



OPEN ACCESS

PAPER

Storage of prescription veterinary medicines on UK dairy farms: a cross-sectional study

Gwen M Rees,¹ David C Barrett,¹ Henry Buller,² Harriet L Mills,^{1,3} Kristen K Reyher¹

Prescription veterinary medicine (PVM) use in the UK is an area of increasing focus for the veterinary profession. While many studies measure antimicrobial use on dairy farms, none report the quantity of antimicrobials stored on farms, nor the ways in which they are stored. The majority of PVM treatments occur in the absence of the prescribing veterinarian, yet there is an identifiable knowledge gap surrounding PVM use and farmer decision making. To provide an evidence base for future work on PVM use, data were collected from 27 dairy farms in England and Wales in Autumn 2016. The number of different PVMs stored on farms ranged from 9 to 35, with antimicrobials being the most common therapeutic group stored. Injectable antimicrobials comprised the greatest weight of active ingredient found, while intramammary antimicrobials were the most frequent unit of medicine stored. Antimicrobials classed by the European Medicines Agency as critically important to human health were present on most farms, and the presence of expired medicines and medicines not licensed for use in dairy cattle was also common. The medicine resources available to farmers are likely to influence their treatment decisions; therefore, evidence of the PVM stored on farms can help inform understanding of medicine use.

Introduction

Prescription veterinary medicine (PVM) use in the UK is an area of increasing focus for the veterinary profession, agricultural sector, government and food retailers.¹ The agricultural sector is a significant user of antimicrobials,² and reducing its overall use along with improving data collection were key recommendations of the O'Neill report.³ According to the list published by the Veterinary Medicines Directorate in the UK, as of January 1, 2018, there are 1876 prescription-only veterinary medicines (POM-V), of which 142 are licensed to treat solely cattle and 456 are licensed to treat multiple species including cattle. These comprise 152 different listed active ingredients.⁴ There are 233 different antimicrobial preparations (containing 60 listed active ingredients) licensed for use in cattle, with 75 licensed POM-V classed by the European Medicines Agency as

highest priority, critically important antimicrobials (HP-CIA) to human health.⁵ Antimicrobial resistance is a recognised global threat, and there have been many calls for improved understanding of antimicrobial prescription, use and recording.^{1,3,6-8} Currently in the UK, antimicrobial use (AMU) in the dairy industry is measured through a combination of pharmaceutical production/import data and more recently using a sample of individual veterinary practice sales data. This has improved data granularity but may not represent actual use on farms.² Data for other PVMs such as vaccines, NSAIDs or mechanical teat sealants are not currently measured or published nationally.

Farmers in the UK can purchase and store PVM on farm for use at a later date.⁹ Many studies measure AMU on dairy farms^{7,10-15}; however, few/none report the quantity of antimicrobials stored on farms directly nor the way in which they are stored. Medicine storage on farms is an important part of compliance with Health and Safety Executive and farm assurance guidelines,^{16,17} which require PVM to be placed in a secure, lockable location away from children, animals and thieves.¹⁸ In addition, medicines should be stored at the temperature requirements stated on the packaging. Despite this, a recent study found that vaccines were routinely being stored at inappropriate temperatures on UK farms.¹⁹ There is currently little evidence available to determine whether PVMs are used in the way the prescribing

Veterinary Record (2018)

doi: 10.1136/vr.105041

¹Bristol Veterinary School, University of Bristol, Bristol, UK

²MRC Integrative Epidemiology Unit, Bristol Medical School, University of Bristol, Bristol, UK

³College of Life and Environmental Sciences, University of Exeter, Exeter, Devon, UK

E-mail for correspondence: gwen.rees@bristol.ac.uk

Provenance and peer review Not commissioned; externally peer reviewed.

Received May 30, 2018

Revised August 24, 2018

Accepted October 12, 2018

veterinarian intended, or whether farmers are making decisions based on other factors while using stored PVM which may be expired or not licensed for use in dairy cattle.

There is evidence in human health research that prescription medicines are often stored in the home for use at a later date, despite the prescription having been intended for immediate use.^{20 21} Studies have found that a proportion of patients deliberately planned to stop taking a course of prescribed antibiotics early in order to have a supply for self-use in the future.^{22 23} Non-compliant use of medicines is commonly seen,²⁴ and there is evidence that medicines are taken in ways other than that indicated by the prescriber.^{25 26} It follows therefore that there is an urgent need for research into PVM storage and compliance in agriculture.

The aims of this study were to provide data on the storage practices of PVM on UK dairy farms and to investigate the quantity and composition of PVM being stored.

Materials and methods

Study design and population

This article was written according to the Strengthening the Reporting of Observational Studies in Epidemiology statement for scientific reporting of cross-sectional studies.²⁷

Data in this study formed part of a wider project investigating PVM use on UK dairy farms. Twenty-seven dairy farms in South West England and South Wales were enrolled. Veterinary practices within the study area were asked to recruit dairy farms. Mixed-species farms were only included where PVM purchase and storage for the dairy herd were kept separate from other PVM. Selection of farms was purposive based on varying herd size, production levels and management practices. Veterinary practices were asked to nominate farms across the spectrum of perceived medicine storage compliance to minimise selection bias. All farms were visited once by the lead author in a six-week period in Autumn 2016.

On the day of the visit, a structured interview was conducted with the self-identified 'main treatment decision-maker' (hereafter called the farmer) to gather information on farm demographics, management practices, animal health and productivity. Stock numbers, production, health and fertility data were ascertained to the best of the farmer's knowledge aided by consultation with on-farm records. For the PVM inventory the farmer was asked to indicate areas on the farm where PVM might be found. The designated medicine cupboard was examined first, and certain high-probability storage areas were directly inquired about (eg, household refrigerator, calf shed, milking parlour). Permission was also requested to search for PVM anywhere on the farm. A photograph of the

medicine cupboard was taken and field notes written as an *aide-memoire* about the storage systems.

All PVMs found were entered on-location into a preprepared spreadsheet. Location, drug name, pack size, number of packs, quantity remaining in each pack and expiry dates were noted. Where the product label was illegible, it was disregarded. Where the expiry date was illegible, it was assumed to be within date. Volume remaining was estimated by eye to the nearest 10 per cent of pack size (ie, for a 100-ml pack of liquid, volume was estimated to the nearest 10 ml; and for a 50-g pack of powder, quantity was estimated to the nearest 5 g). All POM-V medicines were recorded along with any vaccines licensed for use in cattle and all pour-on, oral and injectable endectocides (anthelmintics). Vaccines were recorded in number of doses rather than volume. All intramammary and ocular medicines were recorded as single units per tube because one tube is equivalent to one dose.

Data analysis

All data were entered into separate spreadsheets, one per study farm. The data from these spreadsheets were

Table 1 Demographic and management characteristics of the 27 participating farms

Characteristics	Response	Farms (n)
Age of farmer (years)	18–30	5
	31–40	5
	41–50	5
	>50	12
Education level of farmer	Basic schooling	3
	O level/GCSE/A level	4
	HNC/HND/NVQ	16
	University bachelor's degree	4
Total herd size	100–199	6
	200–299	12
	300–699	10
	>700	5
Total number of cows in milk	1–99	5
	100–199	11
	200–299	4
	>300	7
Calving pattern	Year-round	22
	Seasonal—Spring	4
	Seasonal—Autumn	1
Primary cow type	Holstein	16
	British Friesian	4
	Channel Island	3
	Crossbreed	2
	Other	2
Waste milk feeding	Yes—all calves	13
	Yes—beef calves only	7
	No	7
Dry cow antimicrobial therapy	Blanket therapy	18
	Selective therapy	9

Basic schooling: no qualifications gained; blanket therapy: all dry cows treated with intramammary antimicrobial; farmer: self-described main treatment decision maker; selective therapy: certain dry cows not treated with intramammary antimicrobial based on somatic cell count and mastitis risk assessment.
GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; NVQ, National Vocational Certificate.

Table 2 Production, health and medicine storage characteristics of the 27 participating farms

Property/Characteristics	Median or mean*	Range (median) or sd (mean)*
Total herd size	320	119–1271
Number of cows in milk	175	65–600
Total annual milk volume (million litres)	1.1	0.5–4
Total annual milk sales per cow (litres)	7500	3600–11 300
Milk price (pence per litre)	22.5*	15.3*
Somatic cell count (cells per millilitre)	176 407*	50 466*
Bactoscan (1000 bacteria per millilitre)	20.9*	7.5*
Mastitis (cases per 100 cows per year)	36.7*	15.9*
Lameness (cases per 100 cows per year)	22.2*	15.3*
Respiratory disease (cases per 100 calves per year)	10	0–47
GI disease (cases per 100 calves per year)	10	3–59
Number of PVM present on farm (by active ingredient)	19	9–35
Number of PVM present on farm (by medicine unit)	101	28–339

* indicates mean; GI, gastrointestinal; median, non-normally distributed data; mean, normally distributed data; PVM, prescription veterinary medicines.

then collated and analysed by retrieving specific data sets through the R software²⁸ and producing a database for all 27 farms to be compared and analysed together.

Medicine quantities were measured in total milligram of active ingredient present, in milligram per population corrected unit (PCU) in line with nationally reported use data,²⁹ and in the total number of ‘medicine units’ present. Medicine units were defined as one bottle of liquid, one tube of intramammary or ocular suspension, one pack of boluses or tablets, one container of powder, or one tube of ointment. PVMs were grouped according to therapeutic group (eg, antimicrobial, vaccine). Antimicrobials were grouped by antimicrobial class (eg, penicillin, fluoroquinolone) and according to route of administration (eg, injectable, intramammary). Expired medicines were defined as those medicines with an expiry date before the day of the inventory. Milligrams of active ingredient were presented to the nearest 100 mg for the total weight of active ingredient, to the nearest 10mg for milligram per cow in milk and milligram per 1000 litres of milk produced annually, and to the nearest 0.01 mg for mg/PCU.

Data were visually checked for normality. Normally distributed data were reported as a mean with sd in brackets. Non-normally distributed data were reported as a median with range in brackets. Calculations were performed using a combination of Microsoft Excel (V.2016) and R.²⁸ Given the cross-sectional, point-prevalence nature of the data set and the fact that the study farms are not intended to be a representative sample of the population, presented calculations were descriptive and no inferences on causality can be made.

Results

Farm demographics

Thirty-four dairy farms were identified as eligible for the study through self-nomination or nomination by

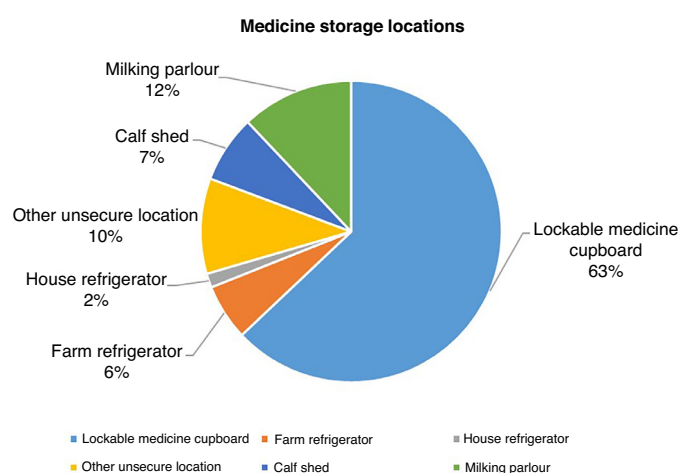


Figure 1 Medicine storage locations across the 27 participating farms.

veterinary practices. All were invited to enrol in the study, and 29 agreed to take part. Two farms dropped out of the study before the medicine inventory visit. Data for the remaining 27 farms were complete. These farms were located across seven counties and under the care of nine veterinary practices.

Farm demographic and management characteristics are described in table 1. In summary, the median total herd size was 320 with 175 cows in milk. Most farms (59 per cent) described the main cattle breed as Holstein and the majority calved year-round (81 per cent). The median total annual milk volume per herd produced was 1.1 million litres, with annual milk sales per cow of 7500 litres. Seventy-four per cent of farmers had some formal specialised education and training in agriculture.

Farm production and health characteristics are presented in table 2. Two-thirds of farms used blanket dry cow therapy (where all cows were dried off with intramammary antimicrobial treatment). Twenty farms routinely fed waste milk containing antimicrobial residues to beef calves, 13 of which also fed waste milk to dairy replacement calves. The mean number of clinical cases of mastitis and lameness per 100 cows per year was 36.7 and 22.2, respectively. There were a median of 10 cases of respiratory disease and 10 cases of gastrointestinal disease per 100 calves per year.

Storage methods

Medicines were stored in six different location types across the study farms as seen in figure 1. Most were stored in a lockable medicine cupboard or refrigerator,

Table 3 Total quantities of antimicrobial stored across all 27 participating farms, by route of administration

Route of administration	Total (mg)	Total (medicine units)
All	5 127 176 (100%)	2801 (100%)
Injectable	3 917 116 (76.4%)	280 (10%)
Intramammary	755 772 (14.7%)	2374 (84.8%)
Topical	284 348 (5.5%)	51 (1.8%)
Oral	54 440 (1.1%)	31 (1.1%)
Intrauterine	115 500 (2.3%)	65 (2.3%)

Table 4 Quantity of antimicrobial stored on the 27 participating farms

Antimicrobial type	Total		Total		Total		Farms where present (n)
	(mg)		(mg/PCU)		(medicine units)		
	Median	Range	Median	Range	Median	Range	
Total antimicrobial	182 200	45 500–442 400	1.54	0.51–5.08	69	22–296	27
Total HP-CIA	10 000	0–68 000	0.12	0.00–0.34	5	0–95	24
Fluoroquinolone	0	0–32 000	0	0.00–0.19	0	0–4	11
Third-generation cephalosporin	5000	0–36 000	0.06	0.00–0.30	1	0–5	19
Fourth-generation cephalosporin	1000	0–9000	0.01	0.00–0.12	0	0–59	13
Injectable (all)	143 600	16 500–393 000	1.19	0.19–4.51	9	1–35	27
Intramammary (all)	21 200	1000–111 400	0.21	0.01–0.49	66	5–248	27
Other (all)	13 200	0–61 800	0.11	0.00–0.63	5	0–24	21
Injectable (HP-CIA)	5000	0–36 000	0.09	0.00–0.34	2	0–6	24
Intramammary (HP-CIA)	1000	0–9000	0.01	0.00–0.12	0	0–93	12
Other (HP-CIA)	0	0	0	0	0	0	0

HP-CIA, highest priority, critically important antimicrobial (ref. European Medicines Agency); PCU, population corrected unit.

although 29 per cent were stored in a non-compliant area such as the milking parlour, the calf shed or the office. Ten farms stored 100 per cent of their medicines in lockable medicine cupboards or lockable refrigerators, and two farms did not store any medicines in a lockable medicine cupboard or lockable refrigerator. No participating farm monitored the temperature of their refrigerator or medicine storage area.

Prescription veterinary medicines

There were a median of 19 (9–35) different types (by active ingredient) of PVM and 101 (28–339) individual medicine units of PVM present on participating farms. Antimicrobials were the therapeutic group most commonly stored both by frequency of occurrence (median 69 (22–296) medicine units) and by total weight (median 182,300 (45,500–442,500) mg) equivalent to 1.54 mg/PCU.

Antimicrobials

The routes of administration for antimicrobials stored are presented in table 3. Of the total antimicrobials stored across all farms, 76.4 per cent were injectable and 14.7 per cent were intramammary. When units were measured, 10 per cent were injectable (bottles) and 84.8 per cent were intramammary tubes.

Data on antimicrobial storage are presented in table 4. The total HP-CIA storage per farm has a median of 10,000mg, or 0.12mg/PCU, with the majority (5000mg) being third-generation cephalosporin. Injectable antimicrobials comprised the greatest total weight, with a median of 143,600mg or 1.19mg/PCU, compared with intramammary antimicrobials which had a median of 21,200mg or 0.21mg/PCU. Conversely, intramammary antimicrobials had the greatest total number of medicine units present, with a median of 66 units compared with nine units of injectable antimicrobials.

Eighty-nine per cent of farms stored at least one HP-CIA. The most frequently occurring injectable antimicrobials were ceftiofur (HP-CIA; n=24) and

penicillin/streptomycin combination (n=24). Also commonly found were oxytetracycline (n=22), tylosin (n=19) and trimethoprim/sulphadiazine (n=16). The three lactating-cow intramammary antimicrobials most commonly identified were potentiated amoxicillin (n=11), the combination streptomycin/neomycin/novobiocin/penicillin (n=11) and cefalexin/kanamycin (n=10). The most frequently occurring dry cow intramammary antimicrobials were cephalonium (n=12), cefquinome (HP-CIA; n=10) and cloxacillin (n=8).

The total milligram per PCU on each farm ranged from 0.51 to 5.08 mg/PCU (figure 2). The total milligram per cow in milk ranged from 430 to 3430 mg (figure 3). The total milligram per 1000 litres of milk produced annually ranged from 40 to 740 mg (figure 4).

Vaccines and other PVM

The total number of vaccine doses stored across all farms was 3541 with a median of 0 (0–1893) dose per farm. Eighteen farms (66.7 per cent) stored no vaccines at the time of the study. The most common diseases for which vaccines were stored were bovine herpesvirus 1 (866 doses; five farms), leptospirosis (835 doses; five farms) and bovine viral diarrhoea (683 doses; five

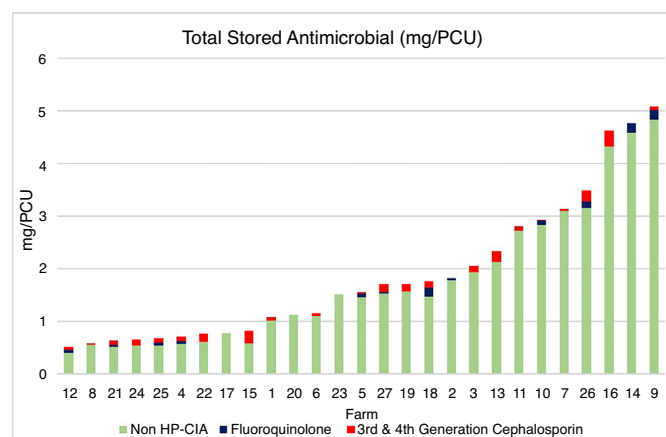


Figure 2 Total quantity of antimicrobial stored on each participating farm (n=27) in mg/PCU. HP-CIA, highest priority critically important antimicrobial; PCU, population corrected unit.

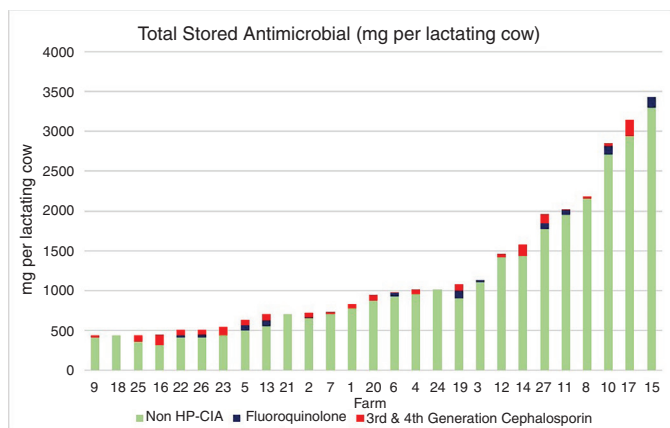


Figure 3 Total quantity of antimicrobial stored on each participating farm in milligrams per lactating cow. HP-CIA, highest priority, critically important antimicrobial.

farms). Other diseases for which vaccines were stored were calf diarrhoea, bluetongue, clostridial diseases, lungworm, mastitis and calf pneumonia.

The total number of units of NSAIDs across all farms was 75, with a median of 2 per farm (0–8). The total number of anthelmintics or antiprotozoals present across all farms was 87, also with a median of 2 per farm (0–14). The total number of units of hormone across all farms was 53, with a median of 1 (0–10) unit per farm. Five farms (19 per cent) stored prostaglandins.

Expired medicines

At least one unit of expired PVM was stored on 25 farms (93 per cent). Eighteen farms (67 per cent) stored at least one expired antimicrobial and six (22 per cent) stored at least one expired vaccine. The total number of expired antimicrobial units across all farms was 201, with each farm storing a median of 2 (0–58) expired antimicrobials. The total number of doses of expired vaccines stored across all farms was 827, with each farm storing a median of 0 (0–725) expired dose.

The median length of time since expiration was 12 (1–200) months. For antimicrobials, the median length of time since expiration was 10 (1–96) months, for anti-inflammatories 6 (2–42) months, for vaccines 20

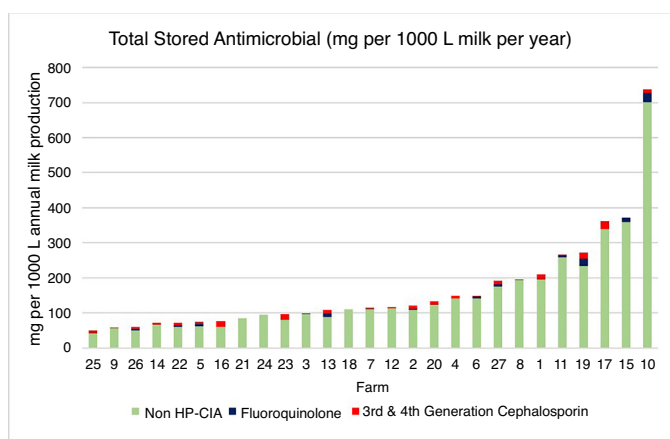


Figure 4 Total quantity of antimicrobial stored on each participating farm in milligrams per 1000 litres of milk produced annually. HP-CIA, highest priority, critically important antimicrobial.

(2–200) and for other medicines 12 (2–120) months, with the majority of the ‘other’ medicines endectocides.

Cascade medicines

Medicines not licensed for use in dairy cattle were found on 16 farms (59 per cent). A total of 30 unlicensed units were stored, comprising 14 different medicines. Seven different unlicensed antimicrobials were identified totalling 709,100 mg of active ingredient. Macrolides were the most common, with 138,600 mg of erythromycin (licensed for use in poultry and pigs) found across seven farms served by two different veterinary practices—2000 mg lincomycin on one farm (licensed for use in pigs) and 200 mg gentamicin (licensed for use in horses not producing milk or meat for human consumption) on one farm. Also found were 500,000 mg of tetracyclines (licensed for use in poultry and pigs) across three farms served by one veterinary practice, 5000 mg metronidazole veterinary tablets (licensed for use in dogs and cats but banned from use in cattle) on one farm, 18,000 mg of first-generation cephalosporin of Hungarian origin and not licensed for sale in the UK on one farm, and 30,000 mg of florfenicol of Dutch origin not licensed for sale in the UK on a different farm. There was no clustering of unlicensed products by farm. Other unlicensed medicines identified were 50 ml of mepivacaine (a local anaesthetic agent licensed for use in horses), 1 tube of acepromazine gel and 30-ml romifidine (sedatives licensed for use in horses), 2 capsules of 2-mg loperamide (an antispasmodic licensed for human use), 200-ml sucralfate, 2 tubes of fusidic acid gel (an antibiotic topical gel licensed for use in cats and dogs) and one bottle of topical miconazole licensed for use in dogs. Where unlicensed medicines were found, farmers confirmed they were present for use in the dairy calves or adult cattle.

Discussion

Most farms in this study stored PVM in the recommended way. However, some PVMs were being stored in inappropriate conditions, for example, in areas at risk from heat or cold damage and exposure to sunlight or gross contamination. Twenty-nine per cent of PVM found were not stored in a lockable cupboard or room. This has direct health and safety implications due to access to potentially harmful medicines by animals or children in addition to risks of theft. Certain medicines should be stored with particular care due to their potential for harm from accidental exposure.¹⁸ Prostaglandins, for example, which made up a proportion of the hormone POM-V reported in the Results section, can be absorbed transcutaneously and lead to miscarriage or serious and even fatal respiratory compromise in susceptible people.³⁰

While some farms stored a wide range of different types and quantities of PVM, others stored a limited number. The fact that the quantity of antimicrobials

stored on farm does not appear to be linked with the number of animals at risk of treatment or the overall production values of the cows on the farm (figures 2–4) suggests that there are other reasons for the range of storage practices seen. Ongoing work by the lead author, as part of a wider study, is exploring these reasons.³¹

As previously noted, a farmer's treatment decisions are to some extent constrained by the PVM resources available to them. It follows therefore that when designing policy interventions aimed at reducing AMU, data on storage practices and farmers' use of stored medicines are extremely important.

Antimicrobial storage

Antimicrobials were the PVM stored in the greatest quantity when measured by total milligram of active ingredient as well as by individual medicine units. Twenty-four farms stored HP-CIAs, indicating that their use is still common in UK dairy farming; however, recent increased efforts to reduce their use mean this is likely to be a rapidly evolving picture. For example, as of June 2018 the Red Tractor Farm Assurance will require HP-CIAs only be used as a last resort, with a veterinary report outlining diagnostic or sensitivity testing.³² While storage does not equate to actual use, it is likely that these antimicrobials are stored with the intention of use, and therefore it may be that the use of HP-CIAs was still common practice during the period of the study. Data from the wider longitudinal research study are in preparation for publication and will report on actual PVM use on these farms including HP-CIA use over a 12-month period.

The number of bottles of injectable antimicrobial present on farms was as high as 35 on one farm, with a median of 9. Keeping a store of antimicrobials like this provides a large resource for the farmer to use without a need to consult her/his veterinarian. One of the most frequently kept injectable antimicrobials was ceftiofur, an HP-CIA. Given the focus on reducing the use of HP-CIAs in the years preceding the study, this may be indicative of a reluctance to move away from their use in the dairy sector. The 0-hour milk withhold carried by ceftiofur and its broad licensing for use in respiratory disease, metritis and interdigital necrobacillosis made it an attractive and cost-effective option for treating disease on farm, and it appears to have remained popular at least until the latter part of 2016. The antimicrobials most commonly used for treating mastitis in the lactation period were not on the current HP-CIA list, although potentiated amoxicillin is not considered to be a first-line treatment.³³ The most commonly stored antimicrobials for treating dry cows included cefquinome, a fourth-generation cephalosporin and HP-CIA.

Many of the first-line, 'responsible' antimicrobials have a relatively high total weight of active ingredient when compared with HP-CIAs, leading to calls for

HP-CIAs to be measured and benchmarked separately from other antimicrobials.^{6 7} This study provides evidence that there is an ongoing need to change behaviour and reduce the use of HP-CIAs on dairy farms.

Interestingly, when measured in mg/PCU or mg/1000-litre milk produced annually, the data show that while most farms stored similar quantities of antimicrobial, a handful of farms stored up to 10 times as much as those farms which stored the smallest amounts. This suggests other factors affect the storage practices of dairy farmers, something being investigated in ongoing work by the authors.

Participating farms stored a broad range of different antimicrobials, thus increasing their options when making treatment decisions. This could lead to a dissonance between the intention of the prescribing veterinarian and the actions of the farmer. Having such a large resource to draw upon could be seen to improve the agency and ownership of the farmer on those decisions, but conversely to decrease the agency and ownership of the veterinarian legally responsible for their use. This serves to emphasise the importance of understanding the treatment decisions, given the relatively few resource constraints.

Expired medicines

While the presence of expired medicines does not equate to their use, the fact that expired PVMs were identified on most participating farms indicates that their use is likely to be common. Expiry dates for drug products are set based on real-time stability testing at appropriate storage conditions to determine whether the drug substance meets its individually set specification.³⁴ A specification 'establishes the set of criteria to which a drug product should conform to be acceptable for its intended use'.³⁵ All but two farms stored at least one expired PVM, with two-thirds storing at least one expired antimicrobial. This is particularly striking when compared with studies of household medicine storage among human health, which have shown a range of 3–22 per cent of stored medicines were expired.^{36 37} Given the average length of time passed since expiry was 12 months, with one farm storing medicine that was over 16 years out-of-date, their presence appears to be accepted by farmers on dairy farms.

The impact of using an expired antimicrobial is ill-defined. It is assumed that the efficacy of an antimicrobial, or indeed any medicine, reduces with time after expiration. However, the evidence base for this is small and contradictory. In one study from human health, it was shown that there was a decreased rate of pathogen susceptibility to expired antimicrobials.³⁸ Other studies have shown that most medicines retain their efficacy for many years beyond their expiration date.^{39 40} To the authors' knowledge, there are no studies on the efficacy of expired antimicrobials in veterinary medicine.

Perhaps more important than the expiry date stated on PVM is the shelf-life of the medicine once broached. In-use shelf-life is determined for multiuse veterinary products by in-use stability testing of physical, chemical and microbial properties. Products approaching the end of their shelf-life are tested, with testing designed to simulate as closely as possible real-life conditions based on likely usage patterns of the product under 'normal environmental conditions' and stored according to the product literature. These drugs are measured against either their original specification or an 'in-use shelf life' specification, as appropriate.⁴¹ While this is often 28 days for injectable products and 24 hours for vaccines, in reality these shelf-lives are rarely observed due to most injectable medicines being sold in 100-ml or 250-ml multidose bottles, and individual animals' treatment courses require varying volumes of medicine. Measuring the presence and use of PVM that had passed its broached shelf-life was beyond the scope of this study; however, future research in this area would be valuable.

Expired or waste PVM should not be disposed of with normal household waste, and most veterinary practices offer a disposal service to clients. Given the prevalence of expired PVM on the study farms, veterinarians should determine whether the farms under their care are disposing of these medicines appropriately or whether they remain on farm with potential for use. Discussion of the use and disposal of expired PVM would make a valuable addition to herd health review meetings, particularly given the veterinarian's ultimate responsibility for the safety of medicines being used in these food-producing animals.

The Cascade

Using PVMs which are not licensed for use in dairy cattle is not illegal if they are prescribed and used according to the Cascade and where there are established maximum residue limits.⁴² However, the use of unlicensed PVM is not currently monitored in the UK. Given the presence of medicines which have been prescribed via the Cascade, further research is urgently needed in this area. In one instance, PVMs were present which are explicitly banned from use in dairy cattle (metronidazole): administration would constitute a transgression of the law.⁴³

Study limitations

The use of purposive sampling through veterinary practice nomination inevitably leads to the possibility of selection bias. The study farms were demographically reflective of the wider UK dairy farm population. According to the Agriculture and Horticulture Development Board (AHDB) the 'average number of adult dairy cows' on UK dairy farms in 2016 was 143,⁴⁴ compared with the study farm median of 175. The larger herd size of the study farms may influence the way in

which PVMs are stored. Larger herds are more likely to have an increased frequency of veterinary visits, which may mean they store fewer PVMs on the farm as they have additional resources available to them through the veterinarian on a regular basis.

Farmers were asked not to alter the medicines stored on their farms for the visit day. Given the prevalence of expired medicines and storage of medicines outside of designated cupboards, it appears that farmers did not significantly improve their storage practices before the visit, and the authors believe the data described are representative of normal medicine storage on the study farms. The volume of medicines in opened bottles was estimated by eye to the nearest 10 ml, which may have led to some overestimation or underestimation of the total volume present on farm. Using reference weights for different medicines and a portable weighing scale to measure the weight of bottles may have improved the accuracy of these measurements.

This study was cross-sectional, and the seasonal nature of dairy farming and disease prevalence should be noted. This study took place in the Autumn, around the time of housing for many farms, and the data may be different if it was to be repeated in different seasons. Where mixed-enterprise farms were included, these stored medicines intended for use in dairy cattle and calves separately from medicines intended for beef or sheep. This did not allow for any measurement of the possibility of medicines stored for use in beef and sheep being used in the dairy cattle. It is also important to note that this study reports storage practices on a small number of dairy farms in South West England and South Wales, and as such may not reflect practices found on other farms or in other regions of the UK. Further research in this area is needed to provide a robust evidence base for future policy decisions aimed at improving responsible medicine use in dairy farming.

Conclusions

These are the first data of their kind published on the UK situation and are useful to help veterinarians understand the ways in which medicines are being used postprescription and to inform future herd health planning. Current UK estimates of PVM use are crude and only through detailed on-site research can real medicine use practices be discerned. The results are also helpful for policy makers and researchers to broaden the evidence base surrounding PVM use.

Acknowledgements The authors would like to thank the participating farmers and veterinary practices for their help with this study.

Funding This study was funded by Langford Trust for Animal Health and Welfare.

Competing interests None declared.

Ethics approval This research was approved by the University of Bristol Faculty of Health Sciences Research Ethics Committee under approval no 33 021.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which

permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, an indication of whether changes were made, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

© British Veterinary Association 2018. Re-use permitted under CC BY-NC. No commercial re-use. Published by BMJ.

References

- Buller H, Hinchliffe S, Hockenull J, *et al*. Systematic review and social research to further understanding of current practice in the context of using antimicrobials in livestock farming and to inform appropriate interventions to reduce antimicrobial resistance within the livestock sector. *DEFRA Report* 2015.
- VMD. UK - Veterinary antibiotic resistance and sales surveillance report 2016. *Veterinary Medicines Directorate* 2017.
- O'Neill J. Tackling Drug Resistant Infections Globally: Final report and recommendations. *The Review on Antimicrobial Resistance* 2016.
- VMD. Product Information Database. 2018 <https://www.vmd.defra.gov.uk/ProductInformationDatabase/> (Accessed 01 Jan 2018).
- EMA. Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals. *European Medicines Agency* 2014.
- Mills HL, Turner A, Morgans L, *et al*. Evaluation of metrics for benchmarking antimicrobial use in the UK dairy industry. *Vet Rec* 2018;182:379.
- Hyde RM, Remnant JG, Bradley AJ, *et al*. Quantitative analysis of antimicrobial use on British dairy farms. *Vet Rec* 2017;181:683.
- Escobar M, Buller H. Projecting Social Science into Defra's evidence base 2014: A review of current research and evidence gaps on the issue of farmer behaviour with respect to animal welfare. *DEFRA Report* 2014.
- VMD. Code of Practice on the responsible use of animal medicines on the farm. *Veterinary Medicines Directorate* 2014.
- Brunton LA, Duncan D, Coldham NG, *et al*. A survey of antimicrobial usage on dairy farms and waste milk feeding practices in England and Wales. *Vet Rec* 2012;171:296–U39.
- Ferner C, Obritzhauser W, Fuchs K, *et al*. Development and evaluation of a system to assess antimicrobial drug use in farm animals: results of an Austrian study. *Vet Rec* 2014;175:429.
- González Pereyra V, Pol M, Pastorino F, *et al*. Quantification of antimicrobial usage in dairy cows and preweaned calves in Argentina. *Prev Vet Med* 2015;122.
- González SM, Steiner A, Gassner B, *et al*. Antimicrobial use in Swiss dairy farms: quantification and evaluation of data quality. *Prev Vet Med* 2010;95(1-2):50–63.
- Pol M, Ruegg PL. Treatment practices and quantification of antimicrobial drug usage in conventional and organic dairy farms in Wisconsin. *J Dairy Sci* 2007;90:249–61.
- Saini V, McClure JT, Léger D, *et al*. Antimicrobial use on Canadian dairy farms. *J Dairy Sci* 2012;95:1209–21.
- HSE. Veterinary medicines: Safe use by farmers and other animal handlers. <http://www.hse.gov.uk/pubns/as31.htm> 2012
- RTA. REd tractor assurance for farms: Dairy standards. 2017. Version 4.0 https://assuranceredtractor.org.uk/contentfiles/Farmers-6802pdf?_=636359680695407277 (Accessed 25 May 2018).
- Carr J, Smith J. Storage and safe use of medicines on farm. *In Pract* 2013;35:36–42.
- Williams PD, Paixão G. On-farm storage of livestock vaccines may be a risk to vaccine efficacy: a study of the performance of on-farm refrigerators to maintain the correct storage temperature. *BMC Vet Res* 2018;14:136.
- Tsiligianni IG, Delgatty C, Alegakis A, *et al*. A household survey on the extent of home medication storage. A cross-sectional study from rural Crete, Greece. *Eur J Gen Pract* 2012;18:3–8.
- Abou-Auda HS. An economic assessment of the extent of medication use and wastage among families in Saudi Arabia and Arabian Gulf countries. *Clin Ther* 2003;25:1276–92.
- Hawkings NJ, Butler CC, Wood F. Antibiotics in the community: a typology of user behaviours. *Patient Educ Couns* 2008;73:146–52.
- Shehadeh M, Suaifan G, Darwish RM, *et al*. Knowledge, attitudes and behavior regarding antibiotics use and misuse among adults in the community of Jordan. A pilot study. *Saudi Pharm J* 2012;20:125–33.
- Hugtenburg JG, Timmers L, Elders PJ, *et al*. Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. *Patient Prefer Adherence* 2013;7:675–82.
- Martin LR, Williams SL, Haskard KB, *et al*. The challenge of patient adherence. *Ther Clin Risk Manag* 2005;1:189–99.
- Svd GEEST, Whyte SR, Hardon A. The anthropology of pharmaceuticals: a biographical approach. *Annual Review of Anthropology* 1996:25.
- von Elm E, Altman DG, Egger M, *et al*. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–9.
- Core Team R. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2012. *Isbn 3-900051-07-0*, *Url* <http://www.R-project.org/>.
- VMD. Understanding the population correction unit used to calculate antibiotic use in food producing animals. 2016 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/580710/1101060-v1-Understanding_the_PCU_-_gov_uk_guidance.pdf.
- NOAH. Estrumate® 250 µg/ml Solution for Injection Datasheet. <http://www.noahcompendium.co.uk/?id=-4618522017>.
- Rees GM, Barrett DC, Buller H, *et al*. "It's cheaper than a dead cow": veterinary medicine use on UK dairy farms. *Cattle Practice* 2017;25.
- Assurance RT. Responsible use of antibiotics on Red Tractor farms: guidance for vets. In: Assurance RT, editor. https://assuranceredtractor.org.uk/contentfiles/Farmers-6910pdf?_=6365851203150701902018.
- World Health Organisation. Critically important antimicrobials for human medicine: World Health Organisation, 2016. 5th Revision.
- EMA. ICH Topic Q 1 A (R2) Stability Testing of new Drug Substances and Products. EMA, ed. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002651.pdf 2003.
- EMA. ICH Topic Q 6 B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. EMA, ed. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002824.pdf 1999.
- Zargazadeh AH, Tavakoli N, Hassanzadeh A. A survey on the extent of medication storage and wastage in urban Iranian households. *Clin Ther* 2005;27:970–8.
- Teni FS, Surur AS, Belay A, *et al*. A household survey of medicine storage practices in Gondar town, northwestern Ethiopia. *BMC Public Health* 2017;17:238.
- Ogunshe A, Adinmonyema P. Evaluation of bacteriostatic potency of expired oral paediatric antibiotics and implications on infant health. *Pan Afr Med J* 2014;19:378.
- Courtney B, Easton J, Inglesby TV, *et al*. Maximizing state and local medical countermeasure stockpile investments through the Shelf-Life Extension Program. *Biosecur Bioterror* 2009;7:101–7.
- Cantrall L, Suchard JR, Wu A, *et al*. Stability of Active Ingredients in Long-Expired Prescription Medicines. *Archives of Internal Medicine* 2012;179.
- EMA. Note for guidance on in-use stability testing of veterinary medicinal products (excluding immunological veterinary medicinal products), EMA, ed. 2001. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004399.pdf
- VMD. The Cascade: prescribing unauthorised medicines. 2015 <https://www.gov.uk/guidance/the-cascade-prescribing-unauthorised-medicines> (Accessed 25 May 2018).
- EU. Commission E, ed. Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. <https://publications.europa.eu/en/publication-detail/-/publication/97469e42-8ef3-4536-86bd-46ef667e8a3d/language-en2009>
- AHDB. Dairy statistics: an insider's guide. *AHDB Dairy 2016 Dairy Statistics* 2016.

