Is Antibiotic Use in Dairy Cattle Causing Antibiotic Resistance?

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Take Home Messages

- Antibiotics are important tools for managing disease in dairy cattle.
- Because of microbial evolution, use of antibiotics will invariably result in some degree of microbial resistance to antibiotics.
- Prudent use of antibiotics can reduce the risk and extent of microbial resistance.
- Antibiotics should not be used as a substitute for good management practices.

Introduction

Antibiotics are used in dairy cattle production primarily to treat or prevent disease and to a lesser extent to increase milk production or improve feed efficiency. Thus, antibiotic use in dairy production can be classified as therapeutic (treatment of an existing disease condition), prophylactic (administration during conditions of high disease risk) or subtherapeutic (administration for enhanced production).

No antibiotic is completely effective at killing all target bacteria within the complex microbial communities that are frequently encountered within agricultural systems. Consequently, it is inevitable that antibiotic therapy will eventually reduce the number of antibiotic-susceptible strains and promote the development of antibiotic-resistant strains. Feeding antibiotics at low, i.e., subtherapeutic, levels can accelerate development of antibiotic resistance, because more bacteria are likely to survive the challenge, and because the period of exposure of the microbial population to the antibiotic is prolonged. Subtherapeutic use of antibiotics, and indeed, use of antibiotics in animal agriculture in general, is coming under increasing scrutiny by policy-makers,

scientists and the general public. Their concerns arise mainly from the possibility that antibiotic-resistant bacteria may be transferred from livestock to humans, though animal to human contact, through the environment (e.g., water, manure) or in contaminated food products (i.e., meat, milk).

Although it is widely accepted that using antibiotics in livestock production can lead to development of resistant bacteria, the risk that this poses to humans is less clear. At present, the scarcity of information on this relationship and the complexity of the events associated with animal to human transfer, make it virtually impossible to accurately predict the risk to human health. Several European countries have already implemented legislation restricting the use of antibiotics in animal agriculture. This paper is presented, therefore, with the objective of providing an update of current knowledge on the development of bacterial resistance to antibiotics as it pertains to the antibiotic use in livestock production. Recommendations will also be made for prudent use of antibiotics to minimize development of antibiotic-resistant bacteria.

■ Antibiotic Use in Dairy Cattle

The microbial world is highly competitive as various microorganisms bid for the substrates that are required for survival, growth and the establishment of climax populations. To gain an edge for growth, various microorganisms (e.g., *Penicillium* spp., *Streptomyces* spp., *Micromonospora* spp. and *Bacillus* spp.) produce natural compounds which kill or inhibit the growth of competing microbes. Many of the antibiotics presently used in dairy cattle production are either direct extracts of these natural compounds or “chemical mimics” that have been synthesized to achieve an anti-microbial response similar to or even superior to the response to the natural antibiotic (Table 1). In addition to antibiotics, other compounds with known bactericidal activity (e.g., sulfamethazine, trimethoprim) have been employed in the control of bacterial diseases.

Table 1. Examples of common antibiotics and antimicrobial agents administered to dairy cattle.

Antibiotic Family (Source)	e.g. Trade names	Target-action
Aminoglycosides *(Micromonospora* spp.*, Streptomyces* spp.)		
Gentamycin	Gentamycin	Primarily Gram negative, Inhibit protein synthesis
Cephalosporins (*Cephalosporium acremonium*)		
Ceftiofur sodium	Excenel	Inhibit cell wall synthesis,
Cephapirin	Metricure Sus.	Broad spectrum activity
Ionophores (*Streptomyces* spp.)		
Monensin	Rumensin	Primarily Gram positive
Lasalocid	Bovatec	Interferes with ion transport
Salinomycin	Posistac	
Macrolides (*Streptomyces* spp.)		
Tilmicosine	Micotil	Primarily Gram positive
Erythromycin	Erythyro-36	Inhibit peptide bond formation
Tylosin	Tylan	
Penicillins *(Penicillium* spp.)		
Penicillin G	Formula 17900 Propen LA, Albacillin	Inhibit cell wall synthesis
Cloaxcillin	Orbenin Quick Release, Dry-Clox	
Ampicillin	Polyflex sterile	
Penicillin		
Tetracyclines (*Streptomyces* spp.)		
Tetracycline HCl		Broad spectrum, inhibit protein synthesis
Chlorotetracycline	Aureomycin	
Oxytetracycline	Oxy LP, Tetraject LP	
HCl	LA 300, Liquamycin	
Others		
Florfenicol	Nuflor	Broad spectrum; inhibits bacterial protein synthesis
Novobiocin	Albadry	Broad spectrum; inhibits protein and nucleic acid synthesis
Pilimycin HCl	Pirsue	Primarily Gram positive; inhibits protein synthesis
Antibacterials		
Trimethoprim/ Sulfadoxine	Trivetrin, Borgal	Broad spectrum Inhibit thymidine synthesis
Sulfamethazine	AS-700	Broad spectrum, Inhibit folic acid synthesis

Administration of antibiotics to dairy cattle is usually therapeutic, that is, in response to development of symptoms of disease. This type of chemotherapy shortens the period of antibiotic administration and usually reduces the amount of antibiotic employed. If label recommendations are followed, the dose is high enough to kill most of the target bacteria and the risk of resistance development is minimized. If resistance does develop, it is likely to be short term, because the the genetic cost of maintaining the resistance trait reduces the competitiveness of resistant bacteria once antibiotic therapy ceases. Thus, in the absence of the chemical challenge, the resistant population is gradually replaced by antibiotic-susceptible bacteria (Figure 1). However, there are instances in which antibiotics are administered prophylactically (e.g., dry cow infusion, medicated milk replacer) and subtherapeutically (e.g., ionophores, sulfonamides) to dairy cattle. Long term, low doses of antibiotic are more likely to produce antibiotic-resistant bacteria (Salyers 1999). In this situation the antibiotic concentration is low enough for continued bacterial growth, but high enough to exert a selective pressure favoring the establishment of resistant bacteria. Furthermore, resistance established in this manner exhibits a high degree of stability, allowing resistant bacteria to compete with antibiotic-susceptible bacteria even in the absence of the antibiotic (Schrag et al. 1997).

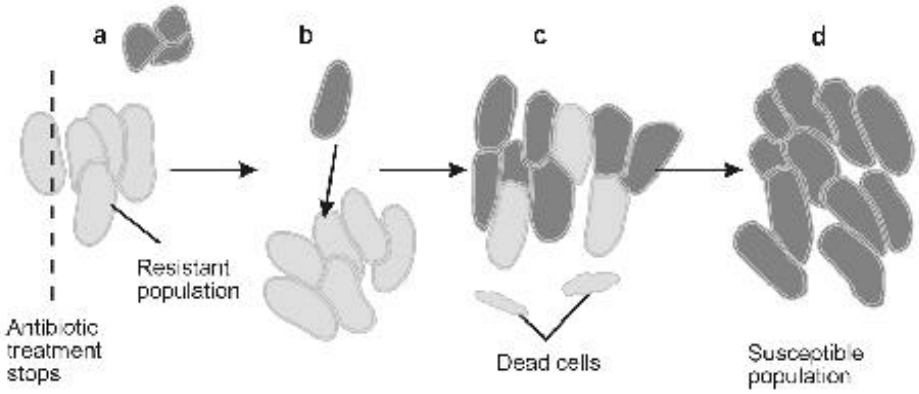

Figure 1. Steps involved in the transition from an antibiotic-resistant bacterial population to an antibiotic-susceptible population once antibiotic therapy has ceased.

Antibiotics inhibit the growth or kill target bacteria by a variety of mechanisms (Table 1). Many antibiotics inhibit the process of protein synthesis, thereby preventing the bacterium from producing the various enzymes and structural proteins required for survival. Other antibiotics interfere with the synthesis of the bacterial cell wall or destabilize the ionic gradients that are required for substrate transport and cellular energetics. An antibiotic's effectiveness is greatly dependent upon the physiology of the target bacterium. Thus, using an antibiotic against bacteria for which it was not designed will not only fail to control the disease, but will also increase the likelihood that other non-target bacteria will develop resistance. Moreover, antibiotics are completely ineffective against viral infections and their use against such infections also increases the risk that bacterial resistance will develop. Consequently, correct identification of the causative agent of the disease and strict adherence to antibiotic label recommendations is one of the easiest ways of reducing the likelihood that antibiotic resistance will develop. Adherence to withdrawal times reduces the risk that antibiotic resistance bacteria will enter the food chain.

In dairy cattle, antibiotics are used to treat a variety of bacterial diseases (Table 2). The first recorded use of antibiotics in dairy cattle was for the treatment of mastitis (Foley et al. 1946) and this disease still accounts for the majority of antibiotic use in dairy production. Despite the widespread use of antibiotics for over 50 years, mastitis is an extremely common disease in most dairies. This attests to the fact that antibiotics cannot be used to "wipe out" disease-causing microorganisms. Rather, they can be used to mediate the disease condition, but the bacteria responsible for the disease will undoubtedly continue to persist within the environment. Antibiotic-resistant bacteria have been shown to persist within water lines (Mulamattathil et al. 2000) and it is likely that without adequate sanitation, similar populations may establish within milking lines. Bacteria are naturally opportunistic and when environmental (e.g., poor hygiene) or physiological conditions (e.g., depressed immunity, nutritional stress) favor their growth, it is inevitable that the disease condition will once again be expressed. Antibiotics are a valuable tool for controlling the expression of disease, but they will remain so only if they are used in a manner that does not promote the development of bacterial resistance.

Table 2. Common bacterial targets of antibiotics and antimicrobial agents in dairy cattle.

Condition	Causative bacteria
Common	
Bovine Respiratory Disease (Pneumonia)	Pasteurella haemolytica Pasteurella multocida Haemophilus somnus Mycoplasma bovis
Enteric Disease (Diarrhea)	Escherichia coli Clostridium perfringes Salmonella spp.
Mastitis	Staphylococcus aureus Streptococcus agalactiae Streptococcus spp. (environment) Klebsiella / E. coli / Enterobacter Pseudomonas spp. Actinomyces pyrogenes
Foot Rot	Fusobacterium necrophorum Bacteroides nodosus
Metritis (Uterine infection)	Actinomyces pyrogenes Fusobacterium necrophorum Bacteroides spp.
Ocular (Pink eye)	Moraxella bovis
Less common	
Lumpy Jaw	Actinomyces bovis
Listeriosis	Listeria spp.
Anaplasmosis	Anaplasma marginale
Tetanus, blackleg	Clostridium spp.
Wooden tongue	Actinobacillus lignieresii

■ Mechanisms of Microbial Resistance

Gene Evolution and Transfer

As with the rest of the natural world, bacteria are in a state of continuous evolution. Unlike complex organisms such as cattle or humans, bacteria have exceedingly short life cycles and entirely new generations can be produced in a matter of hours or days. Consequently, the opportunities for intergenerational evolution in bacteria are far greater than they are in higher life forms. Furthermore, bacteria exist in the environment in unimaginable numbers. For example, there are more bacteria in a cubic centimeter (cc) of rumen fluid (10 billion) than there are people inhabiting the earth. Thus, the likelihood that one individual bacterium will express a unique genetic trait is far greater than with organisms that exist in far lower numbers.

Bacteria have also evolved several mechanisms of exchanging genetic material (Figure 2, Levy 1992). If the genetic material codes for a trait that confers resistance to a particular antibiotic, than there is a significant likelihood that recipient bacteria will become resistant to that same antibiotic. Resistance genes are frequently carried on plasmids, which are loops of DNA that readily undergo both intra- and inter-species transfer (Flint et al. 1987). Bacteria can also become infected with viruses (i.e., bacteriophage) that pick up antibiotic resistance genes and transfer them during the infection of other bacteria. Bacteria may also scavenge portions of DNA that code for antibiotic resistance from adjacent bacteria that have died and underwent cell lysis. Antibiotic resistance genes which are transferred by viruses or from dead cells will only confer resistance if they are integrated into the host's chromosome. In many cases these segments of genetic material have specialized properties that promote chromosomal integration, often introducing whole families of resistant genes in a single transfer event (Bass et al. 1999).

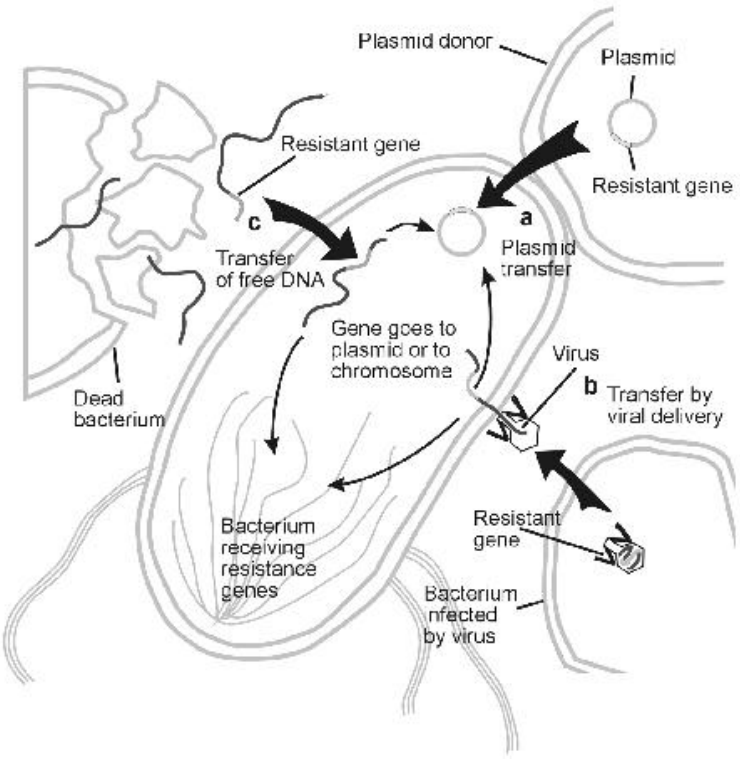

Figure 2. Mechanisms of gene transfer in bacteria, including a) transfer of plasmid from another bacterial cell; b) transfer via viral carrier; c) uptake of free DNA released from another cell.

Mechanisms of Antibiotic Resistance

Bacteria have myriad resistance mechanisms that can be employed to render an antibiotic ineffective (Figure 3). One of the most common mechanisms of resistance is the production of enzymes that degrade the antibiotic (Davies 1994). For example, hydrolysis of the four-membered ∃-lactin ring by ∃-lactamase is largely responsible for widespread resistance to penicillin. Alternatively, by altering their cell surface, bacteria can effectively reduce the affinity of a drug for its target site (Spratt 1994). In some cases, bacteria develop antibiotic efflux mechanisms, which rapidly pump the antibiotic out of the cell before it has a chance to interfere with cellular processes. This is

apparently the mechanism of resistance employed by *Salmonella typhimurium* against the antibiotic florfenicol, the active ingredient in Neuflor® (Arcangioli et al. 2000).

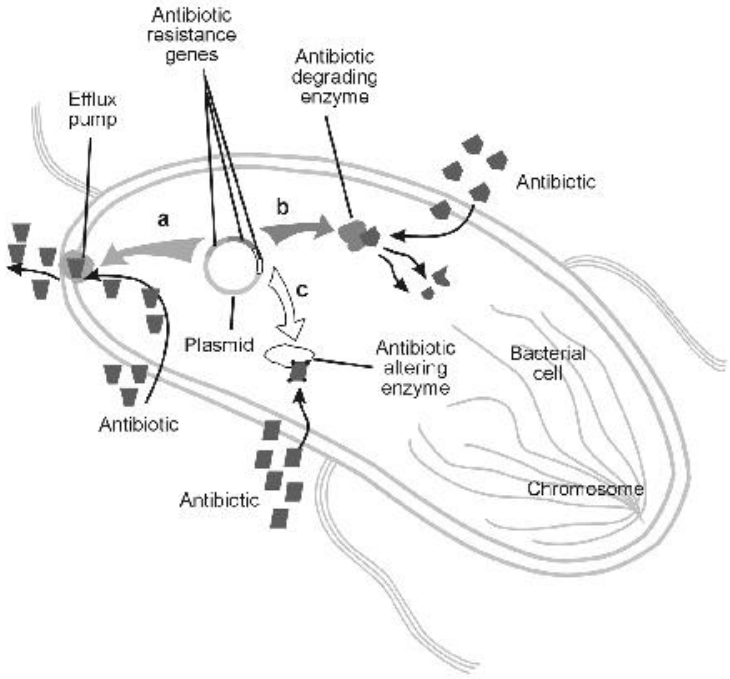

Figure 3. Examples of methods in which bacteria inactivate antibiotics, including a) rapid removal of the antibiotic from the cell prior to cellular damage; b) production of an enzyme which degrades the antibiotic; c) inactivation of the antibiotic through attachment of additional chemical groups.

In other cases, bacteria produce specific enzymes which attach additional chemical structures onto the antibiotic, thereby rendering it inactive. For example, O-phosphorylation of the antibiotic erythromycin has been observed in a number of bacterial isolates (O'Hara et al. 1989). In one of the more complicated mechanisms of resistance, a bacterium will develop metabolic bypasses to override the biochemical reaction that the antibiotic is designed to inhibit. This type of mechanism confers resistance to the antibacterial agent

trimethoprim (Davies 1994). In yet another tactic, bacteria may simply overproduce the targeted metabolic product, thereby overwhelming the amount of antimicrobial that has been administered. This method of resistance is employed against sulfonamides and trimethoprim.

Bacteria may also resist antibiotics by forming biofilms. These are complex microbial communities that limit the interaction of antibiotics with bacterial cells and also provide an environment that promotes exchange of genetic material between cells (Licht et al. 1999). Microbial biofilms are bacteria or fungi existing as a community adherent to a tissue or inert material surface (Potera 1999). In these distinctive growth formations, cells are encased in a secreted exopolysaccharide matrix that also entraps metabolic byproducts which may serve as secondary substrates. Bacterial biofilms play an important role in the dairy herd health as well as food hygiene. Examples of biofilm-related diseases include chronic mastitis (*Staphylococcus* spp. and *Streptococcus* spp.) and chronic pneumonia (*Pasteurella* spp. and *Actinomyces* spp.). Microbial biofilms form on milk line surfaces and can lead to contamination of dairy products. Because they are resistant to removal by antibiotics and biocides, organisms employing this growth form represent a potential source of chronic infection if not properly controlled.

The mechanisms of this biofilm resistance to antibiotics are not clearly understood but are most likely multi-factorial, involving uptake of the drug by the microorganism, inhibition of diffusion of the antibiotic through the biofilm and alterations in bacterial metabolism. Table 3 illustrates the differences in susceptibility to antibiotics of biofilm- and free form- (planktonic) bacterial isolates from clinical mastitis cases. The minimum inhibitory concentration (MIC, ug/ml) is the concentration of drug necessary to prevent the growth of planktonic bacteria; the standard method of measuring the sensitivity of a microorganism to a particular antibiotic. The minimum biofilm eradication concentration (MBEC) was proposed to describe the concentration of a particular antibiotic or biocide necessary to eliminate bacteria growing on a surface as a biofilm. Undoubtedly, the MBEC value more closely represents the effective dose in a clinical situation (Ceri et al. 1999). Killing bacteria associated with biofilms may require concentrations of antibiotic thousands of times higher than those required to kill bacteria floating freely in a fluid environment

Table 3. Comparison of the antibiotic sensitivity of free floating (planktonic) and adherent (biofilm) bacteria.

Antibiotic	***Staph. aureus***		***Strep. uberis***		***E. coli***		***Klebsiella***	
	MIC	**MBEC**	**MIC**	**MBEC**	**MIC**	**MBEC**	**MIC**	**MBEC**
Amikacin	<2	4	8	8	4	16	4	8
Gentamicin	<2	4	<2	<2	<2	4	<2	<2
Tilmicosine	<2	1024	4	1024	128	>1024	512	1024
Pirlimycin	4	>1024	<2	64	1024	>1024	1024	>1024
Cephalothin	<2	1024	<2	128	16	256	16	64
Erythromycin	<2	512	<2	32	64	>1024	256	512
Penicillin G	512	>1024	<2	256	512	512	256	1024
Novobiocin	<2	256	<2	>1024	128	128	128	>1024
Tylosin	<2	1024	<2	512	1024	>1024	512	1024
Cloxacillin	<2	512	<2	512	512	512	1024	36914
Cepthapirin	<2	1024	<2	32	64	128	16	32
Oxy-tetracycline	<2	256	<2	128	256	256	<2	8
Ceftiofur	<2	1024	<2	128	<2	<2	<2	8
Enrofloxacin	<2	64	<2	2	<2	<2	<2	<2
PenG/Novo	<2	512	<2	64	256	1024	256	>1024

Mastitic infections arising from *Staphylococcus aureus* or *Streptococcus uberis* are frequently unresponsive to all antibiotic treatments. Dosages indicated by MIC values would not predict this clinical outcome, but when these pathogens are studied in the biofilm mode of growth, it becomes clear that the antibiotics used to treat these infections will inevitably fail. Moreover, the use of an ineffective antibiotic or biocide to control biofilm bacteria may lead to the development of genetic resistance in planktonic forms of bacteria. Clearly the dairy industry needs new and effective antibiotics to combat infections arising from bacteria in biofilms. Such agents are not presently available - further research and development by the pharmaceutical industry is necessary.

■ Issues of Primary Concern to Human Health

Obviously, bacteria are masters at developing antibiotic resistance. Given their immense evolutionary capacity, it appears that repetitive exposure of bacteria to any particular antibiotic will inevitably result in the development of some degree of resistance. Therefore, the true concern is not whether the use of antibiotics in dairy cattle will lead to the development of resistance, but whether those bacteria that do develop resistance pose a risk to human health.

There are numerous reports of isolation of antibiotic-resistant bacteria from livestock. The majority of these studies have focused on poultry and swine, where antibiotic use is more common. There is evidence that farmers can become colonized by bacteria resistant to the antibiotics being used on the farm (Simonsen et al. 1998). However, few experiments have examined whether or not a similar transfer takes place between dairy cattle and dairy producers. Many of the antibiotics that could potentially lead to antibiotic-resistant pathogens of humans have not been approved for use in North American cattle. Nevertheless, there are examples of antibiotic-resistant bacterial pathogens that could arise as a result of antibiotic use in dairy cattle. Given the continuous evolutionary progression of bacteria, the emergence of antibiotic-resistant strains of bacteria such as *Escherichia coli* or *Campylobacter* spp. cannot be ruled out.

Salmonella spp.

Emergence of antimicrobial-resistant *Salmonella* in humans has been traced back to dairy farms in the past. Two of the more infamous cases involved traceback of chloramphenicol-resistant *Salmonella* in hamburger to a dairy farm (Spika et al. 1987). Other case studies have identified raw milk as a source of antibiotic-resistant *Salmonella* (Tacket et al. 1985). Over 1,000 people exhibited sickness as a result of these incidents. One type of *Salmonella* (i.e., *S. typhimurium* DT104) is of particular concern to human health because this strain already exhibits resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline, and there is evidence that antibiotic-resistant *S. typhimurium* can be passed from cattle to people (Benzanson et al. 1983). The most recent event involved the transmission of a ceftriaxone-resistant *Salmonella* species from dairy calves to a young boy in Nebraska (Fey et al. 2000).

Currently, a fluoroquinolone, ciprofloxacin, is often used as the last-resort antibiotic to control *S. typhimurium* DT104 infections in adults, but fluroquinolones are not approved for use in children. Enrofloxacin (Baytril®) is a fluoroquinolone that has recently been approved for treatment of bovine respiratory disease in the United States. Enrofloxacin has been used in food-producing animals in the United Kingdom since 1993. There is mounting evidence that *S. typhimurium* DT104 isolates from Europe are exhibiting

increasing resistance to other fluoroquinolones (Threlfall et al. 1997). For example, ciprofloxacin-resistant *S. typhimurium* strains have been isolated from cattle in Germany (Heisig et al. 1995). Fluoroquinolones have not been approved for use in food-producing animals in Canada, and a recent Canadian survey of 3,800 strains of *Salmonella* demonstrated that they were still sensitive to ciprofloxacin (Poppe et al. 1999). However, this survey also demonstrated that during the three-year surveillance, the prevalence of *S. typhimurium* DT104 as a percentage of *S. typhimurium* isolates from cattle increased from 19.2 to 76.7%. This trend, together with other data, decrease the likelihood that fluoroquinolones will be approved for use in cattle in Canada. Furthermore, there is growing pressure in the United States for withdrawal of the recent approval for the use of enrofloxacin in cattle. The Food and Drug Administration (FDA) is presently putting forward a proposal to withdraw approval for the use of enrofloxacin in poultry.

Staphylococcus spp.

Coagulase-negative staphylococci are the most common pathogens associated with mastitis, and are the reason for most post-milking antiseptic teat dipping and dry-cow treatments employed routinely in many dairies. Studies suggest that coagulase-negative staphylococci in dairy cattle exhibit greater resistance to antibiotics than does *Staphylococcus aureus* (Owens and Watts 1988). There is also evidence that coagulase-negative staphylococci may serve as a reservoir of antibiotic resistance for *S. aureus*. Of greater concern is the emergence of methicillin-resistant *S. aureus* (MRSA) strains, which are resistant to penicillins, cephalosporins and some of the fluoroquinolones. In Canada, the first MRSA strain was reported in a health care facility in Ontario in 1981. Subsequently, MRSA has been reported at several hospitals and long-term care facilities across Canada (Health Canada 1997). Fortunately, MRSA accounts for less than 5% of the clinical isolates of *S. aureus* collected in Canada. Glycopeptides such as vancomycin are the drugs of last resort for controlling MRSA infections in humans; development of vancomycin-resistant MRSA could be a catastrophe. To date, antibiotic use in dairy cattle has not been linked to the development of antibiotic-resistant staphylococci that are of primary concern of human health. However, given the uneven distribution of antibiotics achieved by mammary infusion (Owens et al. 1989), it seems likely that this practice would promote development of staphylococci resistant to the antibiotics deployed in this manner.

Vancomycin-resistant enterococci

Vancomycin-resistant enterococci (VRE) are emerging as a global threat to public health (Uttley et al. 1988). Several studies have isolated vancomycin-resistant enterococci from poultry and swine (Aarestrup et al. 2000; Borgen et al. 2000; Lemcke and Bulte 2000). A study conducted in Belgium did not identify VRE in ruminants (Devriese et al. 1996). However, VRE has been

found in the ruminal contents of deer (Laukova 2000) and in hamburger (Klein et al. 1998). One reason proposed for the relatively low level of VRE in ruminants as compared to monogastric livestock, is the widespread use of the glycopeptide avoparcin in the diets of swine and poultry in Europe. Avoparcin, which causes cross-resistance to vancomycin, was first used in the European Economic Community (EU) in 1975. Use of avoparcin was suspended in all EU countries in 1997. However, three years after the ban, VRE continues to persist on Norwegian poultry farms (Borgen et al. 2000). This is an excellent example of a case in which the effectiveness of an antibiotic was not regained by the removal of the selective agent and emphasizes the need to take steps to avoid the emergence of antibiotic resistance in the first place.

■ Steps Taken in Other Countries

European Economic Community

Several European countries have already taken steps to curtail the use of antibiotics in livestock. In 1986, Sweden banned the subtherapeutic use of all antibiotics for growth promoting purposes. In 1997, the EU banned the use of avoparcin due to concerns about it causing cross-resistance to vancomycin. In July 1999, use of bacitracin, spiramycin, virginiamycin and tylosin as feed additives was also discontinued. Sweden is also considering restricting the subtherapeutic use of other antibiotics including avilamycin, flavophospholipol, monensin and salinomycin. These bans are being considered even though antibiotics such as monensin and salinomycin are not used in human medicine and are not known to cause cross-resistance to antibiotics of importance to human health.

Extensive antibiotic resistance monitoring programs have been set up in several European countries (Wray and Gnanou 2000), and some countries have taken steps to prevent veterinary practitioners from profiting directly from the sale of antibiotics. This is done in recognition of the obvious conflict of interest that exists when increased antibiotic sales mean increased profit for those recommending them. Also in the EU, there is growing pressure to evaluate the use of antibiotics in livestock based on the “precautionary principle”. The foundation of this principle is that the use of an antibiotic in livestock production should be halted if there is any future possibility that it could lead to the development of resistant bacteria that could threaten human health. If the precautionary principle gains widespread political support, it is likely only a matter of time before the subtherapeutic use of all antibiotics in livestock is outlawed in the EU.

North America

The movement to restrict the use of antibiotics in livestock production is also growing in North America. Organizations such as the Union of Concerned Scientists (UCS) have charged that present figures grossly underestimate the amount of antibiotics used in livestock production. The UCS proposes that animal agriculture in the United States uses about 24.5 million pounds of antibiotic per year (10.3 million pounds in hogs, 10.5 million in poultry and 3.7 million in cattle), a figure far higher than the 17.8 million pounds reported by the Animal Health Institute. The Centre for Science in the Public Interest is presently lobbying the FDA to have seven antibiotics (penicillin, tetracycline, erythromycin, tylosin, lincomycin, virginiamycin and bacitracin) banned from agricultural use.

The North American approach to approval of antibiotics for use in livestock appears to be slightly more rational than the European approach. Antibiotics that cause cross-resistance to last-resort antibiotics used in human medicine are coming under the greatest scrutiny. This is the basis of the FDA proposal to withdraw approval for the use of the fluoroquinolone enrofloxacin (Baytril®) in poultry. The use of the stretogramin antibiotic, virginiamycin, in livestock production is also being reassessed in the United States. Originally, streptogramins were used only in food animals and not in human medicine. However, a new product, Synercid®, which is a combination of the stretogramins quinupristin and dalfopristin, has been found to be effective at controlling VRE infections in humans. There is concern that the use of virginamycin in livestock may be increasing the level of antibiotic resistance to Synercid® (Van den Bogaard et al. 1997). It is possible that this new found use of stretogramins in human medicine may lead to the discontinued use of these streptogramins in livestock. Virginamycin has been approved in Canada for use in poultry and swine, but not in cattle. Fluoroquinolones have not been approved for use in food-producing animals in Canada.

The trend for antibiotic use in humans to take precedence over antibiotic use in livestock will continue to grow. It is highly unlikely that future antibiotics that have any measurable risk of promoting the emergence of antibiotic-resistant human pathogens will be approved for use in livestock. Undoubtedly, various lobby groups will continue to push for an all-out ban of the antibiotics currently used in both livestock production and human medicine. The success of these groups, however, will likely depend as much on the nature of the current political environment as on scientific evidence.

Keys to Prudent Antibiotic Use

The key to prudent use of antibiotics in livestock production is to use the right antibiotic at the right time in the right manner. A few of the key points to keep in mind are listed below:

- Do not use antibiotics to compensate for poor nutrition, poor hygiene, or the lack of immunization or implementation of a herd health program.
- Consider other methods of intervention, (e.g., proper nutrition, stress management, etc.) prior to antibiotic therapy.
- Use antibiotics in consultation with a veterinarian.
- Avoid extralabel use of an antibiotic altogether if possible. If considered absolutely necessary, extralabel use should be done only in consultation with a veterinarian and in accordance with government regulations.
- Select dosing rates and treatment periods in accordance with manufacturers' recommendations. "Cutting" the dose is more likely to lead to emergence of resistance.
- Minimize as much as possible the use of antibiotics considered important for treating human disease.
- Select narrow spectrum antibiotics on the basis of their target organism(s), not on their withdrawal time.
- Whenever practical, culture suspected pathogens for identification, to ensure that the selected antibiotic is targeting the causative organism.
- Limit the use of antibiotics to ill or high-risk animals; minimize the number of animals treated as much as possible.
- Maintain accurate treatment records and select the antibiotics found to be most efficacious within your operation.
- Ensure that antibiotics are properly stored and handled, and dispose of them correctly once their expiry date has passed.

Conclusion

Bacteria are a natural and essential component of the environment. Using antibiotics to declare "all-out war" against bacteria is a war that we cannot win. In fact, heightened use of antibiotics has the potential to reduce, rather than increase, our ability to control disease-causing bacteria. Instead, antibiotics must be used with the precision of a surgeon's knife, being employed strategically against target bacteria, and only as one component of an overall herd health management program. Failure to use antibiotics with respect could

lead to their eventual elimination as a tool in animal production, either through regulatory restrictions or through the loss of their effectiveness due to the emergence of resistant bacterial populations. It is important to remember that the individuals most likely to come into first contact with antibiotic-resistant bacteria in the dairy are the dairy producers and their families.

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