What's Next for Food Animal Antibiotics?

by Dr. Michelle Arnold, University of Kentucky Ruminant Ext. Veterinarian

What is "antibiotic resistance"? When an antibiotic is no longer useful against an infection because the targeted bacteria changed in some way that protected it from the effects of the drug (antibiotic), this is referred to as "antibiotic resistance". The FDA Center for Veterinary Medicine is the government agency responsible for ensuring the safety and effectiveness of animal drugs for their approved uses. FDA has already restricted the use of antibiotics in feed and water through the Veterinary Feed Directive. Now they are gearing up to remove all over-the-counter "medically important" antibiotics approved for food-producing animals within the next two years and place them under veterinary oversight. ("Over-the-counter" means available for purchase at any farm supply or internet retailer without the need for a prescription.) FDA believes veterinary involvement is crucial "… because judicious use of antimicrobial drugs requires an accurate diagnosis of the bacterial disease that is present, or likely to be present, and the selection of a suitable antimicrobial drug to address that disease. The decision by the veterinarian to use a specific approved drug is generally based on multiple factors, such as the mode of antibacterial action, drug distribution in specific tissues, the duration of effective drug levels at the site of infection, past treatment outcomes, local burden of illness information, and concurrent animal health issues. Other important factors veterinarians generally consider when determining the appropriateness of a given antimicrobial use include whether: (1) there is evidence of effectiveness, (2) such use is consistent with accepted veterinary practice, (3) the use is linked to a specific etiologic agent, (4) the use is appropriately targeted to animals with or at risk of developing a specific disease, and (5) no reasonable alternatives for intervention exist. FDA believes that veterinarians are uniquely qualified to make these decisions and to determine appropriately timed administration of the antimicrobial to treat, control, or prevent disease in animals."

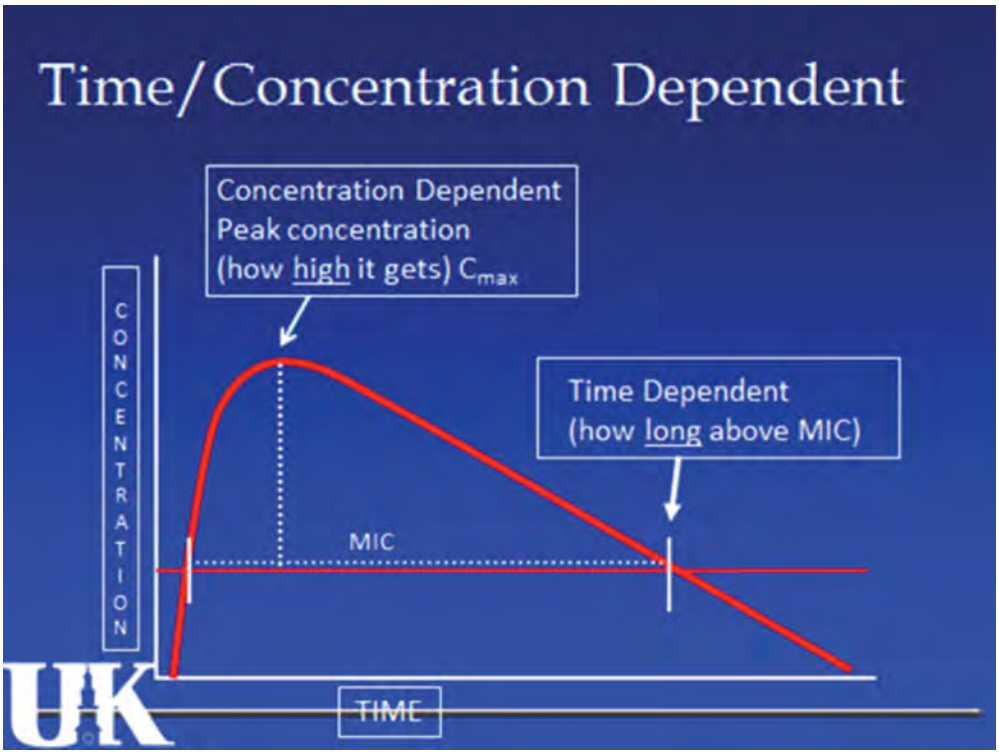

Figure 1: The "MIC" is the "minimum inhibitory concentration" or the minimum level of the drug needed to fight bacteria.

FDA has established three goals to accomplish from 2019 to 2023:

1. Align antimicrobial drug product (antibiotic) use with the principles of antimicrobial stewardship;
2. Foster stewardship of antimicrobials in veterinary settings;
3. Enhance monitoring of antimicrobial resistance and antimicrobial drug use in animals.

This process will begin after the agency considers comments on the draft Guidance for Industry (GFI) #263 and issues the final guidance. In addition, the FDA plans to "engage with affected stakeholders and state partners at public events, such as meetings and conferences, to hear feedback and answer questions about the changes proposed in the draft guidance document." The list of drugs affected by the new draft GFI # 263 is available at the following link: https://www.fda.gov/animal-veterinary/judicious-use-antimicrobials/list-approved-new-animal-drug-applications-affected-draft-gfi-263. Although antibiotic resistance is a concern for the livestock industry, it is not the only reason to re-evaluate how and when antibiotics are used. There are simply no new antibiotics currently in development for future use. Given the need for antibiotics to continue to work for treatment of disease, it is important to review correct antibiotic usage and reasons why antibiotics fail.

Successful treatment of diseases like pneumonia is not simply a matter of grabbing a bottle of antibiotic, drawing up a dose, shooting it in the sick animal and waiting for

the drug to take effect. Instead, full recovery is a joint effort between the animal's immune system and the selected drug to stop the growth of bacteria and invasion of tissue. Antibiotics are designed to hold bacterial growth "in check" while the animal's immune system produces protective cells and mobilizes them to the site of infection. Treatment failure is often due to a delayed immune response because of nutrition-related factors including not enough protein and energy in the diet and trace mineral deficiencies. Sound nutrition and management, especially around the time of kidding/lambing and weaning, will substantially improve the immune response to disease challenge and antibiotic therapy. A clean environment with plenty of space and air movement, clean water and ample bunk space reduces stress and exposure to contagious organisms. Rations formulated to meet nutrient needs, including the proper trace minerals, keep animals from losing weight and rumen microorganisms healthy.

Treatment failure due to human errors include poor timing, use of the wrong drug, improper dose or route of administration, mishandling issues or failure to recognize treatment response. **Timing is crucial**; if animals are treated early in the course of disease, almost any antibiotic will work. Conversely, if calves are treated late in the course of the disease, nothing will work. In addition to timing, dosage is crucial because antibiotics work by different mechanisms. **Figure 1** graphically displays the difference between antibiotics that are considered "time dependent" (effectiveness depends on exposure to the drug for a certain length of time) versus "concentration dependent" (bacteria must be exposed to a high concentration of the drug). If label directions are not followed and only a partial dose is administered or when a second dose is required but not given, the drug is unlikely to work effectively because it cannot reach the necessary minimum target concentration. Selection of the best antibiotic class or "family" is an equally important success factor. **Figure 2** is an illustration of the mechanisms different antibiotic classes use against bacterial cells. Beta-lactams (penicillin, Excede®, Naxcel®, Excenel®) interfere with production of the bacterial cell wall that serves as protection from external threats. Aminoglycosides (gentamicin) and Tetracyclines (LA-300®, Biomycin®, and many others) interfere with protein synthesis within the bacterium by shutting down the machinery in the ribosome (the 30S subunit) needed to build proteins. Macrolides (Draxxin®, Micotil®, Zactran®, Zuprevo®, Tylan®) and Chloramphenicol derivatives (Nuflor®) also interfere with protein synthesis although at a different location on the ribosome, the 50S subunit. (Micotil® is toxic to goats and should not be used). The Fluoroquinolones (Baytril®, Advocin®) block genetic replication by interfering with DNA and RNA synthesis. Why is this information important? If an animal requires retreatment, selection of an antibiotic from a different class will attack the bacteria through a different route and often improve treatment response. Another good example is treatment for *Mycoplasma bovis*, a bacterium frequently found in pneumonia cases. It has no cell wall so treatment with a Beta-lactam (such as penicillin or Excede®) is useless. A veterinarian is trained in antibiotic selection and is the best source of information when choosing a therapy. Since most antibiotics used in small ruminants are "extra-label", meaning they have no directions on the label for use in sheep and goats, a veterinarian is required by law to direct antibiotic usage. Another issue that may affect success is mishandling the product; an antibiotic that gets too hot or is allowed to freeze will inactivate the drug in most cases. Lastly, treatment failure is not always a "failure" but rather an inability to recognize recovery. An animal that is eating, drinking and looks better after treatment but still has a slight fever often needs additional time to fully recover since fever is one of the last clinical signs to disappear.

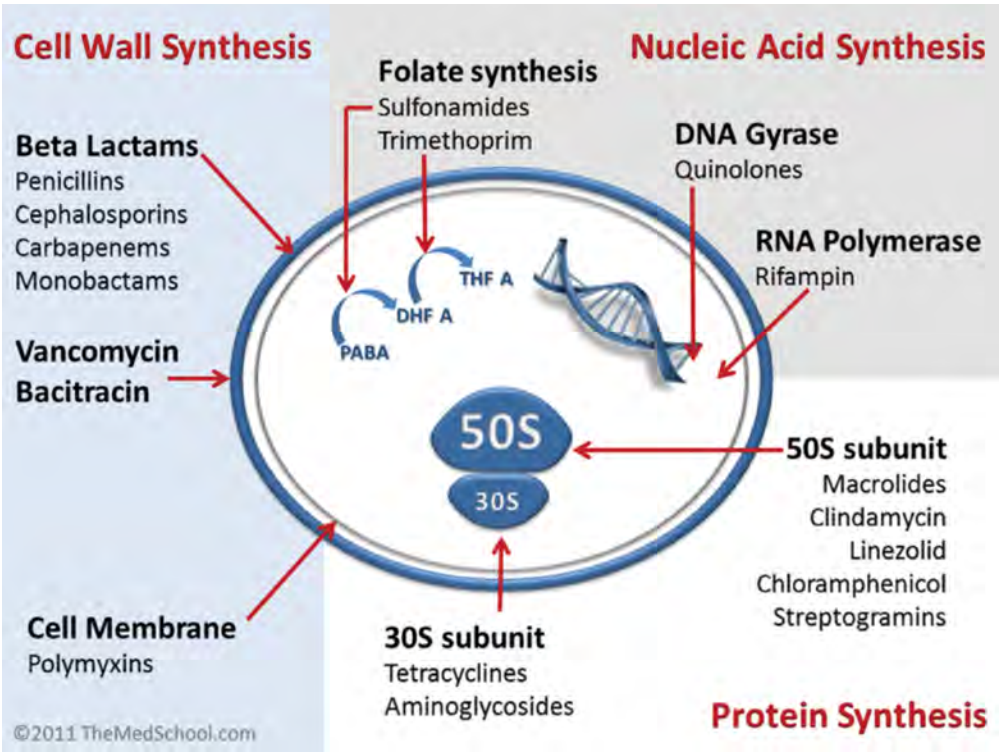

Figure 2: Drawing of a bacterium illustrating the ways different "classes" of antibiotics fight against them. By Kendrick Johnson (Own work) [CC BY-SA 3.0 (http://creativecommons.org/licenses/by-sa/3.0)], via Wikimedia Commons

Strategic and correct use of antibiotics will continue to be of importance for the livestock industry from this point forward. Consumers are increasingly aware and demanding reduced antimicrobial use in the production of wholesome food. FDA is responding by decreasing antibiotic availability to the public and will soon place this responsibility completely in the hands of veterinarians. Careful attention to timing of treatment, drug selection, dose, and handling of the product will reduce the human factors that contribute to antibiotic failure. However, by addressing the underlying management factors that contribute to disease in the first place through stress reduction, providing a clean environment and correcting nutrition-related disorders will lead to better overall health and less reliance on all medications in livestock operations.

Dr. Michelle Arnold *is a native of Louisville, KY and received her DVM from the University of TN in 1990. Her areas of expertise are herd health programs, bovine respiratory disease, biosecurity, and information management. Michelle currently resides in Fayette County and her two boys both attend and live at the University of KY: Briscoe (23) is a Senior, majoring in Mechanical Engineering and Brody (21) is a Junior in Pre-Med.*