Antimicrobial Resistance and the Use of Antibiotics in the Dairy Industry: Facing Consumer Perceptions and Producer Realities

John Barlow

Department of Animal Science, University of Vermont, Burlington VT 05445
Email: john.barlow@uvm.edu

■ Take Home Messages

- Antibiotics are an important tool for treatment of bacterial infections in food animals and humans.
- A number of antibiotic classes are used for growth promotion and disease prevention in food animals.
- Antimicrobial use for growth promotion, disease prevention, and treatment contributes to improved health and productivity of food animals, which benefits human health.
- The use of antimicrobial compounds creates a selective pressure on bacterial populations and contributes to antimicrobial resistance development, which negatively impacts human health.
- Antimicrobial use in food animal production is under increased scrutiny.
- The use of antimicrobial compounds in food animals creates a selective pressure on bacterial populations in food animals and contributes to antimicrobial resistance in these populations.
- Consumers consider antimicrobial use a relatively high concern among technologies used in food production.
- The extent to which antimicrobial use in food animals contributes to human health problems associated with antimicrobial resistance is likely small but perhaps not inconsequential.
- The issue is complex and controversial, and while a science-based approach is frequently advocated, emotive arguments are frequently presented.

▪ The Issue of Antimicrobial Use and Resistance in Food Animals

There are concerns that use of antibiotics in food animals contributes to the development of resistance in foodborne pathogens which can be transferred to humans and presents a threat to human health. There are also specific concerns that the routine exposure of food animals to low doses of antimicrobials that are also used in human medicine limits the ability to treat human infections with these classes of drugs. Appropriate and prudent use of antimicrobials and antimicrobial resistance are important issues for agriculture, biomedical science and society.

▪ Recent Events In The US Highlighting The Issue

Media Events

In February, 2010 Katie Couric of CBS News presented a special report entitled “Animal Antibiotic Overuse Hurting Humans? - Katie Couric Investigates Feeding Healthy Farm Animals Antibiotics. Is it Creating New Drug-Resistant Bacteria?” (Couric, 2010a). In an accompanying news report Ms. Couric reported on “Denmark’s Ban on Antibiotics in Livestock” (Couric, 2010b). The first report focused on health issues experienced by poultry and swine farm workers in the U.S., specifically associating human infections caused by methicillin resistant *Staphylococcus aureus* (MRSA) in these individuals with antibiotic use on the farms where they worked. The second report described the “Danish experiment” where Denmark has banned the use of subtherapeutic antibiotics in livestock. The reports made numerous references to “factory farms” where “animals are packed into confinement pens”, “antibiotics are used to keep disease from spreading like wildfire” and “the same classes” of antibiotics that are used to treat infections in humans are given to animals that are “not sick.” The reports indicated “MRSA has been found in the nation’s meat supply,” suggested that “Americans may be acquiring drug-resistant MRSA - not from eating, but from handling tainted meat from animals that were given antibiotics,” and that “Danish scientists believe if the U.S. doesn't stop pumping its farm animals with antibiotics, drug-resistant diseases in people will only spread.” Following these news reports, a coalition of agriculture advocacy groups including the American Association of Bovine Practitioners, the American Association of Swine Veterinarians, American Farm Bureau Federation, and the National Pork Board responded suggesting that they “lacked any attempt at balance”, were “irresponsible and could alarm viewers needlessly”, and contained “numerous errors” (Anonymous, 2010a). Frequent editorials in agriculture trade magazines referenced Dr. H. Scott Hurd’s response outlining the limitations in the CBS reporting (Hurd, 2010), and it appears that the news investigations focused on a number of unsubstantiated claims, used provocative or emotive language, and lacked sufficient scope to do justice to this complicated issue.

While dairy production practices were not implicated in these recent reports, consumer concerns regarding food safety, antimicrobial use, and antimicrobial resistance clearly impact the dairy industry.

Legislative Events

The Preservation of Antibiotics for Medical Treatment Act (PAMTA, H.R. 1549) was introduced by Congresswoman Louise M. Slaughter (D-NY 28th district) in the 111th session of the U.S. Congress. Representative Slaughter, frequently described as “the only microbiologist in Congress” holds a Bachelor of Science degree (1951) in Microbiology and a Master of Science degree (1953) in Public Health from the University of Kentucky. A Senate version of the PAMTA (S. 691) was introduced by Senators Edward Kennedy (D-MA) and Olympia Snowe (R-ME) in this session of Congress. Previous Senate and House versions of the PAMTA have been introduced in each of the 3 Congressional sessions since 2003. In each of the prior sessions the legislation never progressed out of Committee. The current legislation has 127 co-sponsors (out of 435 representatives in the House) where it has been referred to the Committee on Energy and Commerce, and the Committee on Rules. There are 18 co-sponsors of PAMTA in the Senate where it is currently in the Health, Education, Labor and Pensions Committee.

The intent of the current legislation is to phase out non-therapeutic use of medically important antimicrobials in livestock. In other words, with passage of the legislation, antimicrobials identified as identical or closely related to drugs used in human medicine would be withdrawn from use in food animals at sub-therapeutic levels, eliminating antibiotic use in feed or water for growth promotion (i.e. ‘feed efficiency, weight gain’) or prophylaxis (i.e. ‘routine disease prevention’). This is not a new legislative issue, for example the Antibiotic Preservation Act and the Antibiotic Protection Act were introduced in 1980 and 1984, respectively. House committee hearings were held in 2009 and included testimony from internationally recognized human and veterinary health experts, federal food safety regulators, and national food supply representatives (copies of testimony are available at Congressional web sites) (Anonymous 2010b). More than 375 organizations have endorsed the PAMTA including the American Medical Association, American Academy of Pediatrics, American Public Health Association, the Union of Concerned Scientists, and the Humane Society of the United States (Anonymous 2010c). Individuals and organizations testifying in support of the legislation stated that there is a clear link between feeding of low doses of antimicrobials in food animals and human infections with antibiotic resistant pathogens. National organizations, including the American Veterinary Medical Association, oppose the “legislation because it would increase animal disease and death - an unfortunate and unintended consequence - without assurance of improving human health” and is neither “risk-based” nor “based upon the science supporting the issue” (Anonymous 2010d). A review of the conflicting ‘science-based’ testimony demonstrates that attributing human illness caused by antimicrobial resistant pathogens to antimicrobial use in food animals and specifically to routine feeding of subtherapeutic antibiotics is complex and controversial. The truth is that it is not clear what extent low dose use of antibiotics in food animals can contribute to the risk of human foodborne infections.

It is widely acknowledged that antimicrobial resistance is a significant public health concern. The issue is whether current antimicrobial use practices in food animal production are contributing to the problem of antimicrobial resistance in humans to an extent that warrants limiting or discontinuing subtherapeutic use in food animals for drugs that are used to treat human disease.

Regulatory Events

The U.S. Food and Drug Administration (FDA) regulates human and veterinary drugs. The FDA Center for Veterinary Medicine (CVM) is specifically tasked with regulating manufacture and distribution of food additives and drugs that will be given to animals. Two FDA guidance documents are relevant to the issue of antimicrobial use in animals and antimicrobial resistance. Guidance #152 addresses methods to evaluate the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. The guidance document outlines a risk assessment approach for evaluating antimicrobial resistance developing from use of antimicrobial drugs in food producing animals, with a focus on food-borne bacteria that may be transmitted to humans through the consumption of animal derived foods (Anonymous, 2010e). Criticism of guidance #152 is that it should be a mandatory regulation and applied to all previously approved antibiotics, not just new animal drugs (Anonymous, 2010f). FDA Guidance #209, released in 2010, provides background information and recommendations for the judicious use of medically important antimicrobial drugs in food producing animals (Anonymous, 2010g). The key principles of judicious use include:

- 1) The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health, and,
- 2) The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation.

In this document the FDA states "the use of medically important antimicrobial drugs in food-producing animals for production purposes (e.g., to promote growth or improve feed efficiency) represents an injudicious use of these important drugs." However, the FDA recognizes antimicrobial uses for some disease prevention indications are necessary and judicious, and "uses that are associated with the treatment, control, or prevention of specific diseases, including administration through feed and water… are necessary for assuring the health of food-producing animals."

The Veterinary Drug Directorate (VDD) of Health Canada provides similar principles or strategies including that "all veterinary antimicrobial agents that are used for disease treatment and control should be available by prescription only" (Anonymous, 2010h). These strategies arose from the 2002 report of the Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health.

■ Surveillance Programs In Canada And The US

Both the U.S. and Canada have active antimicrobial resistance surveillance programs targeting resistant pathogens in the food chain. The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) is administered by the Public Health Agency of Canada (analogous to the U.S. CDC) with support from Health Canada (analogous to U.S. FDA) and the Canadian Food Inspection Agency (analogous to USDA Food Safety and Inspection Service), while the U.S. National Antimicrobial Resistance Monitoring System (NARMS) is administered by the FDA in partnership with the CDC and USDA.

The U.S. Federal Food, Drug, and Cosmetic Act was amended in 2008 to require the FDA to make annual summaries of the amount of active ingredients for antimicrobial drugs for use in food-producing animals sold or distributed domestically and for export. The first summary report of 2009 annual domestic sales and distribution data listed 13,067,100 kilograms of antimicrobial drugs in 17 classes, with ionophores and tetracyclines representing 64% of the total. These reports appear to be an initial step in quantifying antimicrobial use in food animal production systems; however these reports lack quantitative contextual data describing how antibiotic use is distributed across commodity groups, and age or production classes within those groups. Improved use surveillance, including class specific estimates of dosing per animal unit per time period, is required to accurately attribute risk to specific production systems (Hurd et al. 2010, Pol and Ruegg, 2007). Although, for dairy production it has been suggested antimicrobial use estimates may be extrapolated from dairy cattle disease incidence data because the majority of antimicrobial use is for disease treatment (Sisco, 2006).

Public Perception

Dr. Dale Moore (2008) provided a review of public perception of drug use in food animals. In this review she outlined the connections between media reports and public perception, but also the disconnect between consumer perception, knowledge, and behavior. Moore suggested that “we have not effectively or comprehensively marketed the value of antibiotic use in food animals and that we have not been effective in our risk communications about the difference between residues and resistance.”

Moore referenced work of DeSilva et al. (2004) describing print media coverage of antimicrobial resistance from major newspapers in the US and Canada from 1998 to 2002. Thirty percent of the articles mentioned that over-prescription of antibiotics by physicians can contribute to antimicrobial resistance, while 24 percent of articles described antibiotic use in livestock and agriculture contributing to the problem. DeSilva et al. did not appear to include analysis describing whether the news articles presented information on the types of antimicrobial use practices in agriculture, nor the relative level of contribution of those practices to antimicrobial resistance in humans. It may be hypothesized that U.S. and Canadian consumers are presented with limited and non-quantitative information on these aspects of the issue and have very limited knowledge of specifics regarding antimicrobial use in food animals. DeSilva et al. (2004) suggested newspapers could improve their coverage of the issue “by presenting more contextually precise information about the incidence of antibiotic resistance (i.e., presenting numerator/denominator–level information). They could also present that numerator/denominator information in the form of natural frequencies more often, a format that is explicit about the reference class involved.” These authors also found that a very small proportion (6%) of articles presented more than one recommendation for measures that the public could take to reduce the risk of acquiring antibiotic resistant infections. Interestingly these authors did not report that any articles included frequent hand-washing while handling raw food and appropriate cooking practices as measures to limit acquisition of foodborne infections including those that may be caused by antimicrobial resistant bacteria. Within the farm to table continuum, public health and agriculture agencies in both Canada and the U.S. have established educational initiatives targeting consumer awareness and key risk reduction practices for both farmers and consumers. Understanding how these public agency campaigns have influenced recent media reports and consumer perceptions and behaviors is critical to estimating their impact.

In a mail survey of U.S. residents regarding concerns about food technologies, concerns about antibiotics were rated equivalent to concerns about genetically modified ingredients, but less than concerns regarding pesticides or artificial growth hormones, and more than concerns about irradiation, preservatives, artificial colors/flavors or pasteurization (Hwang et al. 2005). However, individuals who expressed high concern over antibiotics were also likely to rank pesticides as a high concern, suggesting these two technologies clustered among individuals with similar demographic characteristics (more likely to have formal education beyond high school, shop at farmers' markets, and be concerned for how domestic produce is grown and handled.) Again, estimates of the level of consumer knowledge on specific antimicrobial use practices on farms are lacking, and it seems likely that emotive language like "pumping animals with antibiotics," and "given a multitude of chemicals and drugs" lacks necessary precision and creates misconceptions.

▪ Producer Realities – Antimicrobial Use And Resistance On Dairy Farms

On dairy farms antimicrobials are primarily used for disease treatment, prophylaxis and metaphylaxis. With the exception of ionophore use in weaned heifers, there is limited use of antimicrobials for growth promotion in the U.S. dairy industry. Routine antimicrobial use for either increasing feed efficiency ('growth promotion') or disease prevention and treatment (prophylaxis and metaphylaxis) in groups of dairy cattle is principally limited to: 1) prophylactic or metaphylactic use of medicated milk replacers in pre-weaned heifers, 2) inclusion of antibiotics in weaned heifer rations for disease prevention or growth promotion, and 3) routine use of intramammary dry-cow therapy in lactating adult cattle.

The 2007 USDA National Animal Health Monitoring System (NAHMS) Dairy report estimated that approximately 58% of farms feed pre-weaned calves medicated milk replacer and approximately 50% of farms feed either ionophores (32.7% of farms) or antibiotics other than ionophores (18.2%) in weaned heifer rations (USDA 2010a). Among farms feeding milk replacers containing antibiotics, tetracyclines (e.g. chlortetracycline, oxytetracycline) were used on 83.5% of operations and oxytetracycline in combination with neomycin was most commonly added to milk replacers (50% of farms). Recent research on a Californian calf ranch indicates that while feeding milk replacers containing antibiotics at a disease prevention ("metaphylactic") concentration reduced calf morbidity and improved calf growth rates, appropriate passive transfer of immunity through adequate colostrum feeding was most important for reducing morbidity and mortality (Berge, 2005). These researchers and others have shown that prophylactic use of antibiotics in milk replacers is associated with increased carriage of antimicrobial resistant *Escherichia coli* (Berg et al. 2006, Kaneene et al. 2008) and removal of antibiotics from milk replacers can result in a transient increase in susceptibility of isolates (Kaneene et al. 2009). In the study by Berg et al. (2005), reductions in prophylactic use of antimicrobials resulted in increased therapeutic uses while in the herds enrolled in the study of Kaneene et al. (2008) no impact on disease incidence was observed in the herds where medicated milk replacer use was discontinued. Differences between the observations in these studies may be best explained by differences in management practices, especially those impacting passive transfer of immunity. It is not clear from these studies if antimicrobial resistance in these calf populations persists into other age classes and within the herds or how current antimicrobial use in weaned heifer age classes continues to select for antimicrobial resistant organisms.

Several classes of antibiotics are used on U.S. dairy farms for disease treatment, including: 1) cephalosporins, lincosamides, and non-cephalosporin beta-lactams for mastitis, 2) tetracyclines, cephalosporins, and non-cephalosporin beta-lactams for lameness and reproductive disorders, and 3) cephalosporins, and non-cephalosporin beta-lactams for respiratory disease (USDA 2008). Seventy-two percent of herds treat 100% of cows with dry-cow therapy at the end of a lactation, and the most common dry-cow antibiotics used are cephapirin (31.0 percent of cows) and penicillin G (procaine) / dihydrostreptomycin (36.9 percent of cows) (USDA 2008). Despite the routine and common use of lactating- and dry-cow therapy there appears to be little change in antimicrobial resistance patterns of mastitis pathogens over the past 2 decades (Oliver et al. 2010). However Oliver et al. (2010) appear to have ignored the recent emergence of a food animal associated MRSA (strain type 398) and the links to human infections with this strain in farm workers in Denmark and the Netherlands (Graveland et al. 2010; Vanderhaeghen et al. 2010). There is conflicting evidence that antimicrobial resistance of mastitis pathogens contributes to reduced efficacy of mastitis therapy in dairy cattle (Oliver et al. 2010). Continued monitoring of antimicrobial resistance in mastitis pathogens, and the potential impact of resistance on efficacy of mastitis therapy is warranted, especially as new intramammary antimicrobial formulations and treatment regimens are approved and implemented.

▪ Does Antimicrobial Use on Dairy Farms Impact Human Health?

The U.S. Pasteurized Milk Ordinance establishes procedures to ensure that milk for human consumption is free from antibiotic residues. Human health risks associated with consumption of pasteurized milk have been minimized as a result of these public health regulations. The human health risks associated with consumption of raw or unpasteurized milk and milk products are well established and have been reviewed (Oliver et al. 2010). In comparison, a number of case reports have traced antimicrobial resistant infections in humans to origins in dairy cattle beef, yet few studies have estimated the increased human health risk associated with antimicrobial resistant infections linked to the use of antimicrobials in dairy production systems.

Dairy cattle are reservoirs for a number of human pathogens including shiga-toxin-producing *E. coli* (STEC), *Salmonella*, and *Campylobacter*, all of which have been shown to carry antimicrobial resistance. Each of these organisms has also been documented to cause cases of human disease arising from consumption of raw, undercooked, or contaminated food products including beef and milk (Oliver et al. 2010). Hurd et al. (2010) estimated the use of enrofloxacin in dairy heifers for treatment of respiratory disease is associated with small increases in compromised fluoroquinolone treatment of human infections in the U.S. population (18 years of age and over). As a part of the U.S. FDA requirement for post-approval monitoring of enrofloxacin use in dairy heifers and following guidance document 152, these authors estimated compromised human fluoroquinolone treatment resulting in persistent symptoms to be a mean annual increased risk of 1 in 61 billion (one case every 293 years) for Salmonella, 1 in 33 billion (one case every 58 years) for MDR Salmonella, and 1 in 2.8 billion (one case every 13 years) for Campylobacter. Thus antibiotic use in dairy cattle does contribute to the development of antimicrobial resistance, and may, to a small degree, add to the burden of human disease caused by resistant enteric pathogens. Human MRSA infections are also a significant public health concern linked to the use of antibiotics in food animals. To date antibiotic use for the treatment of mastitis has not been associated with the development of resistance in Staphylococci (including MRSA) that are a primary human health concern.

In considering banning or limiting antimicrobial use on dairy farms it seems that aspects including animal welfare, animal disease incidence, and food quality, quantity, and costs and how these factors may influence human health should be considered. Addressing the issue from a commodity specific approach by developing prudent antimicrobial use practices for sectors of each industry has been a recent approach in both Canada and the U.S.

▪ Prudent Antimicrobial Use Guidelines

Section 4 of the Canadian Quality Milk On-Farm Food Safety Program Reference manual outlines best management practices associated with antimicrobial use on dairy farms targeting avoidance of residues in milk and meat (http://www.dairyfarmers.ca/what-we-do/programs/canadian-quality-milk). Guidelines for avoidance of residues may not address strategies for avoidance of antimicrobial resistance. Alternatively, groups including the Canadian Veterinary Medical Association and the American Association of Bovine Practitioners have developed prudent antimicrobial use guidelines which address strategies that may influence the development of antimicrobial resistance (http://canadianveterinarians.net/ShowText.aspx?ResourceID=86 and http://www.avma.org/issues/policy/jtua_cattle.asp). These guidelines rely on establishing veterinary-client-patient relationships and consider practicing veterinarians to be the primary source of information and guidance for their producer clients. Foremost, both organizations recognize that veterinarians have a primary responsibility to their clients "to help design management, immunization, housing and nutritional programs that will reduce the incidence of disease and the need for antimicrobials."

Dairy producers are encouraged to work with veterinary practitioners to develop strategies for prudent use of antimicrobials on their individual farms and for specific circumstances. Aspects of antimicrobial use to consider in the development of farm specific strategies may include identification of pathogens causing specific health problems, determination of the most appropriate drug classes to use for treatments, ensuring appropriate treatment regimens including dosage, route of administration, and duration of therapy, and monitoring for changes in pathogen susceptibility profiles. Strategies should be reviewed regularly and revised to meet changing circumstances.

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