Antimicrobial usage on farm

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Introduction

Antimicrobial resistance (AMR) is an increasing problem both in human and veterinary medicine. Recently, guidelines to reduce the risk of emergence of antimicrobial resistance have been released by the British government, the Centre for Disease Control in the United States, and the United States Department of Agriculture amongst others. These strategies all broadly include components of measurement of drug usage, surveillance for antimicrobial resistance, prudent usage and an emphasis on alternatives to antimicrobial (AM) usage.

Estimates of AM usage are important to monitor usage of specific drug classes, assess AM sensitivity data, manage potential risks for AMR, monitor drug usage across time and regions, and to use as a proxy for disease incidence. Usage may be assessed at national, regional, veterinary practice or farm level. Methodologies employed vary depending on availability of data, the detail required, and the inferences that are sought from a study.

At the national level, total drug sales are reported by registrants to MPI who report these along with some commentary. These data are limited by the fact that species and indication are not always clear. For example, a product registered for multiple species and for multiple indications can't be assigned to specific disease or even species. Additionally the population of animals treated may be unknown. Where the population is increasing or decreasing, the mass of drug/animal used may alter simply due to the same treatment rates within the population, but different numbers of animals year to year. Alternatively changes in disease incidence and drug usage may not be detected due to year to year population changes. Hence this national approach, while relatively cheap and easy to implement, may be of limited value when determining exposure of animals and bacteria to antimicrobials.

The European Medicines Agency (EMA) uses a process to estimate population numbers and weights of animals in the population and to estimate average animal exposure to antimicrobials, i.e. a defined daily dose/kg (DDDvet) and average dose for a course of treatment (DCDvet; Anon 2015). This process has been developed to standardise reporting across countries and is specifically used for country level reporting. Complexities include defining the exposure with long acting antimicrobials (i.e. dose/day) where a single injection is given, but the drug is effective over several days. The same issue applies to dry cow therapy (DCT), where a single infusion may result in concentrations above minimum inhibitory concentration for many days. The EMA has assigned four units (i.e. four intramammary tubes) of DCT as one DCDvet (i.e. one course). Where a product contains multiple antimicrobial actives, the approach is to define the DDD for only one of the actives, that is a combination of actives is assigned the same DDD as if there was only one active in the product.

Antimicrobial usage at an individual farm level may be estimated via drug sales onto that farm or by analysis of on-farm recording of drug usage. Calculations of average daily usage/kg using drug sales data requires assumptions about dose, frequency of usage, class of stock that the products are used on, and the assumption that all drugs sold on the farm are actually used on that farm within the time period of interest. For drugs with very specific indications (for example dry cow therapy) then usage and dosing can be relatively safely assumed to be on label. In contrast, drugs with a broad set of indications (disease processes) and a wide range of stock classes (for example calves, heifers, cows) that it could be used on, assumptions about usage pattern are more difficult. Additionally, assumptions need to be made about the average weight of stock and hence the average daily dose (ADD). Collecting on-farm records of use (either hard copy or electronic formats) may offer a more direct measure of usage patterns, but compliance with on-farm recording is not always complete, and shortcuts in recording by farmers may not allow assessment of actual usage patterns.

Antimicrobials have been classified on the basis of their importance to human medicine and/or their usage to treat pathogens that are potentially zoonotic. Critically important antimicrobials (Class A) are those that are used to treat zoonotic pathogens and are drugs of last resort in human medicine. These include the fluoroquinolones, macrolides and the third and fourth generation cephalosporins. Class B antimicrobials include, for example, first and second generation cephalosporins, aminoglycosides and the semisynthetic penicillins. Class C antimicrobials include penicillin and oxytetracycline.

This study describes antimicrobial usage on dairy farms using sales records from two veterinary businesses in New Zealand.

Materials and methods

Herds (n=80) were enrolled in a prospective observational study. The herds were drawn at random from client lists of two veterinary practices in the North and South Islands (AnexaFVC and Vetlife, respectively). The herdowners provided written permission to access all records related to the farm, including electronic records (for example those held in Minda, LIC, Hamilton, New Zealand), on-farm records (for example dairy diaries, yellow books) and drug sales from the clinic. To reduce potential errors associated with drug sales, herds that were part of business structures that had multiple farms under the one management and under the one veterinary account were not enrolled.

Herds were visited on a six monthly basis and all hard copy records were photocopied and entered into a relational database (Access, Microsoft, USA). Additionally, cow demographic data were obtained from electronic sources (LIC, Hamilton, New Zealand) including age, breed, calving date, any disease and treatment records.

All drug sales for enrolled farms were extracted from the accounting packages of the veterinary businesses. Sales data for purchases of products containing antibiotics and administrable by injectable, intramammary, intrauterine or oral routes was retrieved from accounting software. The time period of interest was 1 January to 31 December 2015.

The number of milking cows was calculated from electronic records of the herd. Dates of removal (where this occurred) were retrieved. For each cow, the time at risk over the 2015 calendar year was calculated. For those present throughout the year this was 365 days, whereas those that died or were removed before the end of the calendar year were censored at that time point. It was assumed that rising two-year-old animals were only at risk from the day of calving in the 2015 year through to the end of that year. Note non-lactating animals were excluded from these analyses as were products specifically labelled for treatment of calf diarrhoea.

Animal daily dose was derived from the on-label dose rate (mg/kg) and daily dosing frequency multiplied by the average LWT of the animal class for its main indication of usage. The average LWT for adult dairy cows was defined as 450kg from breed and age-weighted averages (DairyNZ 2012). Where a range of on label dose rates was provided, the mid-point of the range was used for calculations. For dry cow therapy products, four injectors were considered an animal dose; for lactating cow intramammary products, daily dosing was modelled for one gland; and for long-acting injectable products, the daily dose was calculated from the recommended rate and the inverse of the interval between recommended successive doses. Thus average daily usage rate (ADUR) was defined at the herd level as the number of ADD divided by the sum of time at risk for each cow in the herd, multiplied by 365 days. The indication was based on the label. So for example intramammary preparations were assumed to be used for mastitis therapy (either lactating or dry cow therapy depending on product). For antimicrobials specifically labelled for intra uterine use (for example cephapirin) then this was assigned to endometritis. Where antimicrobials had a broad range of indications these were coded to the general category.

Results

A total of 78 herds, managing 63,500 lactating cows, had sufficient data to calculate the ADUR, 39 in each of the North and South islands. The median ADUR was 1.59 daily doses per cow per year (interquartile range 1.37-2.05; Table 1, Figure 1). The predominant use of antimicrobials was mastitis-related, either dry cow therapy (DCT) or for treatment of clinical or subclinical mastitis during lactation (LCT; Table 1).

	Total ADUR	ADUR by indication				
		DCT[1]	LCT[2]	Endometritis	General	Metritis
Average	1.72	0.68	0.67	0.06	0.32	0.03
Stdev	0.59	0.29	0.36	0.05	0.21	0.04
Minimum	0.50	0.05	0.12	0.00	0.04	0.00
25%	1.37	0.47	0.43	0.03	0.15	0.00
50%	1.59	0.81	0.64	0.05	0.27	0.01
75%	2.05	0.85	0.82	0.07	0.43	0.05
90%	2.58	0.90	1.10	0.12	0.61	0.08
Maximum	3.55	1.50	2.16	0.26	1.12	0.09

[1]Dry cow therapy (DCT); [2]Lactating cow therapy (LCT) for mastitis

Table 1. Descriptive statistics of total average daily usage rate (ADUR) of antimicrobials of 78 New Zealand dairy farms, and every average daily usage rate by indication

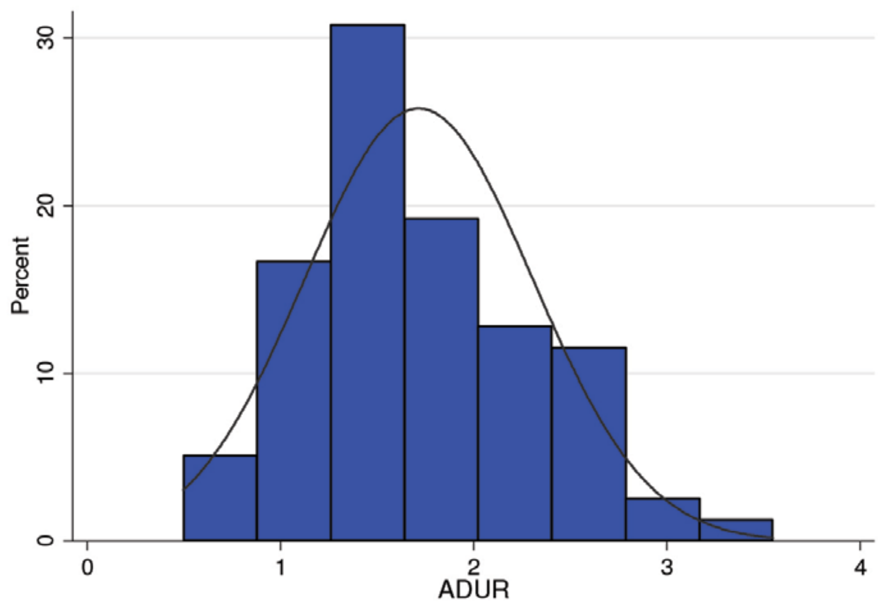

Figure 1. Frequency histogram of the average daily antibiotic use (daily doses per cow per year) for 78 dairy herds for the 2015 calendar year

The highest ADUR was associated with Class B antimicrobials, followed by Class C, then Class A (Table 2). Fifteen of the 78 herds (19%) were not supplied with Class A antimicrobials in 2015. There was variation in the percentage of ADUR associated with Class A usage, ranging from 0 to 12.6% (Table 2).

	ADUR by class			
	Class A	Class B	Class C	Class A %
Average	0.05	1.06	0.60	3.11
Stdev	0.06	0.37	0.43	3.41
Minimum	0.00	0.17	0.09	0.00
25%	0.01	0.88	0.33	0.39
50%	0.03	1.06	0.42	2.14
75%	0.08	1.31	0.77	4.49
90%	0.16	1.50	1.29	7.81
Maximum	0.29	1.98	2.07	12.64

Table 2. Descriptive statistics of average daily usage rate (ADUR) by antimicrobial class, and the percentage of ADUR that were Class A antimicrobials.

Herds from the North Island practice tended to use more antibiotics than those in the South Island practice (1.76 ± 0.66 versus 1.68 ± 0.51, mean ADUR ± standard deviation, for North and South Island, respectively; P = 0.11).

There was no association between herd size and ADUR (P=0.16; R^2=0.005; Figure 2).

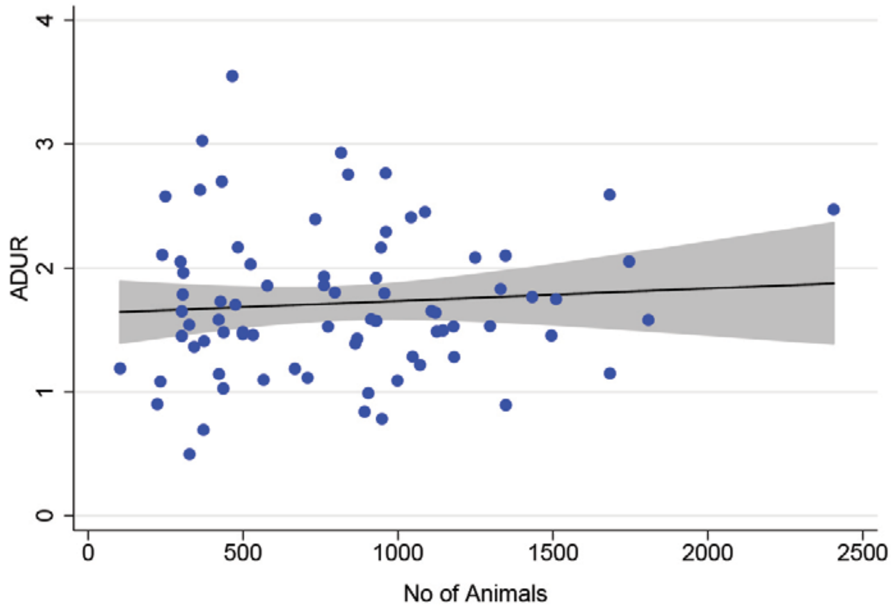

Figure 2. Scatter plot and line of best fit with 95% confidence intervals for number of cows in the herd (No of Animals) and ADUR

Discussion

We have calculated the average daily use of antimicrobials (number of daily doses of antibiotics per cow per year) for 78 herds, split equally between the North and South Island of New Zealand.

There was a tendency for North Island herds to have a higher antibiotic use than the South Island herds, for reasons that are not clear. There was no association between size of the herd and antibiotic use.

The calculated average daily usage of approximately 1.7 cow days of antibody usage per year is in line with previous New Zealand estimates (Compton and McDougall 2015) and less than recent international estimates: Pol and Ruegg (2007) reported annual ADUR of 5.4 from farmer records in the USA, and both Saini *et al.* (2012) and Lam (2013) reported annual ADUR of 5.3 from used product audit data in Canada and from treatment records in the Netherlands, respectively. The range of usage amongst herds was relatively narrow with between one and four ADUR. However, there were a number of herds that were outside the 95% confidence interval for the population and hence are outliers in terms of antibiotic use. It is not clear at this stage whether these outliers are due to a higher than average disease incidence in the herd, requiring greater antibiotic use, or related to sensitivity of diagnosis and hence the risk of overtreatment. The second year of this study will examine recorded on-farm usage patterns and potentially identify where over/under diagnosis and usage is occurring.

The use of critically important (Class A) antimicrobials was relatively low with approximately a fifth of the farms not using them at all, and the remaining farms using, on average, 0.05 daily doses per cow per year.

There are some potential limitations of the current data and analytical approach. It is assumed that all antibiotics sold from the veterinary businesses in the calendar year of 2015 were actually used within this time frame. While generally farmers keep relatively small stocks of antibiotics on hand, and these stocks remained fairly consistent across time, there is a risk of over or underestimation of usage because of this. This is likely to be relatively small but any bias will be investigated in a subsequent analysis of on-farm animal treatment records. Another assumption is that the antibiotics were used on label. For intra mammary preparations (for example, lactating cow mastitis therapy and dry cow therapy) it is reasonable to assume that one and four tubes, respectively, is one treatment. However, for injectable antibiotics there is some range of doses for some products depending on actual reason (indication) for use. So while the common on label usage doses were used for the calculations, it is feasible that these calculations may not accurately estimate daily usage because of variations in the actual dose used. Again further analysis of the dataset will allow assessment of compliance with on-label recommended doses across these herds.

Data from this study was derived from clients of two veterinary businesses over one calendar year. The variation in ADUR between subsequent years was relatively small in one study (Compton and McDougall 2015), but the variation amongst veterinary businesses in prescribing and diagnostic approaches is not known. Hence further data is required to gain representative national data relating to farm level antimicrobial usage.

Acknowledgments

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