Bugs and Drug Resistance –
What are the concerns?

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Overview of perspectives on antimicrobial resistance, food safety and public health risk

Underlying Concern

Each year nearly 2 million patients in the United States get an infection in a hospital. The CDC estimates that 90,000 people die as a result of a hospital acquired infections and that 70% of these infections are resistant to at least one of the drugs mostly commonly used to treat them. Even though the majority of these resistant infections have been developed and transferred within hospitals, there is concern that antimicrobial use in food animals contributes to resistant infections in humans. It has been estimated that less than 4% of the resistant bacterial population causing human health problems are of animal origin (Bywater and Casewell, 2000). In a society that is used to getting its news in sound bites, it is important to develop a better perspective of the role that each of us as consumers, producers or veterinarians has in reducing the public health risk to resistant bacteria and at the same time, maintaining the availability of effective antibiotics for animals health.

The consumer

The consumer would like to have an adequate supply of safe, inexpensive, wholesome food that is produced with consideration for animal well-being. To be safe, food should be free of potentially toxic residues and harmful bacteria. Zoonotic bacteria are bacteria that exist in animals and can be transmitted to humans and cause disease. Although the list of zoonotic bacteria is long, from a food safety perspective, the pathogens of primary concern include Salmonella, Campylobacteria, E. coli O157:H7, and Enterococci. There are two primary concerns relative to food safety. The first goal is to prevent or minimize the contamination of the food supply with zoonotic bacteria that can result in infections of humans. Second, should these bacteria infect humans, it is important that the infection can be treated with antibiotics that are effective. The prevention of the development of antibacterial resistance is key to maintaining the effectiveness of therapeutic antibiotics for humans.

In the case of Salmonella, the key concern is the maintenance of cephalosporin and fluoroquinolone antibiotics efficacy for the treatment of salmonellosis in humans. From a public health perspective, the use of cephalosporin antibiotics in food animals is considered a risk for the development of antibiotic resistance to salmonella for the cephalosporin class of antibiotics in general, and in particular, ceftriaxone, which is the drug of choice for treatment of children. In the case of campylobacteria, the key concern is the maintenance of the effectiveness of ciprofloxacin, a fluoroquinolone antibiotic, for the treatment of campylobacteriosis in humans. Antibiotic resistance to key antibiotics for these zoonotic bacteria can occur in humans by
multiple methods. The first is by direct exposure through food contaminated with antibiotic resistant *Salmonella* or *Campylobacteria*. The second method is direct contact with animals. Third, enteric bacteria that are not pathogens as such but may be carrying the genetic material for antibiotic resistance and could potentially transfer the genes associated with antibiotic resistance to gut bacteria in humans.

An important point to recognize is that consumers are not a homogenous group. Consumers vary in food preferences from being vegetarians, to vegans, to those that include fish, poultry and red meat as an integral and essential part of their diet. Only a small part of the consumer population has intimate contact with farms and food production practices today. Yet all consumers have empathy for the well-being of food producing animals. Most consumers buy their food in grocery stores or supermarkets, but few have first hand knowledge of food production systems, know a crop or dairy farmer personally, understand reasons for today’s agricultural practices and the issues facing production agriculture. The voice of the consumer varies from what might be considered radical extremists groups to the main-stream consumer to those that perceive the term “organic” makes food safer or better. Yet all have access to the safe and wholesome food.

**Animal Agriculture**

One of the most obvious goals of food animal agriculture is to produce a safe and wholesome food product at a profit. At the same time, animal agriculture is being scrutinized by organizations outside of agriculture relative to animal welfare and production practices. Infectious diseases are an important cause of morbidity and mortality in food animals. The treatment of animals with infectious diseases is important not only from economic but also from an animal welfare perspective. Antibiotics can be used in food animals therapeutically and non-therapeutically. The therapeutic uses of antibiotics are:

1) The treatment of animals following the diagnosis of an infectious disease caused by bacteria.
2) The prophylactic treatment of animals that are at high risk of developing a disease. An example of the latter would be beef calves that have been weaned, collected and commingled at sales barn, and transported to a feedlot.
3) The preventative treatment is the treatment of animals that are pen-mates to animals showing signs of clinical disease and because of the exposure to these animals, are likely to develop the same disease.

Non-therapeutic uses occur when antibiotics that are fed to food animals at sub-therapeutic levels to improve feed efficiency, enhance rate of growth and health, and improve profitability. The practice of feeding antibiotics at sub-therapeutic levels has been around for over fifty years but has become controversial because it has been associated the development of antibiotic resistant bacteria. The practice has been banned in some European countries. The use of sub-therapeutic antibiotics in feeds needs to be evaluated with respect to the specific bacterial species that develop antibiotic resistance to a class of antibiotics and the risk it pose to human health both from exposure of humans to zoonotic bacteria and exposure to antibiotic resistant bacteria.

**Pharmaceutical industry**
Most of the companies that produce anti-infective drugs for animals are companies whose primary business is the production of human pharmaceuticals. The development of an antibiotic for the treatment of an animal disease is expensive and is a process that is highly regulated by the Food and Drug Administration (FDA). The FDA approval process has three components; safety, efficacy, and quality. For an antibiotic to be approved for use in animals, the antibiotic must have demonstrated efficacy and safety for the specific disease for which approval is sought. Safety also includes assessment of human and animal safety in terms of toxicological effects and environmental impact. In addition, appropriate food safety issues must be addressed including the adequate withhold times following treatment for meat, milk, or eggs to be safe for humans. For antimicrobial products, human safety also includes assessing effects of residues on gut flora and potential impacts of antimicrobial resistant bacteria to human health. As a business, pharmaceutical companies are not going to invest in the development and approval of new antibiotics without a return on the investment, especially if the new antibiotics possess a threat to the human side of the business.

**Government: Food and Drug Administration and Food Safety and Inspection Service**

The FDA regulates the approval process for anti-infective drugs that are to be used in food animals. Anti-infective drugs must have demonstrated efficacy in the treatment of the disease for which the drug is being approved. They must also have been determined to be safe for humans in terms of consumption of meat, milk or eggs following appropriate withhold periods following treatment. Food safety is regulated through two principal agencies which are involved in the monitoring for antibiotic residues in meat, poultry and egg products: the Food Safety and Inspection Service (FSIS) of the US Department of Agriculture (USDA) and the FDA.

The FDA recognizes the need for producers and veterinarians to have access to drugs that are effective in the treatment of sick animals. When an antibiotic is approved by FDA for use in a food animal, the package insert that accompanies the drug includes the species for which the drug has been approved, the disease or diseases for which the drug has an approved use, the dosage, treatment interval, and route of administration, and appropriate withhold times for meat, and/or milk following treatment. It should be obvious that the list of disease for which the drug has approval is going to be limited to a few of the most common indications because of the cost of adding additional diseases to the list. The FDA recognizes this and has created guidelines by which a veterinarian can use an antibiotic to treat a disease that is not on the list of approved diseases.

**Veterinarians**

The Animal Medicinal Drug Use Clarification Act (AMDUCA) was enacted in 1994 and provides guidelines for Extra-label Drug Use (ELDU) in animals. Package inserts that accompany antibiotics for use in food animals define the disease condition for which the drug was intended, the intended species, dosage, treatment interval, route of administration, duration of therapy and guidelines for withhold times from the food chain for eggs, milk, and meat. If an antibiotic is used in any manner other than the guidelines stated on the package insert, the antibiotic is being used in an Extra-label manner. The requirements for ELDU are:
1. ELDU is permitted only by or under the supervision of a veterinarian.
2. ELDU is allowed only for FDA approved animal and human drugs.
3. A valid Veterinarian/Client/Patient Relationship is a prerequisite for all ELDU.
4. ELDU is allowed for therapeutic purposes only (animal’s suffering or health is threatened). Extra-label use in not allowed for enhancement of production.
5. Rules apply to dosage, form of drugs and drugs administered in water. ELDU in feed is prohibited.
6. ELDU is not permitted if it results in a violative food residue, or any residue which may present a risk to public health.

**Addressing the areas of common concern: Maintaining Antibiotic Effectiveness**

**Bacteria and Antibiotics of Concern**

The bacteria and recommended therapeutic antibiotics that are of concern relative to antibacterial resistance include:

1) The treatment of salmonellosis in humans with 3rd generation cephalosporins and fluoroquinolones. Patients at higher risk of serious morbidity and mortality due to salmonellosis are infants, the elderly, and the immunocompromised. Fluoroquinolones and 3rd generation cephalosporins are frequently the drugs of first choice when antimicrobial therapy is indicated. Fluoroquinolones are contraindicated in children.

2) The treatment of campylobacterosis in humans with fluoroquinolones.

3) The treatment of infections in humans caused by Enterococci with antibiotics.


5) There is concern for cephalosporin resistance in *E. coli* (and other non-targeted bacteria) associated with animals. *E. coli* may not be a human pathogen as such, but it may be capable of transferring the resistance gene to human pathogens once in the human host.

**Microbial Safety**

**Animal Health Safety:**

One of the primary concerns relative to animal safety is that antimicrobial resistance compromises the efficacy of antimicrobial drugs used to treat the targeted pathogen(s). The package insert that accompanies each vial of antibiotics provides information on the indicated uses of the antibiotic which includes the animal species, diseases, bacteria, dose, treatment interval and route of administration and appropriate milk and/or meat withhold times to prevent drug residues in the food supply. As an example Pfizer Animal Health (PAH) addresses the concern of maintaining effectiveness of Ceftiofur (Naxel, Excenel, and Excede) to the label pathogen(s) through technical support, education, and monitoring as follows:
PAH provides technical guidance and support as well as educational materials for ceftiofur products to aid in herd health management, appropriate diagnosis, and use of PAH antimicrobial drugs, thereby supporting judicious use practices. 

2. PAH has developed performance standards and interpretive criteria for minimum inhibitory concentrations (MIC) and disk diffusion tests of antimicrobial susceptibility testing of ceftiofur against label pathogens.

3. PAH conducts a national program to monitor acquired resistance among field isolates obtained from accredited veterinary diagnostic laboratories. The pathogens monitored include bovine respiratory disease (BRD), swine respiratory disease (SRD), and mastitis pathogens.

**Human Health Safety:**

Human health safety is concerned with drug residues in edible tissue, bacterial safety with zoonotic bacteria and antimicrobial resistance. The key concern relative of antimicrobial resistance is that it will occur in bacteria associated with animals at the animal production site, and that this resistance will subsequently be transferred directly or indirectly to humans, resulting in antimicrobial treatment failure. Although antibiotics are not routinely used in the treatment of Salmonella and Campylobacter, it is important that effective antibiotics are available when immunocompromised patients need antibiotic therapy. The immediate human health concern is the failure of antimicrobial drug treatment of humans infected with resistant zoonotic pathogens (e.g., *Campylobacter, Salmonella*), and that these resistant bacteria were transferred directly from the animal to humans (e.g., veterinarians, animal handlers or others working with the animals), or transferred indirectly via food products derived from the animals.

Potential treatment failure could include these scenarios: A failure of a third generation cephalosporin (ceftriaxone) used to treat salmonellosis in humans when antibiotic therapy is indicated. Patients at higher risk of serious morbidity and mortality due to salmonellosis are infants, the elderly, and the immunocompromised. Fluoroquinolones are frequently also used when antimicrobial therapy is indicated, but fluoroquinolones are contraindicated in children. *Campylobacter*, with the main drug for treatment being fluoroquinolones and macrolides. *E. coli* O157:H7 is a foodborne zoonotic pathogen found primarily in ground beef that can cause severe diarrhea, kidney failure and even death in humans. Although most *E. coli* and *Enterococcus* may not be pathogens as such, there is concern the *E. coli* and *Klebsiella* spp. may develop and carry the genes for antibiotic resistance to fluoroquinolones and late generation cephalosporins while *Enterococcus* show resistance to gentamicin and vancomycin. These bacteria could become foodborne and pass their genes for antibiotic resistance to pathogens, once in humans. Methacillin-resistant S. aureus (MRSA) have been identified on some farms and are of concern as a human pathogen.

**Therapeutic use of antibiotics**

There are three categories of antibiotic use in food animals. They are as follows:

1. Treatment. The first and most obvious use of antibiotics for the treatment of an infectious disease process caused by bacteria.
2) Control. The second is the treatment of a herd or flock when some individuals within the herd or flock are showing symptoms of an infectious disease and history or experience has shown that there is a high risk that the disease will spread through the herd or flock.

3) Prevention. The third is the treatment of a herd or flock when few or no animals are showing signs of a bacterial infectious disease process but experience has shown that the herd or flock is at high risk for developing the disease. An example of such a situation would be the case where a herd experiences a high historical incidence of pneumonia in calves post-weaning and as a result, all calves are treated preventively with a long acting antibiotic.

Subtherapeutic use of antibiotics

Subtherapeutic use of antibiotics occurs when low levels of antibiotics are administered to a herd or flock through feed or water for the purpose of improving feed efficiency, increasing rate of gain, and improving the health of individuals. This is the most controversial use of antibiotics because the exposure of bacteria to low levels of antibiotics creates a selection pressure for bacteria that are resistant to the antibiotic that is being used. An estimated 70 percent of all antibiotics used in the United States are administered to swine, poultry and beef cattle for non-therapeutic or subtherapeutic purposes. In the U.S., the poultry swine industry is the largest user of antibiotics for animal growth promotion (AGP). In the dairy industry, the most common use of antibiotics at a subtherapeutic level are the antibiotics added to milk replacers.

The use of subtherapeutic levels of antibiotics may have conflicting results with respect to human health risks. On one hand, the subtherapeutic use of antibiotics in poultry results in bacteria that become resistant to the antibiotics that are being used. On the other hand, the feeding of subtherapeutic levels of antibiotics results in a more uniform population of birds at slaughter and as a result, there is less bacterial contamination of carcasses from *Salmonella* due to fecal contamination from the mechanical evisceration process when birds are more uniform in size. Lower contamination results in lower incidence of *Salmonella* exposure to humans when preparing the food. The European Union has banned the use of antibiotics for AGP in food animals and has seen a reduction in the prevalence of bacteria with antibiotic resistance. Conversely, producers have seen an increase in the use of antibiotics for the therapeutic treatment of disease in animals when AGP was removed from the early growth phases of animal production. The conclusion of a 1999 National Research Council report was that there is a link among the use of antibiotics in food animals, the development of bacterial-resistance to these drugs, and human disease — but the incidence of diseases attributed to this connection was very low.

Taking a proactive approach to maintaining the food safety and effectiveness of antibiotic effectiveness – A Hazard Analysis and Critical Control Point (HACCP) Approach

The consumer

Relative to food safety and bacterial contamination with zoonotic pathogens, the primary concerns should be Campylobacteriosis and Salmonellosis. It is apparent that poultry presents a
substantial risk of exposure to *Salmonella* and *Campylobacteria* contamination to anything that comes in contact with the poultry including kitchen counters, utensils, and the hands of those preparing the food. Kitchen counters and utensils should be sanitized and hands washed with soap and water following handling and the food prepared at temperatures to kill the bacterial contaminants. Ground meats may also contain zoonotic bacteria and the best prevention practice is to make sure the food has achieved adequate cooking temperatures.

**Animal Agriculture**

The goal for animal agriculture is to produce a safe and wholesome food for society while improving animal well-being. This implies a food free of antibiotic residue and a minimal risk of zoonotic bacteria, in particular Campylobacter and Salmonella. It is implicit that food has a minimal risk of exposure to zoonotic bacteria that are resistant to antibiotics critical for the treatment of these zoonotic infections in humans. It also implies reducing the exposure of humans to bacteria carrying the genes for antibiotic resistance through food. Animal agriculture can take steps to proactively maintain the safety and wholesomeness of food while reducing the development of antibiotic resistant bacteria.

1. **Take steps to decrease the need to treat animals with antibiotics.**
   a. Appropriate vaccination programs.
   b. Sound nutrition programs to maintain strong immune systems.
   c. Developing biosecurity plans.
   d. Use Veterinary service to develop health monitoring systems and treatment protocols.
   e. In dairy operations, assure adequate passive transfer in calves through good colostrum management.
   f. Appropriate animal handling procedures, animal densities in pens, pen moves including isolation and hospital pen management.

2. **Take steps to prevent food adulteration of with antibiotic residues.**
   a. Develop diagnostic criteria to identify diseases.
   b. Develop treatment protocols for specific disease with your veterinarian.
   c. Develop records systems to identify appropriate meat and/or milk withhold times.
   d. Appropriate training of personnel that are treating animals.
      i. Understand the appropriate, dose, route and duration of treatment and evaluate response to treatment.
      ii. Understand the importance of treatment records.

3. **Follow the guidelines of Judicious use of antibiotics for the treatment of disease.**
   a. Develop a veterinary/client/patient relationship with your veterinarian.
   b. Obtain an etiological (the bacteria causing the infection) diagnosis of the disease.
   c. Use an approved antibiotic for treating the disease at an appropriate dose, route of administration, adequate prescribed duration.
   d. Observe the indicated withhold times.
Veterinarians

The availability and effectiveness of antibiotics is important to both veterinarians and producers. The veterinarian’s oath includes “protection of animal health, the relief of animal suffering, the conservation of livestock resources, the promotion of public health.” Appropriate use of antibiotics is one of the key tools to achieve these goals. In circumstances not covered by the antibiotic label, FDA has provided the guidelines for veterinarians to use antimicrobials in an extralabel manner under the Animal Medicinal Drug Use Clarification Act amendments to the Food, Drug, and Cosmetic Act and its regulations.

Pharmaceutical manufactures

The pharmaceutical manufactures want to meet the needs of food animal producers with antibiotics that are safe and effective. The animal health part of the pharmaceutical industry is strictly regulated and monitored by FDA and USDA. While meeting this need the industry is concerned with maintaining the effectiveness of antibiotics for the treatment of human diseases. The FDA requires pharmaceutical manufactures to continually monitor safety and efficacy of drugs post-approval.

Government role in food safety

The FDA regulates the approval process for antibiotics that are going to be used for the treatment of infections in food animals. Three general components are assessed; safety, efficacy, and quality. Safety includes assessment of human and animal safety for toxicological effects and environmental assessments. Human safety includes assessing effects of residues on gut flora and potential impacts on antimicrobial resistant bacteria to human health. Efficacy refers to trials that allow for demonstration of clinical benefit of the compound on animal health. The Center for Veterinary Medicine (CVM) approves antimicrobial drug products for various uses, such as treatment, control, prevention, and for performance enhancement claims. Quality consists of manufacturing facility inspectors, assurance of product stability, adherence to Good Manufacturing Practices (GMPs), and product stability.

Level 1: Animal drug approval process

The first level of protection conferred by the drug approval process is the key to ensuring that only efficacious products which are safe for humans are approved for manufacture according to quality standards.

Level 2: Post approval Review

Antimicrobials that have been approved by the FDA and have met all safety and efficacy requirements are continually monitored to determine whether they remain safe and effective for their label indications. FDA has also undertaken a re-evaluation of existing antimicrobial products intended for use in feed using risk analysis principles to determine whether the product
should remain on the market, be withdrawn entirely, or the label be modified in some way to maintain public health.

**Level 3: Food safety monitoring programs**

The USDA, FDA, and CDC participate in a program to test for antimicrobial resistant food borne bacteria in meat and poultry and from human food borne patients. This information is important for tracking potential human health impacts resulting from the use of antimicrobials in food animal agriculture.

**Level 4: Responsible Use**

The AVMA, species-specific veterinary groups such as the American Association of Bovine Practitioners, and feed and producer groups have all worked with government agencies including FDA to produce guidelines for safe and judicious use of antimicrobials for use in managing infectious diseases.

**Level 5: Pathogen reduction in food processing plants.**

FSIS implemented the HACCP/Pathogen Reduction program in all slaughter and processing plants over the last 10 years beginning with larger plants and finally bringing all federally inspected plants on-line. The program requires each plant to have an approved HACCP plan in place which identifies the potential physical, chemical or microbiological hazards with the production of the particular meat and poultry product, the critical points which must be monitored to insure that occurrence of potential hazards in finished product are minimized and certain tests will be performed to determine compliance with the plan. Efforts to reduce overall food contamination and food borne illness has a direct effect on reducing antimicrobial resistant bacteria in meat and poultry since resistant bacteria are a small subset of the total bacterial load on carcasses.

**Take Home Messages:**

1) We, as consumers, producers, and veterinarians, all have a vested interest in having access to a safe, wholesome, inexpensive food supply.
2) We only have one planet and we need to care about the environmental impact that the food we produce and consume has on the environment.
3) We live in a sound-bite society which doesn’t serve us well when trying to understand complex issues like food production and food safety. We need to take time to try to understand the issues that affect each of us.
4) We need to be concerned about food safety and maintaining the effectiveness of antibiotics for the treatment of animal and human disease.
Selected bibliography:


