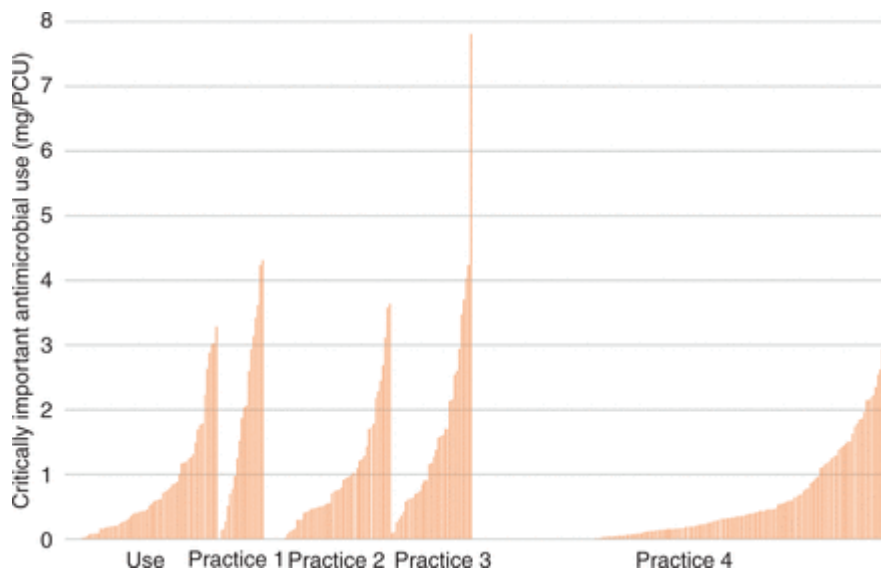


FIG 5: Critically important antimicrobial usage (mg/PCU) from sales data to farms (n=292) from four veterinary practices and for usage data from farms (n=66) recording medicines usage electronically on farm. PCU, population correction unit.

Pressure will no doubt continue to mount on the livestock industry to monitor and reduce AMU, and it will be important to monitor AMU at farm level across all livestock sectors, employing both mass-based and dose-based metrics. This study provides a benchmark for dairy cattle AMU in Britain and identifies several factors associated with high AMU. While this study suggests that most dairy farms exhibit lower AMU than the UK livestock average, there remains an outlying population of farms with high levels of AMU. Identifying high AMU

farms at a practice or national level will enable AMU reduction efforts to be efficiently targeted, and future studies should include the effect of such interventions on levels of both AMU and AMR. A proactive veterinary approach to herd health management to reduce disease incidence will result in fewer antimicrobial treatments being required and will play an important role in the reduction of dairy cattle AMU.

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