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ORIGINAL RESEARCH

Longitudinal study of antimicrobial use patterns, vaccination and disease prevalence in British sheep flocks

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Abstract

Background: The aim of the study was to describe the longitudinal dynamics of antimicrobial use (AMU) on sheep farms and explore associations between AMU and management factors, vaccination strategies, reproductive performance and prevalence of lameness.

Methods: Antimicrobial supply data were collected for 272 British sheep farms for 3–6 consecutive years between 2015 and 2021. These data were obtained from the farms' veterinary practices.

Results: Annual median AMU ranged from 8.1 to 11.8 mg/kg population corrected unit. AMU was skewed in each year with a small proportion of very high users. AMU within farms varied substantially between years. High AMU farms in 1 year were not necessarily high in other years. No associations between AMU and either vaccine usage or lameness prevalence were found.

Limitations: The study design requires veterinarians and farmers to volunteer their data. This unavoidably introduces the potential for a participation bias.

Conclusions: AMU on sheep farms is generally low, with a small number of farms being responsible for high usage. Targeting antimicrobial stewardship effort towards the small minority of persistently high users may be more appropriate than a focus on generic, industry-wide attempts to reduce overall AMU.

INTRODUCTION

Following the completion of the Review on Antimicrobial Resistance (AMR) in 2016,[1] the UK government identified reducing antimicrobial use (AMU) in livestock production as a priority and called for the implementation of sector-specific targets. This role was taken on by the Responsible Use of Medicine in Agriculture Target Task Force[2] to achieve the overall target of 50 mg/kg population corrected unit (PCU) as the maximum average figure for the whole of UK livestock production. The UK is unusual within Europe in that it has a very large sheep population, larger than any other livestock sector in the UK. Indeed, the UK has the largest sheep industry in Europe and one of the largest globally. The sheep sector as a whole is regarded as relatively low input, low AMU and extensive in comparison to dairy cattle, pig or poultry production. However, the sheep industry represents 40% of the livestock biomass in the UK,[3] and the human population is physically exposed to sheep more often than other livestock species by virtue of the shared use of pasture land for sheep grazing and public recreation. For example, the relative livestock density mapping data published by the UK government[4] illustrate the correlation between areas of high sheep density (and low dairy cattle and pig density) and areas of high visitor numbers, such as the upland National Parks of England and Wales.

In order to develop useful and rational targets/guidelines for AMU in any livestock sector, it is crucial to understand the dynamics of species and farm-level AMU, including the magnitude and variability of AMU within a farm as well as between farms over several years or production cycles. Industry antimicrobial stewardship initiatives introduced numerical targets for reducing antibiotic use and also introduced other health proxy metrics. Vaccine usage is one such proxy metric that has been promoted for its presumed correlation with improved health and reduced reliance on antibiotics. There is some evidence from human medicine of correlation between vaccine adoption and the incidence of antimicrobial treatment and prevalence of AMR.[5] However, as far as the authors are aware, there is no equivalent evidence in veterinary medicine. Therefore, in this study, we collected usage data for a range of the most commonly used vaccines for infectious diseases, including interdigital dermatitis and footrot, which are the most prevalent causes of lameness in the UK sheep population. Lameness in sheep is overwhelmingly due to infectious bacterial pathogens that are in turn treated with antimicrobials in the UK sheep sector.[6] Furthermore, the antimicrobials used to treat lameness represent the majority of AMU in sheep flocks.[7] Lameness is therefore a suitable context to explore the association between vaccination usage and antibiotic usage in this study.

This retrospective longitudinal study builds on a previous cross-sectional study of commercial UK flocks.[7] The primary aim was to evaluate the variation in AMU over multiple years and production cycles. The secondary aim was to describe associations between both management factors and vaccine usage with AMU. The third aim of this study was to explore the relationship between the reported lameness prevalence and AMU at the farm level.

MATERIALS AND METHODS

All UK veterinary practices registered with the RCVS and self-declared as treating sheep were invited by email to participate in the study ($n = 568$) in 2018 and 2021. Participating veterinary practices consented to providing the research team with anonymised survey data of flock management practices and electronic records of all antibiotic sales (during the specified period) for clients who consented to participate in the study. The study was restricted to farms managing sheep and no other livestock species to avoid the risk of exaggerated estimation of AMU through the miss-attribution of antimicrobial sales to species other than sheep. A minimum breeding ewe flock size of 100 ewes was used to reduce the potential bias associated with unnecessarily large pack sizes of antimicrobial products being supplied for small flocks, where unused product could represent a large proportion of the purchased total. This assumption is based upon the number of doses per pack/bottle relative to the flock size and the expected incidence of clinical cases requiring antibiotic treatment within the shelf life of the product.

Participation criteria required veterinary surgeons to submit anonymous sales data for all antimicrobial and vaccine products supplied to eligible farms for as many complete calendar years (January–December) as possible between 2015 and 2021. AMU data (date, product, quantity) were supplied electronically from the practice management software systems. Hardcopy questionnaires on disease patterns and usage practices were distributed to all farmers via their veterinary practice. Non-responders were contacted in person or by telephone to complete the questionnaire. Questionnaires were returned to the research team individually identified with the same unique anonymous reference code as applied to the farm antimicrobial sales records to facilitate anonymous matching of the two data sources.

The mass of antimicrobial active ingredients per PCU was calculated for each prescribed product using the manufacturer-supplied product specification and the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) standard methodology,[3] using approximate average bodyweights of adults (75 kg) and weighted average weight for slaughtered lambs (20 kg). To calculate the lamb component of the PCU, the standardised method was used as previously described[7]: the mean rearing percent of lambs per ewe (143.5%) in the reference period was estimated using the UK levy board benchmarking data as a coefficient of the standard ESVAC lamb weight value (20 kg).

For comparison, a second method for calculating mg/kg PCU per farm was generated from the individual ultrasound pregnancy diagnosis data from each flock in a reference year (2017). This individually calculated flock mg/kg PCU was based on farmer reported scanning percentage of less than 10% to account for lamb mortality. Use of a fixed lamb mortality percentage in the calculation is a necessary simplification of reality that will not necessarily reflect the true mortality on a given farm in a given year, but in the absence of reliable data and in the interests of clarity, a fixed percentage was adopted. Statistical analysis was conducted in R (version 4.2.1)[8] and Minitab 19.[9] Exploratory data analysis was conducted in R using the Tidyverse package,[10] and statistical modelling was conducted using the lmer package.[11]

For a subset of farms ($n = 161$), the following management and vaccination variables were available: number of lambs, number of ewes, scanning percentage, percentage of ewes receiving *Toxoplasma gondii* vaccines, percentage of ewes receiving *Chlamydophia abortus* vaccines, percentage of ewes receiving *Dichelobacter nodosus* vaccines, proportion of ewes lambing indoors and percentage of ewes classed as lame. Variables were entered into a mixed effects model using the lmer package,[11] with farm as a random effect, and removed if non-significant after fitting at p-value less than 0.05 using a backwards stepwise approach. Residuals were checked visually to ensure model fit, and removed variables were reintroduced individually to the final model to check for no significant changes to model fit.

RESULTS

Of the 36 veterinary practices that expressed an interest in participating, 17 supplied the requested antimicrobial data for a total of 495 farms for 1–6 consecutive years and completed farm disease information questionnaires for 289 farms. Two hundred and seventy-two farms met the inclusion criteria, that is, a breeding flock of more than 100 ewes and having both AMU information for at least 3 calendar years within the 6-year study period and matching farm management/disease information. Farms were distributed throughout England, Wales and Scotland. The number of breeding ewes per eligible flock ranged

TABLE 1 Antimicrobial usage (mg/kg population corrected unit) over time across all farms.

Year	Farms, *n*	Minimum	Q1	Median	Q3	Maximum
2015	137	0.32	3.86	9.06	17.81	175.83
2016	152	0.37	5.87	11.75	22.58	139.52
2017	152	0.32	5.29	11.03	18.04	165.56
2018	138	0.30	4.68	10.16	16.51	171.83
2019	217	0.00	5.55	11.50	20.88	170.55
2020	199	0.00	2.74	8.11	15.23	166.00
2021	111	0.32	3.99	10.41	18.47	135.16

from 104 to 3224, with a mean and median of 555 and 394 ewes, respectively. The two alternative methods of calculating a mg/kg PCU metric were compared. The individual-flock calculated AMU based on mg/kg PCU using farmer reported scanning percentage less a mortality estimate was very similar to the standard ESVAC PCU calculation method in all years. Pearson's correlation between the two PCU calculation methodologies was high, with $r = 89.6\%$ ($p < 0.001$) and Spearman's $\rho = 82.9\%$ ($p < 0.001$). Due to the high degree of correlation, and in the interests of clarity, all the analysis presented is based upon the widely used ESVAC mg/kg PCU metric rather than the individual-flock calculated PCU metric unless explicitly stated otherwise.

Patterns of AMU over time

There was limited variation in median AMU per year, with a median of 10.28 mg/kg PCU (median ranging from 8.11 to 11.75; Table 1). Multilevel variance partitioning of AMU indicated that 23% of the variation occurred at the practice level and the remainder at the farm level. While there was no overall trend in AMU that could be detected in this sample of farms, AMU of flocks associated with two individual veterinary practices did fall significantly ($p = 0.04$) from 2018 to 2020, by 39% and 43%, respectively.

Patterns of antibiotic class use over time

In every year of the study period, oxytetracycline was the most prescribed class of antibiotic by mass. Over the entire study period, oxytetracycline represented 49.1% of the total mass, followed by penicillin, which includes the extended spectrum product formulations at 27.7%, aminoglycosides at 10.2%, macrolides at 8%, sulphonamides and trimethoprim at 1.9% and fluoroquinolones at 0.31%. The remaining 2.6% comprised thiamphenicol, florfenicol and lincomycin.

Patterns of administration over time

In comparison to the previous study, which related to the period from August 2015 to July 2016,[7] an overall shift was observed in the route of administration, away from oral preparations for neonatal lambs (23% reduction) and off-licence, powdered antimicrobial products used for footbaths (45% reduction). In contrast, the use of injectable and topical spray preparations has increased by 15% and 23%, respectively. Injectable preparations remain the dominant administration route at 86% by mass. The seasonal distribution of usage and class was very consistent between years. AMU by class was compared between the first and fourth quartiles of the distribution of farms ranked by use in mg/kg PCU but revealed no significant class preference between high and low users.

Variability in AMU between years by farm

The median variation between the highest and lowest annual AMU value per farm was 9.1 mg/kg PCU (interquartile [IQR]: 4.53, 17.10). Nine percent of flocks exceeded 50 mg/kg PCU in at least one of the calendar years, and 40% of flocks exceeded 20 mg/kg PCU in at least 1 year, while 1.4% of flocks exceeded the 50 mg/kg PCU threshold in every year. In contrast, 8% of flocks did not exceed 5 mg/kg PCU in any calendar year (Figure 1).

Patterns of antibiotic and vaccine usage

A subset of 163 farms answered questions relating to vaccine usage (Table 2), of which 52 flocks (32%) used a *Toxoplasma* vaccine, 28 flocks (17%) used a *Chlamydophila* vaccine and 19 flocks (12%) used a *Dichelobacter nodosus* (footrot) vaccine. Nineteen flocks (12%) used both a *Chlamydophila* and a *Toxoplasma* vaccine, while seven flocks (4%) used all three vaccine groups. In contrast, 95 flocks (58%) used none of these vaccines. Associations between vaccine usage and AMU are shown in Figure 2. There were no significant correlations between abortion vaccine use, reported annual lameness prevalence, scanning percentage and AMU.

Flock management practices and AMU

The proportion of ewes lambing indoors was used as a proxy metric for the intensity and risk of bacterial transmission and disease. Seventeen percent of flocks reported that they lambed the entire flock outdoors, and 31% reported that they lambed all ewes indoors. A larger proportion of indoor-lambing flocks (77%) purchased orally administered antimicrobial products during the lambing period compared to outdoor-lambing flocks (31%). Within these two subpopulations who purchased any licensed oral antimicrobials, oral AMU was higher among indoor-lambing flocks, with a median of 0.77 mg/kg PCU (IQR: 0.39, 1.21) for flocks lambing exclusively indoors, compared with a

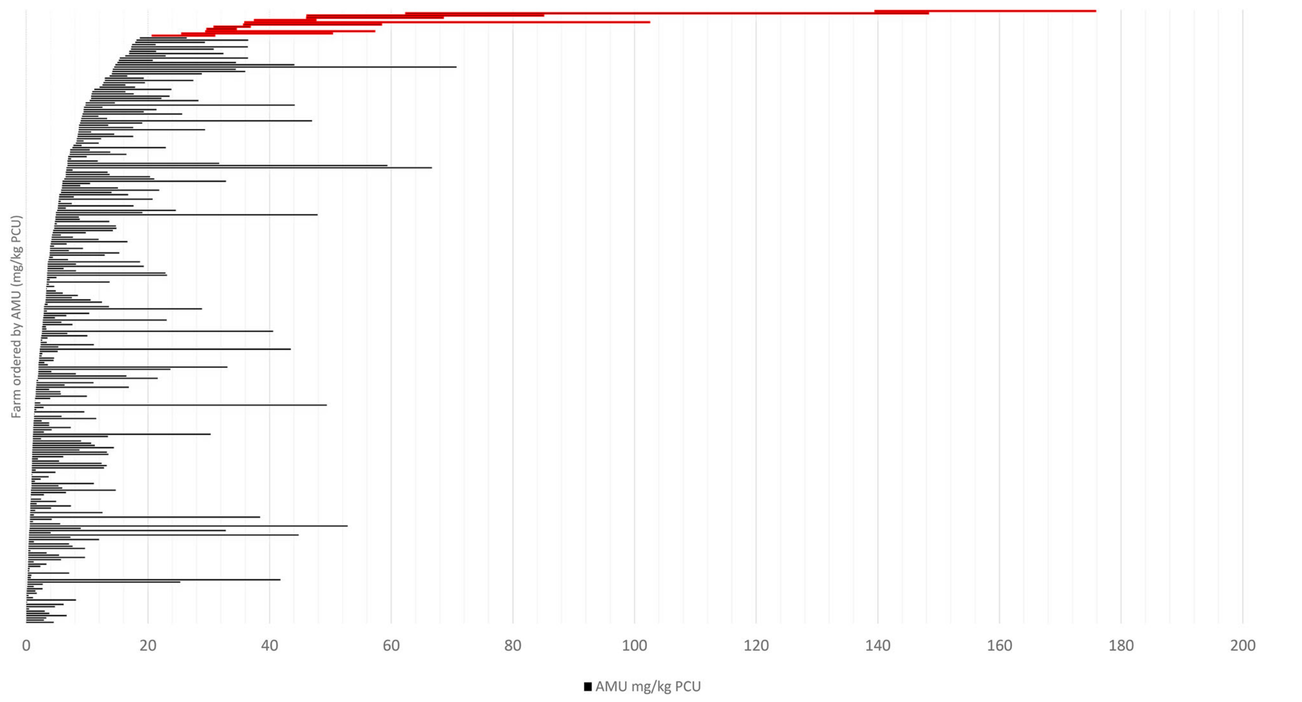

FIGURE 1 Distribution of annual antimicrobial use (AMU) (mg/kg population corrected unit [PCU]) per farm over the study period. Farms in red have a minimum AMU greater than 20 mg/kg PCU

TABLE 2 Descriptive figures for the subset of farms that responded to the questionnaire and provided detailed management information.

Variable	Number responses, *n*	Minimum	Q1	Median	Q3	Maximum
Number of ewes	161	40	200	385	656	3224
Number of lambs	161	57	287	552	941	4626
Proportion ewes receiving *Chlamydophila* vaccine (%)	140	0	0	0	18	100
Proportion ewes receiving *Toxoplama* vaccine (%)	141	0	0	0	17	100
Proportion ewes reported lame (%)	149	1	2	5	10	75
Proportion ewes lambing indoors (%)	159	0	38	96	100	100
Scan percent (%)	136	98	155	175	188	236

TABLE 3 Results from the mixed effects model exploring associations between both management factors and vaccine usage on antimicrobial usage (mg/kg population corrected unit).

Term	Coefficient (95% confidence interval)
Intercept	6.14 (0.01–12.28)
Proportion of flock lambing indoors (%)	0.06 (0–0.12)

Note: The coefficient of determination (R^2) for this model was 24%.

median of 0.20 mg/kg PCU (IQR: 0.12, 0.38) for flocks lambing exclusively outside.

Associations between management factors and AMU are shown in Figure 2. Analysis of these variables using a mixed effects model identified associations between indoor-lambing flocks and increased AMU (Table 3). The proportion of flocks lambing indoors was associated with higher mg/kg PCU, with a 1% increase in indoor lambing being associated with an increase in AMU of 0.06 mg/kg PCU (95% confidence interval: 0–0.11), although the coefficients in these models are relatively modest (a 10% increase in proportion of flock lambing indoors is associated with a 0.6 mg/PCU increase in AMU). Mean AMU mg/kg PCU was 4.8, 6.9, 6.3 and 11.7 for farms lambing less than 25%, 26%–50%, 51%–75% and more than 75% of the flock inside, respectively.

Associations between AMU, lameness and Footvax vaccine use

One hundred and fifty farms provided an estimated average lameness prevalence for 2017, of which 12% reported using the licensed footrot vaccine Footvax. The mean lameness prevalence was 6.7%, and the median was 5.0% (IQR: 2.0, 10.0), with an overall range from 0% to 30%. There was no correlation between AMU and the reported annual lameness prevalence for that year. There were no significant associations

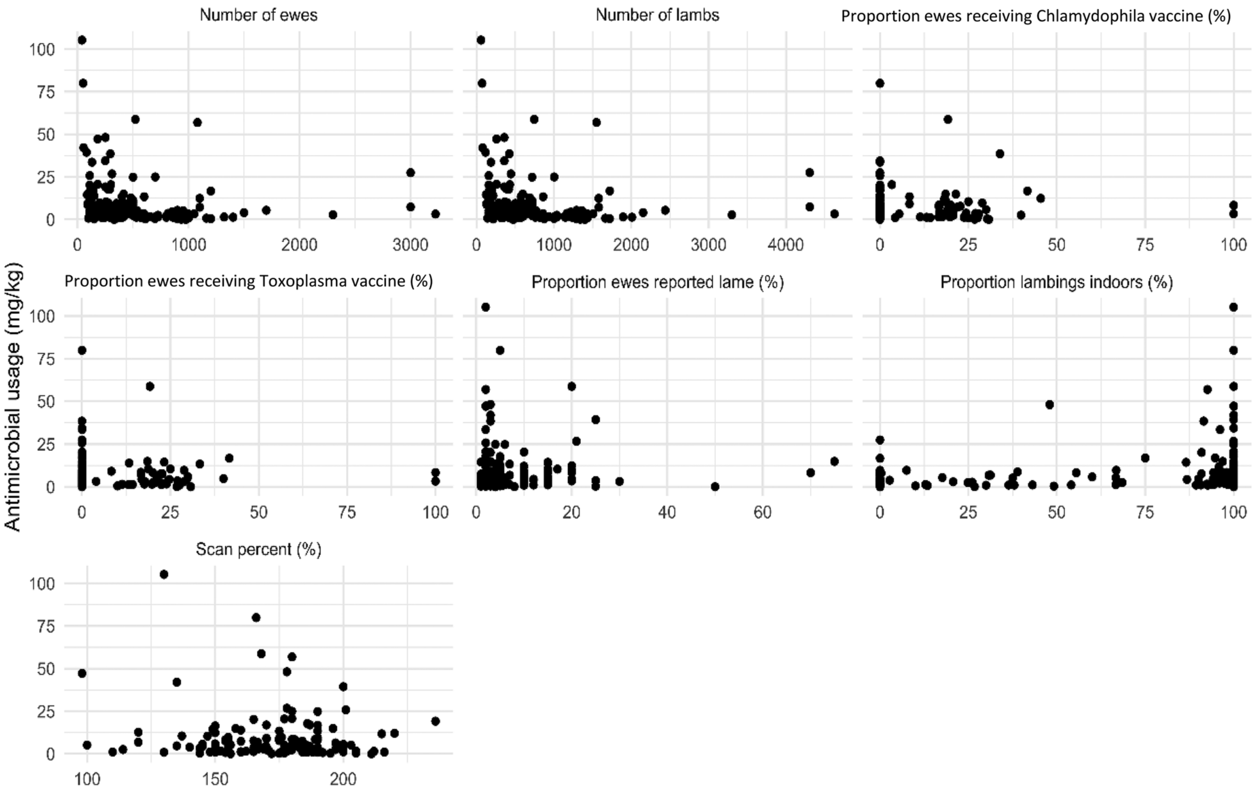

FIGURE 2 Associations between management variables and antimicrobial usage (mg/kg population corrected unit)

between Footvax vaccination status and either AMU or lameness prevalence.

DISCUSSION

AMR poses a direct threat to the health and welfare of livestock species, including sheep, as well as to the wider human population through the food chain and the environment. It is essential that all livestock sectors appreciate these three 'One Health' dimensions to AMR and AMU. The sheep industry is in a unique position in comparison to other livestock sectors, in that AMU is already comparatively low. However, sheep are the livestock species most directly in contact with the general public through the shared use of pastureland for grazing and recreation. The management strategies and critical control points used to reduce the risk of AMR transmission to humans from more intensive sectors, such as dairy cattle, pigs or poultry, may well not apply to extensive sheep production systems. In order to understand what husbandry and policy changes to AMU may be appropriate, we need to understand the dynamics of AMU. We also need to understand the actual and relative risk of transmitting AMR genes and/or pathogens between humans and animals in both directions. Without a robust and comprehensive characterisation and quantification of these AMR risks, policy makers and the livestock industry are unable to make fully informed decisions on what should constitute appropriate and proportionate AMU targets, AMU limits or best practice guidelines.

The results from this study support those of previous studies indicating that the large majority of UK flocks are low users of antimicrobials.[7] However, a very small proportion of flocks appear to be habitually high users of antimicrobials, well above the maximum target threshold of 50 mg/kg PCU. A larger group of farmers are intermittently high users of antimicrobials, despite typically being low users. These results suggest that a high AMU event for a sheep farm might be a sporadic event for a given year, potentially in response to a disease challenge, and the farm might not be a consistently high user of antimicrobials.

If policy were to target or penalise a 'high user' in a given year, this might unfairly target farms that are usually low users of antimicrobials and are responding to a specific situation for a short time period. While the majority of farms are consistently low users, to robustly identify farms potentially using antimicrobials in a non-judicious manner, it will be important to capture multiple years' worth of data to identify consistently high AMU farms. Targeting the minority of consistently high AMU farms might be more effective in reducing AMU than targeting a small reduction for the majority of the population that are already low users of antimicrobials.

It is not yet understood to what extent the intermittent or habitual high use of antimicrobials will influence AMR selection, amplification or transmission. The relative selection pressure of oral compared to parenteral antimicrobial treatments is also poorly understood, especially in the context of ruminant farming systems. These knowledge gaps present some challenges for researchers and policy makers alike.

The aim of national or industry initiatives and benchmarking programmes has been to reduce the total AMU of the population of farms. However, the highly skewed distribution of AMU across the population of farms in this study raises an important question about this strategy. There is a pressing need to focus on apparent 'outliers' with habitually high usage because they represent a disproportionately high risk for resistance selection and transmission.

The findings from this study highlight the urgent need for a robust means of AMU surveillance across UK sheep flocks. Sheep farms commonly manage other livestock in integrated systems with their sheep, most frequently beef cattle. This generates further complexity in accurately attributing AMU to individual species.

For the purposes of this study, mass-based metrics were used, and it should be noted that defined daily dose (DDD) metrics are also widely used as a measure of AMU. Both types of metrics have their limitations, especially when comparing between classes; however, for the sheep sector in the UK, we have the particular situation where the overwhelming popularity of oxytetracycline and amoxicillin injectable products results in a close correlation between the mass-based and dose-based metrics. The macrolide antibiotics present an interesting challenge in this respect as their (mg/kg bodyweight) dose rate is substantially lower and therefore PCU and DDD metrics are less well correlated than many other more commonly used classes. However, in the UK veterinary market at the present time, the relatively high cost of macrolides compared to oxytetracycline and amoxicillin presents a substantial economic disincentive to adoption of macrolide antibiotics as an alternative to either oxytetracycline or amoxicillin.

This study clearly demonstrates the value of and urgent need for the wide adoption of a universal AMU benchmarking system for both flocks and their prescribing veterinarians, such as that provided for by the Agriculture and Horticulture Development Board (AHDB) Medicine Hub and the Welsh Lamb and Beef Producers AMU calculator.

Veterinary practice antimicrobial sales data, as used in this study, are considered the easiest to collect and represent an upper estimate of all the antimicrobials entering the farm. In the UK and much of northern Europe, the veterinary practitioner responsible for the farm has a monopoly on the prescription of antimicrobials. This provides a useful critical control point for automated data collection if that data can be organised and analysed appropriately.

This study has indicated a poor correlation between AMU and vaccine usage. That is not to say vaccine use and AMU are independent but simply that the relationship is not as simple as we may wish or expect. While vaccine usage and other preventative measures can be considered preferable to AMU on ethical and welfare grounds, there is currently insufficient evidence to conclude that those farms that adopt vaccination strategies to control common bacterial diseases are also farms that use fewer antimicrobials. Use of metrics such as vaccine use as proxies for AMU or disease burden would appear overly simplistic based on the results of this study and are likely to be equally poor proxies for overall AMR. A wide range of potential confounding factors (biological and behavioural) may influence the relationship between vaccine use, vaccine efficacy, disease prevalence and AMU, but unravelling this complex relationship is outside the scope of this study.

The methodology adopted in this study relies on the active engagement of stakeholders. This inevitably and unavoidably introduces the risk of a degree of participation bias at both the veterinarian and farmer level. The impact of such a bias on the direction or degree of the results is extremely difficult to estimate but remains a limitation of this type of voluntary participation study. There is a clear argument for a universal national, compulsory AMU benchmarking system for UK veterinarians and livestock producers, as is currently practiced in other jurisdictions such as Denmark (VetStat)[12] and the Netherlands.[13–15] This type of compulsory, universal system is a valuable research resource. However, manual recording is notoriously prone to recall error and accidental mistakes and omissions, in addition to being extremely laborious and costly for farmers if reporting does not take advantage of streamlined, automated data collation systems.

At present, the evidence base for linkage between AMU in ruminants and AMR is limited and has forced policy to follow the precautionary principal without the evidence base to determine a rational trade-off between reducing AMU in order to minimise AMR versus allowing AMU to maintain health and productivity. This study has demonstrated that the majority of sheep farms are low antibiotic users. While the promotion of good stewardship principles is crucial to maintain the reputation of the UK sheep industry, penalising an individual farm based on a single year of higher AMU would appear unfair and potentially counterproductive, as sporadic peaks in AMU are more likely to be in response to a disease outbreak rather than a symptom of inappropriate or avoidable reliance upon antimicrobials.

AUTHOR CONTRIBUTIONS

Peers L. Davies and Fiona M. Lovatt designed the study and recruited the participating veterinary practices. Peers L. Davies and Robert M. Hyde conducted the analysis. Peers L. Davies drafted the manuscript, which was edited by all authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The study was approved by the ethics committee of the University of Nottingham School of Veterinary Medicine and Science.

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