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Mr. Chairman and Members of the Subcommittee:

Thank you for providing me with the opportunity to discuss the role of antibiotics in animal agriculture and the potential risks and benefits to animal and public health associated with these antibiotic uses. I am an Associate Professor of Infectious Disease Epidemiology and Ecology at the University of Minnesota. I have a dual appointment at the university, both in the College of Veterinary Medicine and the School of Public Health. I am a veterinarian by training with a degree from the University of California at Davis. Following my veterinary degree, I obtained a PhD in epidemiology from the University of California at Davis. I have worked as a professor of epidemiology since 1999, first at the University of Illinois, Urbana-Champaign and now at the University of Minnesota. I have spent the past 10 years engaged in research, teaching and service activities related to antibiotic use and antibiotic resistance in human and animal health. I will focus my discussion on four questions that I think are critically important:

1. What are antibiotics and how are they used in animal agriculture?
2. What is antibiotic resistance and how is it selected?
3. How do we assess and manage the risks of antibiotic use in animal agriculture?
4. Are there benefits to antibiotic use in animal agriculture?

What are antibiotics and how are they used in animal agriculture?

Although many people assume that antibiotics are human-made compounds, antibiotics are actually small molecules that are naturally produced by microorganisms in the environment. Humans have created synthetic analogs to these naturally occurring compounds to improve their efficacy. The function of these molecules in nature is still not entirely understood. Because bacteria in the environment have been exposed to these antibiotics for eons, they have developed mechanisms for survival in the presence of these compounds. These mechanisms are what we refer to as antibiotic resistance, or a way for the bacterium to resist the action of the antibiotic. The presence of naturally produced antibiotics in the environment is rarely considered as a contributor to the amount of resistance that is found in bacteria around the world, and yet it is this environmental pool of resistance, lately termed the resistome (5), that is the basis for the resistance observed today. Antibiotic resistant microorganisms can be found in areas with little to no obvious human influence or impact, emphasizing that there is a large background reservoir of resistance that exists in the natural world.

Antibiotics are used in animal agriculture in four major ways: disease treatment, disease control, disease prevention, and growth promotion. Briefly, disease treatment refers to the use of the antibiotic in an ill animal. Disease control refers to the use of the antibiotic in a population of animals during a time of illness. Not all of the animals receiving the antibiotic are necessarily ill at the time of antibiotic administration. Disease prevention refers to the use of the antibiotic in an animal or in a population of animals at a time when it is known that the animals are susceptible to disease. Finally, growth promotion refers to the use of the antibiotic in a low-dose fashion to improve the weight gain and feed efficiency of the animal. All four of these uses result in an improved health of the animal receiving the antibiotic, and as will be discussed later, can thereby improve the safety of the food supply.

Even though all four of these uses can improve the health of the animal, there has still been confusion about them. One area of confusion is related to the amount of antibiotic that is administered. Because disease control, disease prevention and growth promotion can use smaller amounts of the antibiotic than is given to the sick animal during disease treatment, these uses have sometimes been labeled as “subtherapeutic” or “nontherapeutic”. Given that animals receiving an antibiotic in this manner are healthier than if they had not received the antibiotic, these terms are misnomers. Another area of confusion is related to the route of administration. Uses of antibiotics that are “in-feed” are often equated with growth promotion uses and are assumed to be long-term low-dose regimens of antibiotic administration for the sole purpose of improving weight gain. In fact, all of these uses can be applied via the feed or the water because the only realistic way to give antibiotic to populations of animals, such as a flock of chickens, is through the feed or the water. Antibiotics used for disease treatment and disease control are often given via the drinking water because sick animals may stop eating but often continue to consume water.

What is antibiotic resistance and how does it develop?

Antibiotic resistance refers to the ability of a microorganism to survive the effects of an antibiotic. As stated previously, antibiotics are naturally produced by environmental microorganisms, and as a result, many microorganisms possess mechanisms that enable them to resist the action of the antibiotic. Some microorganisms are intrinsically resistant to the action of certain antibiotics, meaning that the antibiotic has no function on the organism. This type of resistance can not be spread and is not of concern when considering antibiotic uses. Instead, we are typically concerned about antibiotic resistance that is acquired by the microorganism. The two major mechanisms by which the microorganism can acquire resistance are through random changes in the genetic makeup, known as mutation, or through the sharing of genetic material with other microorganisms.

When an antibiotic is applied to a population of bacteria, those bacteria that are not intrinsically resistant to its action must find a way to survive. The antibiotic will either kill or suppress the bacteria that are susceptible to the antibiotic. For this reason, the antibiotic is said to select for resistant bacteria because only the resistant ones can withstand the pressure imposed by the antibiotic. During the course of the antibiotic, the rates at which bacteria can acquire resistance might increase, and consequently, the use of the antibiotic may pose a risk to human and animal health through the selection of a more resistant bacterial population. The problem, stated simply, is how do we ensure that the human and animal health benefits of antibiotic use in animal agriculture outweigh the risks?

How do we assess and manage the risks of antibiotic use?

There are two primary approaches for assessing and managing the potential risks associated with antibiotic use in animal agriculture. One approach is to employ the precautionary principle. In this argument, the precise public health risks associated with animal antibiotic use might not be known. Because there is a perceived potential for serious negative consequences, it is deemed better to avoid the action entirely rather than to suffer the potential consequences. Europe has used this principle to withdraw certain antibiotic uses from animal agriculture (1). One reason why this approach is often relied upon, especially in the case of antibiotic use and resistance, is the belief that antibiotic use is negatively impacting human health. It is extremely difficult to design, implement and analyze the decisive study that will prove or disprove this theory. Caution would dictate that by the time such a study is complete, any negative effects associated with continued antibiotic use might be irreversible. Consequently, the precautionary principle approach to managing antibiotic use in animal agriculture has only one real option: withdraw the antibiotic use that might result in a negative human health consequence. Unfortunately, there can be negative unintended consequences associated with a precautionary measure (4) as will be discussed later.

A more objective way to evaluate the potential consequences of antibiotic use in livestock and poultry is to develop scientifically-based predictions, and through these models, evaluate interventions that reduce potential human and animal health risks associated with certain antibiotic uses in animal agriculture. This approach includes the methodology known as risk assessment. For example, in 2003 the FDA Center for Veterinary Medicine (FDA-CVM), which uses a scientific approach to regulatory decisions, issued a Guidance for Industry document #152 that described a qualitative risk assessment process that is utilized in the approval of all applications for new animal antibiotics and the reassessment of existing animal antibiotics. I was recently part of a team that conducted a risk assessment following the document #152 approach. Specifically, we assessed the risk that the agricultural use of a family of antibiotics known as macrolide antibiotics poses to human health (7). The concern is that macrolide antibiotics are also used in human medicine, and therefore, the use of macrolide antibiotics in animal agriculture could compromise the efficacy of these antibiotics in human medicine and potentially increase the number of macrolide-resistant bacterial infections in people. We developed a semi-quantitative risk assessment model following the format of document #152. We found that all macrolide antibiotic uses in animal agriculture in the U.S. posed a very low risk to human health. The highest risk was associated with macrolide-resistant *Campylobacter* infections acquired from poultry, but this risk was still estimated to be less than 1 in 10 million and would thus meet the standard of "reasonable certainty of no harm" employed by FDA-CVM.

Currently, the international body Codex Alimentarius has formed a Task Force to delineate international standards for the conduct of risk assessment and risk management in the context of antibiotic use in animal agriculture. The main purposes of the Codex Alimentarius are "protecting health of the consumers and ensuring fair trade practices in the food trade, and promoting coordination of all food standards work undertaken by international governmental and non-governmental organizations." Once this Task Force has completed its objective, there will be a set of accepted, scientifically-based approaches for determining if antibiotic uses in animal agriculture pose a risk to human health, and if so, how these risks should be managed. Perhaps most important, the final document of this Task Force will outline procedures for assessing whether interventions that are used to mitigate risk have succeeded or whether they have been counter-productive.

Unfortunately, most risk assessments conducted to date in antibiotic resistance that have been used for regulatory purposes have not included specific interventions that can be implemented to reduce the human and animal health risks. Instead, the assessments seem to have been designed for the sole purpose of making the dichotomous decision of whether or not to withdraw an antibiotic from use. For risk assessments to be useful, they must include evaluations of potential interventions for reducing the risks to human and animal health. In the U.S. FDA-CVM risk assessment of fluoroquinolone use in chickens (2), the model only estimated the potential human health impact of this antibiotic use and did not evaluate ways for minimizing the risk associated with fluoroquinolone use in poultry. For example, the model could have examined the possibility of processing chickens from treated poultry flocks separately from chickens from untreated flocks as a potential risk reduction strategy. This separated processing could help reduce the chance of cross-contamination of chicken meat from non-treated poultry flocks with the bacteria from treated flocks. The model could have examined a potential intervention in which farms that have received fluoroquinolones are cleaned in a more intensive manner than the normal cleaning, and all litter from these flocks is sterilized. Finally, the model could have assessed an intervention in which flocks that have been treated with antibiotics would have to wait for a longer period of time before processing. This type of approach would resemble the mandatory withdrawal times associated with antibiotic residues. Guidelines could then be developed to determine when specific antibiotic uses should be ceased in flocks before they go to processing in order to reduce the amount of antibiotic resistant bacteria in the birds. Consideration of such risk mitigation interventions rather than complete withdrawal of these drugs would have been very important to poultry veterinarians. Prescription drugs like the fluoroquinolones are a valuable option to control fatal respiratory disease in chickens since other effective therapeutic alternatives are not available.

These types of interventions might sound labor-intensive and costly. They are, and that is the point. Under certain circumstances, it might be cost-effective and ethical for a veterinarian to use a powerful antibiotic to control a severe disease in the herd or flock, but this use would then have major repercussions on how the herd or flock as well as the farm are subsequently managed. Producers might not opt for this intensive measure, but at least they would have a choice that is accepted as scientifically-sound for reducing both the human and animal health risks associated with the antibiotic use on their farm. As we begin to gain a better understanding of the ecology of resistance and its relation to animal and human health, we will need these scientifically-based strategies for minimizing the impacts of antibiotic use on animal, human and environmental health.

Are there benefits to antibiotic use in animals?

The models that we build to assess the potential risks of antibiotic use in livestock and poultry must begin to take a more holistic view of health into consideration. Specifically, these models need to include the potential risks and the potential benefits associated with antibiotic use. Phrased another way, are there potential unintended consequences of removing antibiotics from use in food animals? Recent models have predicted that there might be significant negative human health consequences associated with the removal of certain antibiotics from animal production. This is an instance in which the precautionary principle would lead to an action of banning antibiotics in animal agriculture, but that action could have even worse unintended consequences. It might not be intuitive, however, how an antibiotic that is used in animal agriculture can actually benefit human health.

The health status of animals that are processed for meat can potentially affect food safety in two major ways. First, animals that are less healthy may shed higher levels of harmful bacteria, such as *Salmonella* and *Campylobacter*. Second, groups of animals that have experienced illness, either clinically or subclinically, can be smaller in size and more variable in size. During processing, these factors can contribute to an increased likelihood of the gastrointestinal tract being ruptured, and this processing error can lead to increased contamination and cross-contamination of the meat and thus increase the risk of human foodborne illness. Reducing animal illness likely plays a critical role in reducing the chances of contamination during processing.

I recently was part of a team that developed a mathematical model that relates animal illness to human illness (8). In our model, there was a large increase in human illness associated with small increases in animal illness, suggesting that agricultural management strategies may have significant impacts on human health. Antibiotics administered in feed at low doses over several weeks raise concern about their potential to increase rates of antibiotic resistance, posing a risk to human health. However, these applications also improve animal health and promote size uniformity among animals in the herd or flock. Antibiotic uses in animals can therefore have potential human health risks and benefits. Our model was able to evaluate simultaneously the human health risks and benefits associated with antibiotic use in animal agriculture. Specifically, the model addressed the relationship between the negative human health impact of increased antibiotic resistance and the positive human health impact of fewer foodborne infections, both of which are due to the use of the antibiotic in animal agriculture. The model showed that the potential benefits to human health associated with the use of antibiotics in animal agriculture can far outweigh the potential risks. This finding has now been validated by additional studies (3)(6).

In summary, Mr. Chairman and Members of the Subcommittee, thank you again for the opportunity to discuss the role of antibiotics in animal agriculture. Antibiotics are an integral component of animal health. All uses of antibiotics improve animal health, and these improvements in animal health can substantially improve human health. All uses of antibiotics also pose a risk, mainly associated with increases in antibiotic resistance. The key is to assess the ability of interventions to maximize the benefits and minimize the risks associated with the agricultural use of antibiotics. Simply removing antibiotics from use in animal agriculture may help reduce some of the antibiotic resistance circulating today, but it might also have severe unintended consequences. The best way to manage antibiotic uses in animal agriculture is through sound, rational, science-based policy.

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