Antimicrobial use monitoring – A useful tool, or a disciplinary stick?

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Abstract

Antimicrobial use in livestock is under increasing scrutiny by various regulatory, industry, and consumer groups. It is likely that in the future, production systems will be required to document antimicrobial use in order to have access to some supply chains. Regardless of from what direction this requirement comes, the veterinarian is in a unique position to help guide the formation and the application of this "documentation". There are clearly many ways to define, measure, and document antimicrobial use. This project focuses on differentiating measures that would be useful tools for managing antimicrobial use for infectious disease from those that are suitable only for monitoring macrotrends related to use reduction.

Key words: antimicrobial stewardship, antimicrobial use metrics

Résumé

L'utilisation des antimicrobiens chez le bétail fait l'objet d'un examen de plus en plus minutieux par les groupes de réglementation, de consommateurs et de l'industrie. Dans le futur, il est probable que les systèmes de production devront documenter le recours aux antimicrobiens pour avoir accès à certaines chaînes d'approvisionnement. Peu importe d'où ces directives émanent, le vétérinaire est dans une position unique pour aider à orienter la formation et l'application de cette 'documentation'. Il y a certainement plusieurs façons de définir, de mesurer et de documenter l'utilisation des antimicrobiens. Ce projet se concentre sur la distinction entre les mesures qui seraient des outils utiles pour la gestion de l'utilisation des antimicrobiens pour les maladies infectieuses et celles qui seraient seulement appropriées pour la surveillance des grandes tendances reliées à la réduction de l'utilisation.

Project Overview

This project is funded by an FDA cooperative grant structured to protect the anonymity and data of participating farms while evaluating necessary resources for detailed benchmarking analysis within cooperating production systems, exploring options for antimicrobial use measures, and evaluating the comparative accuracy of surveys compared to actual use data. The goal is to explore the implications of different measures at the farm level, and learn how these might (or might not) be useful tools for driving antimicrobial stewardship with an emphasis on managing the disease pressure that drives antimicrobial use. Identification of confounders and potential misinterpretations is also a main priority.

The core objectives of this project are the following.

1. Collect antimicrobial use data from beef feedlots and dairies while documenting available record systems.
2. Establish a scalable system to create an aggregate report of antimicrobial use in these facilities using multiple metrics.
3. Provide more detailed benchmark reports back to each participating facility.
4. Provide an estimate of resources required to expand this program to a representative sample of the beef and dairy industries on a yearly basis.
5. Identify optimal record system formats and explore ways to expand their use in the beef and dairy industries.

Antimicrobial Stewardship – The Underlying Goal

We propose that there are basic inclusions in antimicrobial stewardship regardless of branch of medicine or animal species. Finding ways to define and apply these ideas can be challenging. The American Association of Bovine Practitioners has a guideline document entitled Key Elements for Implementing Antimicrobial Stewardship Plans in Bovine Veterinary Practices Working with Beef and Dairy Operations.[1] This document defines antimicrobial stewardship as "the commitment to reducing the need for antimicrobial drugs by preventing infectious disease in cattle, and when antimicrobial drugs are needed, a commitment that antimicrobials are used appropriately to optimize health and minimize selection for antimicrobial resistance."

This has been a consistent theme for the AABP, having also stated in a 2013 guideline entitled Prudent Antimicrobial Use Guidelines for Cattle, "The veterinarian's primary responsibility is to help design management, immunization, housing and nutritional programs that will aid in reducing the incidence of disease and, thereby, the need for antimicrobials."[2] The American Veterinary Medical Association (AVMA) recently defined antimicrobial stewardship and core principles.[3] "Antimicrobial stewardship refers to the actions veterinarians take individually and as a profession to preserve the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public, and environmental health." Core principles as defined by the AVMA are... "Antimicrobial stewardship involves maintaining animal health and welfare by implementing a variety of preventive and management strategies to prevent common diseases; using an evidence-based approach in making decisions to use antimicrobial drugs; and then using antimicrobials judiciously, sparingly, and with continual evaluation of the outcomes of therapy, respecting the client's available resources." More details on the principles are provided on the AVMA website.

While all of these definitions of antimicrobial stewardship are useful for defining the overall construct of efforts, they lack in how a veterinarian actually defines where the key areas of focus should be for an individual client.

Monitoring Antimicrobial Use as an Indicator of Stewardship

The nature of different production systems creates a situation in which the optimal antimicrobial stewardship benchmarking metrics are often specific to the species, and the production system type within species.

Table 1 illustrates what we would like to have, and like not to have in an antimicrobial use monitoring system. To change this from a wish list to a reality list, switch "easy" and "resource intensive" between their respective columns; Table 1 now becomes 2 lists comparing the realistic characteristics of monitoring systems and programs. You can have more easily obtained data which are lacking in useful detail, or you can have data which are useful for on-farm evaluation of practices related to other systems, but which require increased resource allocation. In our evaluation of monitoring systems, the desire to actually allow benchmarking of on-farm use is correlated with both high granularity (detail) of the data and a high resource intensity requirement. This extra expenditure of resources is worthwhile if aspects of antimicrobial use may be benchmarked in a manner that allows veterinarians and their clients to compare disease pressures and the antimicrobial interventions to the pressures and practices of others.

Table 1. Attributes of an antimicrobial use monitoring system.

What we would like...	We would not like it to be....
Coupled to cause	Uncoupled to cause for use
Accurate	Approximate
Granular	Aggregate
Current	Significant lag
Easy	Resource intensive
Enables benchmarking	Policy driver only

Relating Antimicrobial Use to Antimicrobial Stewardship

Once it is recognized that the first components of antimicrobial stewardship are to accurately characterize disease challenges and to then aggressively pursue non-antimicrobial alternatives, the goal of an effective antimicrobial use monitoring program becomes clear. The main purpose of the system should not be to generate data for punitive actions, or for the enactment of arbitrary antimicrobial use reduction targets. Rather, the optimal approach to sustaining animal welfare, animal production, and preservation of antimicrobial efficacy is to enable investigation of the factors that distinguish the lowest antimicrobial use producers from the highest-use producers.

The reasons for variation in antimicrobial use may be very complex because of multiple factors which contribute to differences between producers; however, an effective antimicrobial use monitoring system is the basis for starting the investigations by capturing not only antimicrobial use data, but more importantly the reasons for use along with differentiating characteristics related to animal class within each food animal species (e.g., calf, yearling, or adult beef cattle).

The premise of this project is that antimicrobial use data for a majority of the animals in beef feedlot and adult dairy production may be captured using existing data structures. An advantage of this type of approach is that it is possible to reach back in time to create a multi-year baseline for evaluation of further changes.

The challenge for representative sampling across all sizes of producers consists of varying degrees of record-keeping sophistication, resulting in some inequitable relationships in resources required vs sampling achieved. For this reason, 1 of the major strengths of this project is to use the producers with more detailed records to evaluate the comparative accuracy of data captured from use records versus surveys or purchases (dairy).

The Challenge of Metrics

Various metrics or measures of antimicrobial use have been extensively reviewed, but still lack standardization.[4,5,7,8,10] In this project the use of MySQL workbench to store data, and R to analyze it allows multiple final measurements to be reported simultaneously. This facilitates comparison of each measure's utility to farm management, consistency with other measures, and relationship to factors that may affect antimicrobial selection pressure.

Data analysis currently is focused on treatment records supplemented by protocols and surveys, with built-in cross checks to purchase records (for the dairy portion). The source of treatment record information was documented to provide transparency about times when incomplete records had to be supplemented with information from surveys, protocols, or purchase records.

The continuous association of antimicrobial use measures with disease has remained a top priority in this project. The goal in doing this is to facilitate the development of measures that can be used to drive true antimicrobial stewardship, which requires disease management at both the prevention and treatment levels. Therefore, current decisions about which data to record and analyze are driven by an attempt to accurately and transparently describe use in a way that acknowledges the disease, drug, dose, number of administrations, and the interval between administrations.

With this as the goal, farm records must be standardized for benchmarking. Examples of dairy record standardization are shown in Table 2. Column headings in black font represent an example of original treatment records. Column headings in blue font represent the standardized version of each treatment record. Eight disease syndromes were used for disease classification: Mastitis, Metritis, Metabolic, Lameness, Digestive, Respiratory, Unknown, and Other (hardware, injury, etc.) Treatments were listed by brand name, and later joined to a table of drug properties in the database. The column "mg" indicates the total mg included in that regimen. The column "mg/Administration" is the dose per administration, "Number of administrations" is the frequency, and the "interval" documents time between administrations in hours. For combination therapy, the regimens were defined separately for each drug. The number of regimens roughly correlates to clinical "Disease Incidence" except where multiple drugs were administered, or when the drug was used for prevention or control.

Table 3 describes the characterization of a few common antimicrobial treatments in beef feedlots. Disease will be broken into several categories including: respiratory, digestive, CNS, musculoskeletal, and other which are listed in the table. Treatment describes the generic name of the antimicrobial used, and whether an injectable or in-feed application. The mg given are the concentration of the antimicrobial, as they may differ between some generic medications with the exception of the mg listed after tylosin. This is the estimated inclusion rate per head per day. mg/kg is the labeled dose for the appropriate label indication. Number of administrations is the number of times an animal is given that antimicrobial for a specific disease (ranging from once for a long-acting injectable to 110 to 340 oral doses for tylosin). Interval is simply the time between doses. Regimen is number of drug, dose, and interval combinations for a specific disease. Disease incidence is given a 1 if treatment for clinical disease and 0 if treatment for control.

Numerator Measures Under Consideration for Benchmarking

Disease Incidence – Recorded disease events associated with any treatment, single or multiple. A disease event is defined as a "new event" when treatment occurs more than 7 days after any treatment for the same disease in the same animal. This measure is included as a potential tool to help differentiate or evaluate disease prevention or disease pressure differences between farms. As a benchmark, the Disease Incidence is presented as the total count of Disease Incidence occurring during the year divided by the average number of animals present on the farm in that year. This provides a benchmarking incidence estimate based on an animal year denominator. It is recognized that case definition as well as other confounders may have drastic influence on this measure. It should also be noted that non-antimicrobial treatments were included in this category, as it is not a useful measure without them.

Regimens – A regimen description includes the *drug*, *dose*, number of *administrations*, and time *interval* between administrations. It is counted as 1 when it is aimed at a single

Table 2. Dairy data standardization.

Event	Remark	Protocols	Disease	Treatment	mg	mg/ administration	No. of administrations	Interval	No. of regimens	Disease incidence
DRY	SPEC-DC	SpectraDry	Mastitis	Spectramast DC	2000	500	4	0	1	0
DRY			Mastitis	Quartermaster P	500	500	4	0	1	0
				Quartermaster D	1000	1000	4	0	1	0
DRY	No tubes		Mastitis	No treat	0	0	4	0	1	0
DRY			Mastitis	ToMORROW	1200	300	4	0	1	0
DRY	tomorrow		Mastitis	ToMORROW	1200	300	4	0	1	0
RP	Excede 22		Metritis	Excede	4400	4400	2	72	1	1
MAST	POLSLCRF		Mastitis	Polyflex	25000	5000	5	24	1	0.5
				Spectramast LC	375	125	3	24	1	0.5
MAST	TODA/3Q	Today	Mastitis	ToDAY	1200	200	6	12	1	1
MAST	RF	Today	Mastitis	ToDAY	400	200	2	12	1	1
MAST	TOD LFRF	Today	Mastitis	ToDAY	800	200	4	12	1	1
LAME	EXN24IM3	EXCENEL	Lameness	Excenel	3750	1250	3	24	1	1
DIRTY	EXN5.25	EXCENEL.SQ	Metritis	Excenel	6250	250	5	24	1	1
RETAINP	EXC\CAL	Excenel\Cal	Metritis	Excenel	7500	1500	5	24	1	1
FRESH2	EXCENEL/	Excenel	Unknown	Excenel	7500	1500	5	24	1	1
TRAUMA	EXEN3D28	EXENEL3.25	Other	Excenel	4200	1400	3	24	1	1
SICK	EXN		Unknown	Excenel	3750	1250	3	24	1	1

Table 3. Feedlot antimicrobial regimen characterization.

Disease	Treatment (injectable)	Mg/mL	Mg/kg	No. of administrations	Interval (hrs)	Regimen	Disease incidence
Respiratory	Tulathromycin	100	2.5	1	0	1	
Respiratory	Tilmicosin	300	20	1	0	1	
Respiratory	Gamithromycin	150	6	1	0	1	
Respiratory	Tildipirosin	180	4	1	0	1	
Respiratory	Ceftiofur CFA	200	6.6	1	0	1	
Musculoskeletal	Ceftiofur CFA	200	6.6	1	0	1	
Disease	**Treatment (in-feed)**	**Mg/head**	**Mg/kg**	**No. of administrations**	**Interval (hrs)**	**Regimen**	**Disease incidence**
Liver abscess	Tylosin	60-90	[redacted]	110-340	24	1	
Respiratory	Chlortetracycline	[redacted]	22	5	24	1	

disease event. For the same drug there might be significant variability in the details of each regimen both within farm as well as between farms. For other drugs, such as dry cow therapy, the regimens are nearly identical within and between farms. Due to this variability, definitions of regimens for each drug are simultaneously reported by their central tendency and associated variation. When there is no combination therapy (treating an animal with multiple drugs for the same disease event) the number of regimens very closely approximates the disease incidence if non-antimicrobial regimens are included.

Days of Therapy (DOT) – Days of therapy has been recommended for use by the Infectious Disease Society of America (IDSA).[4] It is a pragmatically defined number of days for which treatment was delivered for a disease event. For short acting, single-administration drugs it can be defined as the number of calendar days treatment is administered regardless of frequency of administration, or total number of doses.

However, there are significant challenges associated with using DOT for single-injection, long-acting formulations. Note that even when PK/PD is used to try to define this measure for long-acting drugs it is still not a measure of the duration of exposure to the drug, as there is currently a lack of evidence for the majority of single-injection drugs which precisely determines the end point for when the drug is exerting any effect on any microbial species. If more than 1 day is assigned, determining the end point of activity is dependent on, and complicated by, the specific bacterial MICs, i.e., a single drug could have numerous DOT specific to each type of bacteria. Both therapeutic and resistance-selection characteristics of an antimicrobial are dependent on the pharmacokinetics and the pharmacodynamics of the antimicrobial and the characteristics of the pathogen and microbiota populations to which they are exposed. Simply setting the DOT to one day would misrepresent the therapeutically effective duration that is achieved with many formulations. This problem is technically true for all drugs, but with short-acting drugs the re-dosing interval creates a standard that can be more readily agreed upon.

In systems (such as feedlots) where there is frequent use of long-acting formulations, the DOT would have little value as the data is lacking to determine a generalized time endpoint for multiple organisms. For dairy systems where there are very few single-injection, long-acting formulations, DOT may be a useful metric and reasonable approximation of reality, although the same duration-of-effect challenges exist for dry-cow therapy and some single-injection antimicrobials. Further research is necessary to compare in vivo resistance selection pressure exerted by use of the same drug.

Animals Exposed – This measure is still under development, and multiple definitions have been discussed. It refers to the number of animal bacterial populations (microbiomes) exposed to a drug and is calculated as the number of animals receiving an antimicrobial at any point during the reference period (1 yr). One option is to calculate it as the percent of animals exposed to any antimicrobial 1 or more times during the reference period. This same measure can also be stratified by drug, i.e., if an animal receives different drugs they would each count as a new exposure if the drug differs from previous treatments. For benchmarking purposes it is expressed as a percentage of animals "exposed". This number is likely not useful from a disease management perspective, but may have potential use in the research setting where the goal is to measure the relationship between use and resistance selection pressure.

Defined Daily Doses (DDD) – Although commonly used throughout the world for quantifying antimicrobial use, calculations of DDD requires assumptions about regimens (dose, duration, frequency, and animal weight at the time of treatment) that do not necessarily reflect reality. In some systems, such as adult dairy cows, it is a relatively reasonable estimate because the necessary assumptions are often correct and relatively easy to estimate. For example, much of the use in dairy is driven by intramammary formulations that are NOT dosed mg/kg, and weight is a stable number. When this same measurement is applied to growing dairy replacement heifers or beef cattle, these assumptions can vary wildly from reality. The Infectious Disease Society of America (IDSA) recommends DOT rather than DDD for human monitoring applications.[4] At this time our benchmark reports will likely go to the next level of transparency by describing the actual regimens due to a wider range of regimens and a large variety of single-administration regimens.

Measures used for Livestock use in other Countries

The European Medicines Agency releases annual reports on sales data of antimicrobials labeled for use in food animals. This document details the EMA's report of antimicrobial sales data or a DDD as determined by the EMA committee over a population correction unit. However, the breadth and depth of antimicrobial use monitoring in animals varies widely throughout the world. The broadest coverage currently is the World Organization for Animal Health (OIE). The 182 member nations have guidelines, standards, and a phased attempt at collection of antimicrobial use in animals as there is ongoing concern regarding use in food animal production and correlation to antimicrobial resistance in human and animal populations. For some counties, their OIE involvement may be the only AM guidelines followed.[9] Other nations are much more involved with monitoring and, in some cases, have instituted restrictions of AM use in food animal production. A few examples include Denmark's DANMAP, Netherlands' MARAN, and Sweden's SVARM.[6]

Conclusion

Benchmarking of antimicrobial use measures can be useful tools for disease management only if the antimicrobial use measurements evaluate antimicrobial use within its relationship to disease and not separate from it. The potential for misuse of these measures is extremely high if they are taken out of the context of in-depth production system knowledge or interpreted without also including outcome measures such as animal welfare, production efficiency, and economics.

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