Does Animal Agriculture Contribute to Antibiotic Resistance in Humans? Current Insights into Dairy Cattle and their Role in Antibiotic Resistance

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Take Home Messages

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

Introduction

The term antibiotic is used to describe antimicrobial agents that are effective against bacteria. 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 when used to treat an existing disease condition, prophylactic when administered during periods of high disease risk and sub-therapeutic when administered to enhance production.

Antibiotics kill or inhibit the growth of bacteria. No antibiotic is completely effective at inhibiting all target bacteria within the complex microbial communities that are frequently encountered in 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 sub-therapeutic dosages can promote antibiotic resistance as more bacteria may survive the antibiotic challenge and the duration of exposure is often prolonged. Nontherapeutic use of antibiotics, and sub-therapeutic use in particular, 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, through animal to human contact, through the environment (e.g., water, manure) or in contaminated food products (e.g., 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 challenging to predict the true risk to human health. Several European countries have already implemented legislation restricting the use of antimicrobial agents in animal agriculture. Health Canada has recently announced efforts to promote the judicious use of medically important antimicrobial drugs in food animal production by removing claims of growth promotion and/or production and increasing the oversight of veterinarians for antimicrobial use in food animals (Health Canada, 2014). This paper provides an update of current knowledge on the development of bacterial resistance to antibiotics as it pertains to antibiotic use in dairy production. Recommendations will also be made for prudent use of antibiotics to minimize development of antibiotic-resistant bacteria.

■ Antibiotic Use in Dairy Cattle

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 total amount of antibiotic employed. If label recommendations are followed, the dose is high enough to kill or inhibit the target bacteria and the risk of resistance is minimized. If resistance does develop, it is likely to be short term, because 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 sub-therapeutically (e.g., ionophores, sulfonamides) to dairy cattle. Long term, low doses of antibiotics 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. Antibiotics however, are not the only driver for selection.

Often antibiotic resistance genes can be located on mobile genetic elements that also confer other fitness traits, such as virulence and resistance to metals. Consequently, selective pressure for these other traits can result in the co-selection and maintenance of antibiotic resistance genes in the absence of antibiotic selection. Selection and maintenance of antibiotic resistance genes in bacteria is therefore not simply 'black and white'.

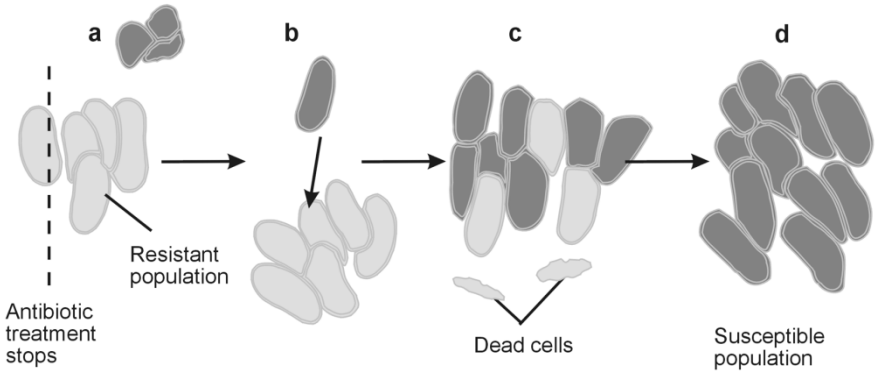

Figure 1. Steps involved in the transition from an antibiotic-resistant bacterial population to an antibiotic-susceptible population once antibiotic therapy has ceased. a) In the presence of the antibiotic the bacterial population consists of resistant cells and some susceptible cells that may have entered a dormant state or survived the antibiotic therapy. b) In the absence of the selective pressure of the antibiotic, susceptible cells may exit dormancy and enter a viable state. c) Eventually susceptible cells start to dominate the population as they may have a competitive advantage over resistant cells in the absence of selective pressure from the antibiotic. d) Eventually the population is dominated by susceptible cells, but there are usually a few resistant cells that persist and will proliferate should the selective pressure of the antibiotic return.

Antibiotics inhibit the growth of, 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 viruses and their use in this

manner increases the likelihood 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 development of antibiotic resistance in bacteria. In addition, withdrawal times are also indicated on labels as a strategy to reduce the amount of antibiotic residues in meat and milk for the purposes of food safety (Table 1).

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

Antibiotic family (Source)	e.g. Trade names	Target-action	Withdrawal times*	
			Milk	Meat
Aminoglycosides (*Micromonospora* spp., *Streptomyces* spp.)				
Gentamicin	Gentamicin	Primarily Gram negative, Inhibit protein synthesis	-	-
Cephalosporins (*Cephalosporium acremonium*)				
Ceftiofur hydrochloride	Excenel	Inhibit cell wall synthesis,	-	4d
Cephapirin	Metricure Sus	Broad spectrum activity	0hr	48hr
Ionophores (*Streptomyces* spp.)				
Monensin	Rumensin	Primarily Gram positive,	-	0d
		Interferes with ion	Non-lac	0d
Lasalocid	Bovatec	transport		
Macrolides (*Streptomyces* spp.)				
Tilmicosin	Micotil	Primarily Gram positive,	Non-lac	28d
Erythromycin	Erythro-36	Inhibit peptide bond	36hr	14d
Tylosin	Tylan	formation	Non-lac	21d
Penicillins (*Penicillium* spp.)				
Penicillin G	Formula 17900	Inhibit cell wall synthesis	72hr	15d
	Dry-Clox			30d
Cloaxcillin	Orbenin Quick Release		Non-lac	28d
Ampicillin	Polyflex sterile		48hr	6d
Tetracyclines (*Streptomyces* spp.)				
Chlorotetracycline	Aureomycin	Broad spectrum, Inhibit	Non-lac	24hr
Oxytetracycline HCl	Liquamycin	protein synthesis	Non-lac	15-28d
Others				
Florfenicol	Nuflor		Non-lac	28d
		Broad spectrum, Inhibits bacterial protein synthesis		IM; 38d SQ
Novobiocin	Albadry	Broad spectrum, Inhibits protein and nucleic acid synthesis	72hr	30d
Pilimycin HCl	Pirsue	Primarily Gram positive, Inhibits protein synthesis	36hr	21d
Antibacterials				
Trimethoprim/Sulfadoxine	Borgal	Broad spectrum, Inhibit thymidine synthesis	96hr	10d
Sulfamethazine	AS-700	Broad spectrum, Inhibit folic acid synthesis	-	7d

*Withdrawal times based on FDA guidelines; Non-lac, non-lactating cattle

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 eradicate disease-causing bacteria. 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. Formation of biofilms is one of the strategies employed by bacteria to persist in the environment and can facilitate the survival of antibiotic-resistant bacteria (Marchand et al., 2012). Antibiotics are a valuable tool for controlling infections, but they will remain so only if they are used in a manner that does not promote the development of bacterial resistance. 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.

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

Condition	Causative bacteria
Common	
Bovine Respiratory Disease (Pneumonia)	*Mannheimia haemolytica* *Pasteurella multocida* *Histophilus somni* *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	*Anaplama marginale*
Tetanus, blackleg	*Clostridium* spp.
Wooden tongue	*Actinobacillus lignieresii*

■ Mechanisms of Antimicrobial 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 opportunity for intergenerational evolution in bacteria is far greater than it is 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 on 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, then there is a significant likelihood that recipient bacteria will become resistant to that same antibiotic. Resistance genes are exchanged via three main routes: conjugation, transduction and transformation (Wozniak et al., 2010). Conjugation is the process through which plasmids are exchanged between bacteria. Resistance genes are frequently carried on plasmids, which are loops of DNA that readily undergo both intra- and inter-species transfer. Transduction is the process whereby bacteria can become infected with viruses (i.e., bacteriophage) that pick up antibiotic resistance genes and transfer them during the infection of other bacteria. Finally, transformation involves the uptake of 'free DNA' that can code for antibiotic resistance from adjacent bacteria that have died and underwent cell lysis. Integration of resistance genes, acquired through transduction or transformation, into the chromosome or plasmids is required for these genes to become functional. 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).

Integrative conjugative elements (ICE) are a form of mobile genetic element (MGE) that have gained much interest in the last couple of years. Unlike other MGE, ICE are self-transmissible as they encode all the machinery required for them to excise from the chromosome, circularize and replicate to a new host through conjugation (Wozniak et al., 2010). ICE have been identified in both gram-positive and gram-negative bacteria, with many occupying a wide host range (Wozniak et al., 2010). ICE can carry genes coding for resistance against many antibiotics. For example, our lab isolated bacteria that cause pneumonia in cattle that were resistant to 11 different antibiotics (Klima et al., 2014). The ability of ICE to carry multiple resistance genes and transfer to a

wide host range makes them an important vehicle in horizontal gene transfer (HGT). Although knowledge of ICE in dairy cattle is limited, the prospect of these mobile elements to alter bacteria from being killed by antibiotics to being resistant to almost all antibiotics used for treating pneumonia in cattle is unnerving.

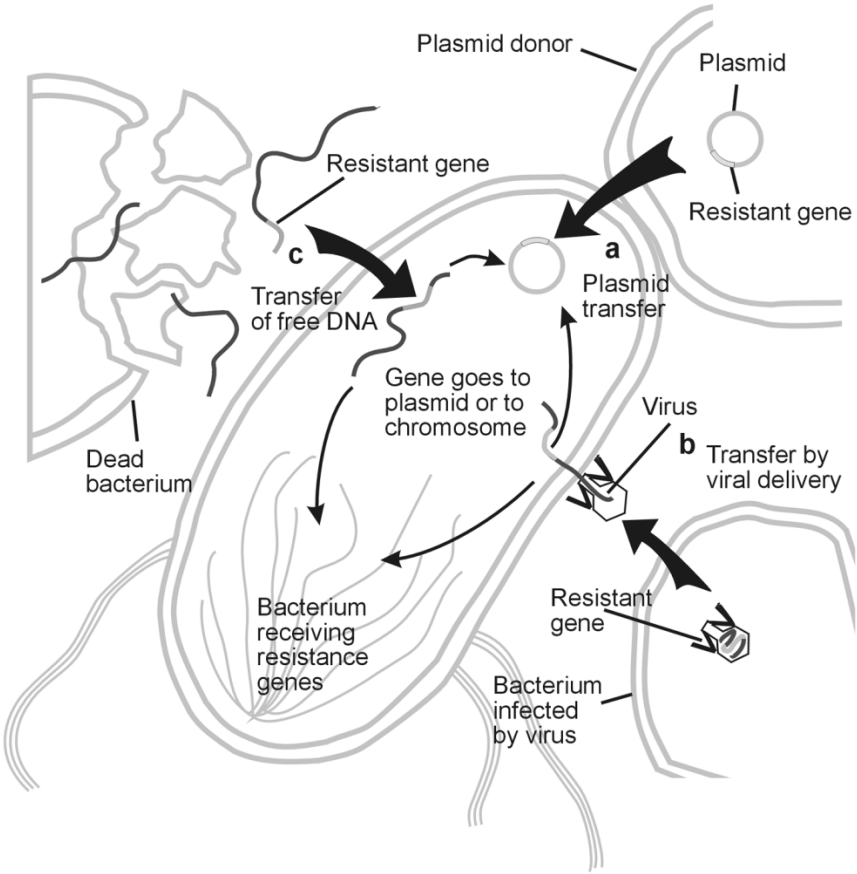

Figure 2. Mechanisms of gene transfer in bacteria, including a) transfer of plasmid from another bacterial cell; b) transfer via viral carrier; c) uptake of free DNA released from another cell.

Mechanisms of Antibiotic Resistance

Bacteria have a myriad of 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 β-lactam ring by β-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®.

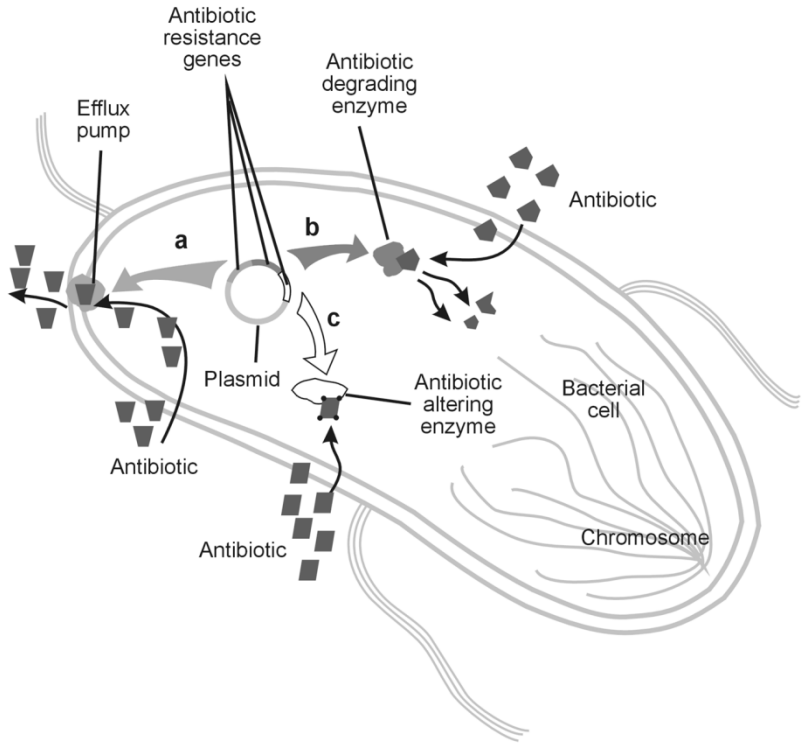

Figure 3. Examples of methods in which bacteria inactivate antibiotics, including a) rapid removal of the antibiotic from the cell prior to cellular damage; b) production of an enzyme which degrades the antibiotic; c) inactivation of the antibiotic through attachment of additional chemical groups.

In other cases, bacteria produce specific enzymes that 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 antibiotic that has been administered. This method of resistance is employed against sulfonamides and trimethoprim.

Bacteria may also resist antibiotics by forming biofilms. Biofilms can form on material commonly found in the milk processing environment, including rubber and stainless steel (Suarez et al., 1992). Biofilms are complex microbial communities that limit the interaction of antibiotics with bacterial cells and also provide an environment that promotes exchange of genetic material among cells (Licht et al., 1999). In biofilms, bacterial 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, being one of the main recontamination sources of milk (Marchand et al., 2012). Examples of biofilm-related diseases include chronic mastitis (*Staphylococcus* spp. and *Streptococcus* spp.) and chronic pneumonia (*Pasteurella* spp. and *Actinomyces* spp.). 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, explaining why some mastitis infections are so difficult to control.

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 bacteria to antibiotics. 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 greater than those required to kill bacteria floating freely in a fluid environment. 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.

Microbial biofilms are often composed of multiple species of microorganisms, which can mutually protect one another against biocidal products during sanitation making elimination more difficult (Vlkova et al., 2008). For example, streptococci form predominantly monospecies biofilms whereas *Pseudomonas* spp. are more likely to produce multispecies biofilms, hence sheltering other spoilage or pathogenic bacteria and allowing them to persist (Marchand et al., 2012). Adequate sanitization procedures are therefore important for effective biofilm control. Sanitation generally involves the sequential use of caustic and acid wash steps, and the procedure varies depending on the equipment being cleaned. Application of sanitizers may also be included in the cleaning process. Continued research into alternative agents and strategies for biofilm control, such as using enzymes and ultrasonic cleaning, are being investigated (Marchand et al., 2012).

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
Tilmicosin	<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

■ Evidence that Antibiotic Use in Dairy Farms is Increasing Antibiotic Resistance

Comparison of amounts of antibiotic resistant bacteria on organic dairy farms, where antibiotics are infrequently used, to conventional dairy farms, where antibiotics are employed, may offer insight into the possibility that antibiotic use in dairy farms is increasing resistance. Studies comparing antibiotic susceptibility of *S. aureus* and other bacteria involved in mastitis have reported mixed results. Some have indicated greater susceptibility to antibiotics in organic compared to conventional dairy farms (Tikofsky et al., 2003), or only for certain antibiotics (Sato et al., 2004b), whereas others have indicated little difference in the amount of antibiotic resistant bacteria between organic and conventional dairies (Roesch et al., 2007). A number of bacteria have been examined, including *Escherichia coli*, *Campylobacter* spp. and

Salmonella spp. and in some instances little difference was found between conventional and organic dairies (Ray et al., 2006; Sato et al., 2004a). Other studies have reported greater resistance with conventional dairies (Halbert et al., 2006; Sato et al., 2005). Consequently, it is not clear if conventional production practices are leading to increased resistance as results vary depending on the type of bacteria and antibiotic examined. The general consensus from these studies is that most bacteria from both production systems remain susceptible to most antibiotics (Halbert et al., 2006; Tikofsky et al., 2003).

▪ Risk of Antibiotic Use in Dairy Farms Impacting on Human Health

There is an increasing trend for people to consume raw (unpasteurized) milk and milk products (Oliver et al., 2009). This increases the risk of exposure to foodborne pathogens, and the incidence of illness and disease in humans. Even of greater concern is the possibility of exposure to multidrug-resistant pathogens through the consumption of contaminated raw milk and milk products. There have been a number of cases where the consumption of raw milk products has been linked to infection with multidrug-resistant *Salmonella* (Cody et al., 1999; Villar et al., 1999). General quality control practices such as pasteurization kill these pathogens and minimize multidrug-resistant pathogens. There is also a risk that milk can become contaminated with multi-drug resistant pathogens after pasteurization. A multidrug-resistant *Salmonella enterica* serotype Typhimurium was linked to an outbreak caused by adulterated milk in Pennsylvania and New Jersey (Olsen et al., 2004). However, if proper hygienic practices are employed exposure to multidrug-resistant pathogens can largely be avoided.

Application of manure to agriculture fields as well as leakage of manure lagoons are other points of concern. Not only does manure introduce bacteria carrying antibiotic resistance genes into the environment, but it can also expose bacterial populations in fields and potentially in water to residual antibiotics (Heuer et al., 2011). Transfer of resistance genes from bacteria in manure to indigenous soil bacteria can promote the persistence of resistance genes in soil (Heuer et al., 2011). Srinivasan et al. (2008) found there was a greater distribution of multiple resistance genes in bacteria isolated from dairy farm soil regularly applied with cow manure compared to nondairy soil with no known history of exposure to manure from animal agriculture. They also found that some bacteria carried class 1 integrons, a form of MGE located on transposons, suggesting the possibility that these bacteria are able to acquire and disseminate resistance genes to other bacteria (Srinivasan et al., 2008). Sequencing of the bacterial DNA in dairy cow manure showed that it contained many novel and diverse antibiotic resistance genes (Wichmann et al., 2014).

Evidence of manure as a potential contributor to the resistance problem suggests that more focus should be placed on how it is managed. Composting of livestock and poultry manure decreases residual antibiotics in manure (Dolliver et al., 2008; Selvam et al., 2012) and reduces the amounts of antibiotic resistant and pathogenic bacteria (Edrington et al. 2009; Sharma et al. 2009). However, antibiotic resistance genes can persist even in composted manure (Sharma et al., 2009). Survival of bacteria carrying resistance determinants can therefore facilitate HGT with soil bacteria. Although composting is an effective practice at reducing residual antibiotics, it is not successful at eliminating all antibiotic resistant bacteria. Factors such as compost temperature and duration may influence the survival of these bacteria.

Application of livestock manure containing residual antibiotics is known to alter the composition of the soil bacterial community. Recently, Udikovic-Kolic et al. (2014) reported that application of manure from dairy cattle that did not receive antibiotics increased the resistance of resident soil bacteria to beta-lactamases. Beta-lactamase resistance was the focus of this study, but it is possible that manure may enrich for other resistant bacteria present in the soil. Many bacteria (e.g., *Penicillium* spp., *Streptomyces* spp., *Micromonospora* spp. and *Bacillus* spp.) naturally produce antibiotics which kill or inhibit the growth of competing bacteria. In fact, many of the antibiotics used in dairy production originated from these bacteria (Table 1). vIt is therefore not surprising that resistance was able to be detected in soil bacteria despite the fact no antibiotics were administered to the dairy herd.

■ Strategies for Addressing Antimicrobial Resistance

Concerns over the impact of the use of antibiotics in food producing animals first arose in 1969 after the release of the Swann report by the Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine. Fears of cross-resistance to vancomycin from the feed additive avoparcin resulted in the European Union (EU) banning its use in 1997. Since 2006, the EU has banned the use of all antibiotics for growth promotion (Capita and Alonso-Calleja, 2013). A number of surveillance programs have been established by various European countries. One of the most extensive monitoring schemes is the European Antimicrobial Resistance Surveillance Network (EARS-Net) which has participation from all 28 EU member states and two European Economic Area (EEA) countries. This surveillance program mainly focuses on human isolates; however, other smaller surveillance programs, such as DANMAP in Denmark and NORM/NORM-VET in Norway, focus on a collection of isolates from both humans and food-producing animals.

In North America, there are movements to begin to phase out the use of

certain antibiotics for enhanced food production. In the USA, the FDA released a guidance document in 2012 on 'The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals'. The purpose of this document is to provide recommendations regarding the appropriate or judicious use of medically important antimicrobial drugs. Medically important drugs are those that are considered important for the treatment of human diseases. Recommendations include limiting medically important antimicrobial drugs to the prevention or treatment of disease and not for growth promotion, and an increase in veterinary oversight and the requirement for consultation (FDA, 2013). This is a voluntary plan that should reduce the use of antibiotics considered important in human medicine in livestock and poultry production. Canada is following a similar approach to the USA (Health Canada, 2014). Surveillance of antibiotic resistance is carried out in Canada and the USA and examines isolates from humans and food production animals to encompass a 'one health' approach for monitoring resistance.

With recent movements to phase out the use of certain antibiotics in North America, antibiotics that are commonly used in dairy production may no longer be available for use in the same capacity as in the past (Table 1). This is even more reason for farmers to ensure they employ good management practices to minimize the need to use antibotics. Third generation cephalosporins, macrolides (erythromycin), trimethoprim/sulfonamides, and fluoroquinolones are classified by the FDA as critically important antibiotics for human medicine (FDA, 2003). These antibiotics are currently used in dairy production and may be the first to be reassessed in terms of their use (Table 1). Others that fall into the highly important category, including aminoglycosides, penicillins and aminopenicillins, may be the next to be targeted. Prudent use of antibiotics maybe essential if some of these antibiotics are to continue to be available for use in dairy production.

■ 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) prior to antibiotic therapy.
- Use antibiotics in consultation with a veterinarian.
- Avoid extra-label use of an antibiotic if possible. If considered absolutely necessary, extra-label use should be done in consultation with a veterinarian and in accordance with government regulations.

- Select dosing rates and treatment periods in accordance with manufacturers' recommendations. "Cutting" or administering a dose lower than what is recommended will increase the likelihood of resistance and reduce the effectiveness of the antibiotic.
- 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 that are most effective for 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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