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Committee on Energy and Commerce

United States House of Representatives

Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture

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Mr. Chairman and Members of the Subcommittee:

Thank you for providing me with the opportunity to discuss the important topic of antibiotics in animal agriculture. 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 12 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 six 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 does it develop?
3. What are the impacts of antibiotic usage in animal agriculture?
4. How do we assess the risks of antibiotic use in animal agriculture?
5. How do we manage the risks of antibiotic use in animal agriculture?
6. How does the *One Health* paradigm apply to antibiotic use in animal agriculture?

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

Although many people think of antibiotics as human-made compounds, antibiotics are actually small molecules that are naturally produced by microorganisms in the environment (30). 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 -- a way for the bacterium to resist the action of these antibiotics. The presence of naturally produced antibiotics in the environment is rarely considered as a contributor to the degree of resistance that is found in bacteria around the world, and yet it is this environmental pool of resistance, recently termed the resistome (7), 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 and a disease risk is present. The importance of prevention should not be underestimated; it is always preferable to prevent disease than to treat a whole flock or herd of diseased and exposed animals once an outbreak has begun. In fact, one of the central tenants of medicine is to minimize health impacts by maintaining a healthy population in the first place. 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. This type of use has been termed “production use” in the recent FDA Draft Guidance document #209 because production uses “are not directed at any identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products (e.g. increasing rate of weight gain or improving feed efficiency)” (28).

All four of these use categories result in an improved health of the animal receiving the antibiotic. Nonetheless, assumptions about these uses often lead to confusion. One 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 four of these

uses can be applied via the feed or the water because the only realistic way to administer an antibiotic to populations of animals, such as a flock of chickens, is through the feed or the water. Further, 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.

Many of the antibiotics currently used in animal agriculture, particularly those used for "production" purposes, were approved in the 1960's. In general, there was a poor understanding of how these compounds worked, but because animals fed antibiotics for production purposes grew faster, the antibiotics were labeled for increased feed efficiency and average daily weight gain. The label claims for these antibiotics have not changed in almost 50 years. In a time when bacteria are becoming increasingly resistant to the action of antibiotics, it might seem injudicious to use an antibiotic solely to increase weight gain and feed efficiency, and this use might be interpreted as having a pure economic value. We now know that low-dose uses of antibiotics improve the overall health of the growing animal, and the outdated label claims of feed efficiency and growth promotion do not do justice to the "gut health" and "disease prevention" attributes that these low doses possess. In general, the improvements seen in feed efficiency and growth are the result of improved health and gut integrity due to disease prevention.

When strictly considering the label claims of improved feed efficiency and average daily weight gain, the "production" uses of antibiotics do not appear to have the same importance they once had. For example, in a study by Dritz *et al*. (9), various antibiotic regimens were tested on growing pigs. Only the growth rate of nursery pigs was significantly improved by some of the regimens. The authors concluded that dramatic improvements in the health management of animals in intensive agricultural facilities as well as improved animal genetics likely led to a diminished need for "production" uses of antibiotics.

A very recent study by Aarestrup *et al.* (2) analyzed antibiotic use and production data from swine raised in Denmark between 1992 and 2008. By January 2000, Denmark had stopped using any antibiotic for growth promotion in swine. The authors concluded that total antibiotic consumption per pound of pig produced decreased over the time span of the study, although the authors included approximately 6 years of data before the ban was even initiated. At the same time, the authors concluded that swine productivity, when analyzed as mean number of pigs per sow per year raised for slaughter and average daily weight gain increased during the time period of the study. Consequently, it would appear from this study that animals can be raised efficiently without the need for "production" uses of antibiotics.

There are several troubling aspects of the data analysis in the paper by Aarestrup *et al.*, however, as well as a key take-home message that was not highlighted in the manuscript. First, according

to the Danish Agriculture and Food Council, the number of pig producers in Denmark dropped from approximately 25,000 in 1995 to less than 10,000 in 2005. Only those with the highest productivity and efficiency survived, and those producers that survived became larger operations and became more integrated and intensive. If more than half of the producers were lost during the timeframe of the study, and if these producers were the least efficient and productive, then estimates of overall productivity would have to increase over time *for no other reason than the fact that only the most productive producers survived*. Unfortunately, information about specific producers and their productivity over time is not available, and therefore it is impossible to do an analysis to determine how much increase there was in productivity on an individual producer basis. Even with this information, though, the fact remains that increases in pig productivity were already being observed in Denmark prior to the bans due to improved animal genetics and improved health management systems.

A final point that is critical to recognize from the paper by Aarestrup *et al*. is demonstrated in Figure 2 of the paper, as shown below:

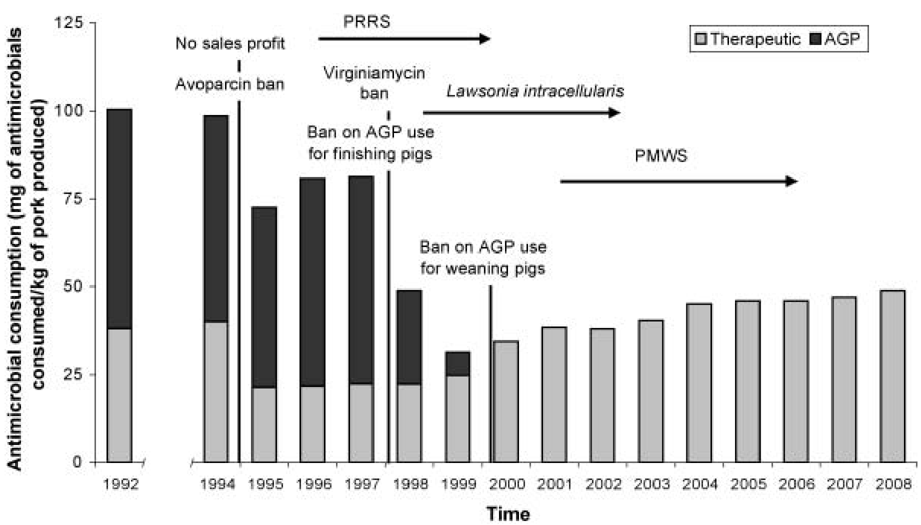


Figure 2 (from Aarestrup et al., 2010 (2) — Consumption of antimicrobials for use as AGPs (black bars) or for therapeutic administration (gray bars) from 1992 to 2007 by the Danish swine production system. Notice the ban on use of avoparcin and on veterinary profits from the prescription and sale of antimicrobials, the ban on AGP use in finishing pigs and on use of virginiamycin in all pigs that was instituted in 1998, and the ban on AGP use in weaning pigs that was instituted in January 2000. Outbreaks of PRRS (1996 to 2000), disease attributable to *Lawsonia intracellularis* (1998 to 2002), and PMWS (2001 to 2006) are indicated (arrows). Weaning and finishing pigs weighed < 35 kg and > 35 kg, respectively.

Over time, and particularly following the ban on growth promoting antibiotics (AGP), there was a steady increase in the use of therapeutic antibiotics. The antibiotics approved for therapy in animal agriculture are often those that would also be considered medically-important in humans.

The authors attempted to explain these increases in therapeutic antibiotic uses by events like an outbreak of *Lawsonia intercellularis* in the period of 1998 through 2002. This is misleading because *Lawsonia intercellularis* is always present on most swine operations and can be kept in check by the administration of disease prevention doses of antibiotics. A take-home message of this paper is the fact that this disease appeared following the removal of "production" uses of antibiotics and should indicate that these uses do have health-related functions far beyond the labeled feed efficiency and average daily weight gain claims. Such uses might include disease prevention doses of antibiotics that would be targeted at specific pathogens typically found on farms, such as *Lawsonia intracellularis,* and would be given to swine at ages when they are most susceptible (i.e. at weaning).

<u>What is antibiotic resistance and how does it develop?</u>

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 these antibiotics. 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 survive despite the pressure imposed by the antibiotic. During the course of the antibiotic, the rates at which bacteria can acquire resistance might increase. Consequently, the use of the antibiotic may pose a risk to human and animal health through the selection of a more resistant bacterial population.

Whereas FDA Guidance Document #209 (28) states in the Executive Summary that "Misuse and overuse of antimicrobial drugs creates selective evolutionary pressure that enables antimicrobial resistant bacteria to increase in numbers more rapidly than antimicrobial susceptible bacteria and thus increases the opportunity for individuals to become infected by resistant bacteria," it is important to recognize that ALL uses of antibiotics select for resistance to some degree in specific bacteria. The question, stated simply, is how to ensure that public health and environmental health are maximized while maintaining animal health. To address this type of holistic question, we must first assess how different uses of antibiotics impact antibiotic resistance.

What are the impacts of antibiotic usage in animal agriculture?

To begin this section on the potential impacts of antibiotic use, it is critical to distinguish between antibiotic resistance and food safety. Nobody should be questioning the fact that bacteria from animals can move through the food chain and cause disease in people. This is the basis of food safety and control programs designed to reduce the burden of illness associated with foodborne disease. Efforts are often focused on controlling the contamination of food products and educating the consumer about the proper ways for handling food products. Foodborne bacteria can cause disease regardless of whether they are susceptible or resistant to antibiotics. The relevant question for this hearing is why are some of these bacteria resistant to antibiotics in the first place, and did the use of antibiotics in animals cause the resistance observed in these bacteria? Unfortunately, many individuals have linked the two issues, leading to the assumption that antibiotic resistant bacteria that infect people through the consumption of food are resistant BECAUSE of the use of antibiotics in animals. This linking of two separate issues has been incorporated into many reports that are being used to set policy, and because many of these reports cite prior reports rather than citing the original research on which the reports are based, these misconceptions have been propagated over time. Two key examples are described below:

One study that was published in 1999 out of Denmark reported on a multi-drug resistant bacterial isolate of *Salmonella* Typhimurium definitive phage type 104 that caused morbidity and mortality in people (20). This bacterium was of particular concern not only because it was multi-drug resistant but also because it was resistant to a very important class of antibiotic, the fluoroquinolones. The authors of this paper concluded in the Abstract that "because of this increase in quinolone resistance in *Salmonella*, the use of fluoroquinolones in food animals should be restricted." If one reads beyond the Abstract of this paper, the authors admit that "There was no indication of fluroquinolone use in the implicated [swine] herds" (p. 1424). They continue to say that it is impossible to determine if this multi-drug resistant *Salmonella* strain "was introduced by pigs from outside Denmark, was introduced by environmental spread (e.g., from wild animals or equipment), or was related to the use of fluoroquinolones at the suspected farms before 1998" (p. 1424). Consequently, this paper is an unfortunate story of severe illness caused by *Salmonella* that potentially originated in swine, but it says nothing about the impacts of the agricultural use of antibiotics. It should be noted that fluoroquinolones, when used in animal agriculture, are used as a therapeutic antibiotic for treating sick animals; they are not "production use" antibiotics. To include this paper in discussions of the potential risks of agricultural uses of antibiotics and in discussions regarding "production use" antibiotics, as has been done in many of the governmental and non-governmental reports on antibiotics in agriculture, seems inappropriate.

A second paper worth noting was published in 2000 and discussed a ceftiofur resistant *Salmonella* strain that was acquired by a child possibly from cattle (11). Ceftiofur is a third-generation cephalosporin related to ceftriaxone, a medically-important antibiotic. In the Abstract, the authors conclude that "This study provides additional evidence that antibiotic-resistant strains of salmonella in the United States evolve primarily in livestock." A statement this strong would suggest that the authors had data demonstrating that ceftiofur was used in the implicated cattle herd, that susceptible *Salmonella* strains were isolated, and that they could document the emergence of a ceftiofur-resistant strain on the implicated farm due to the use of the antibiotic on that farm. The authors state on page 1247 that "It is probable that the use of antimicrobial agents in cattle led to the selection of the ceftriaxone-resistant strain that was subsequently transmitted to the child. Although we were unable to establish its use in these herds, an expanded-spectrum cephalosporin (ceftiofur) is approved for use and is widely used in domestic animals, including cattle." This paper documents an unfortunate severe illness but says nothing about the impacts of antibiotic use in animal agriculture. Once again, the antibiotic addressed in this study, ceftiofur, is a therapeutic antibiotic and should not be included in discussions of "production use" antibiotics. Nonetheless, it remains one of the central citations used to set policy

Studies that have been conducted on the effects of antibiotic administrations in agricultural animals are not numerous. There are more studies on the effects of treatment dose administrations than on the effects of disease prevention and "production" dose administrations. More studies need to be performed in animals in various settings meeting rigorous study design requirements. Dosing regimens need to be evaluated to determine how they impact selection of resistant bacteria. A brief summary of several studies that have evaluated antibiotic administrations are described below.

A series of studies has been conducted in dairy and beef cattle to explore the effects of therapeutic ceftiofur administration on the appearance of ceftiofur-resistant *E. coli*. In one study, treated dairy cows showed a significant decrease in the total *E. coli* population when fecal samples were analyzed (24). There appeared to be a complete decimation of the susceptible *E. coli* population. Animals that possessed *E. coli* with ceftiofur resistance could be detected in some of these samples. Although animals not treated with ceftiofur were confirmed to possess ceftiofur resistant *E. coli* using molecular methods, these animals never had resistant *E. coli* isolated from their fecal samples. Within a week of the cessation of treatment, the susceptible population of *E. coli* returned, and resistant isolates were not recovered again for the remainder of the 30-day study period. The antibiotic treatment provided a window to detect the presence of ceftiofur-resistant *E. coli* but did not cause its emergence or result in its amplification. In a trial with ceftiofur in beef cattle, similar findings were observed (17). In this study, the susceptible *E.*

coli population returned within 28-days, indicating that the effect in this study was somewhat longer lasting. Another study in dairy cattle found that treated animals continued to shed resistant strains 17 days after the initial treatment (16). In an investigation of dairy farms, those dairies that used ceftiofur were significantly more likely to have cows shedding *E. coli* with reduced susceptibility to cephalosporins (26).

These studies and others not mentioned demonstrate a consistent point: high dose therapeutic antibiotic administration can eliminate susceptible populations of bacteria. This effect can lead to a selection of resistant strains. Furthermore, many of the antibiotics used for therapeutic purposes in animals would be considered medically-important to humans, and consequently, their use could be selecting for bacteria that are resistant to the same antibiotics used in human medicine. Further research is needed to determine how to minimize this risk and also how to control the release of resistant bacteria from the farm.

Studies on antibiotic uses at "production" and disease prevention doses can also show a higher rate of resistance in the treated animals versus the control animals. For example, in pigs treated with apramycin (an antibiotic no longer marketed in the US), apramycin resistant *E. coli* levels were higher in the treated versus the control groups but quickly returned to baseline levels as in the previously cited treatment dose studies (18,19). Effects such as these are not always observed, as evidenced by a recent study of feeding trials in finishing pigs with tylosin or chlortetracycline under different dosing regimes (29). This study found no difference in resistance in either *Salmonella* or *E. coli* between the treatment and control groups. Another effect occasionally assessed in these studies is the potential for the low-dose antibiotics to decrease shedding of important foodborne bacteria such as *Salmonella*. This effect has been suggested by studies that have observed lower levels of *Salmonella* shedding in pigs that have been fed antibiotics (10,12,19). One recent study observed a decrease in *Salmonella* shedding over time in the antibiotic-treated groups, but the effect was not statistically significant (29).

Perhaps the best place to look for some of the impacts that "production" uses of agricultural antibiotics have is in Denmark and the European Union. It is often reported that levels of antibiotic resistance in bacteria isolated from animals and people in Denmark declined following the complete ban of "production uses" of antibiotics in the late 1990's. Furthermore, it is often stated that antibiotic use levels also declined. Both of these statements, however, depend on how the data are analyzed.

Figure 27 from the 2008 DANMAP report (8), shown below, shows that the prevalence of resistance to certain antibiotics in *Salmonella* Typhimurium has actually increased over time.

This is important because of the public health relevance and burden of illness associated with this bacterium.

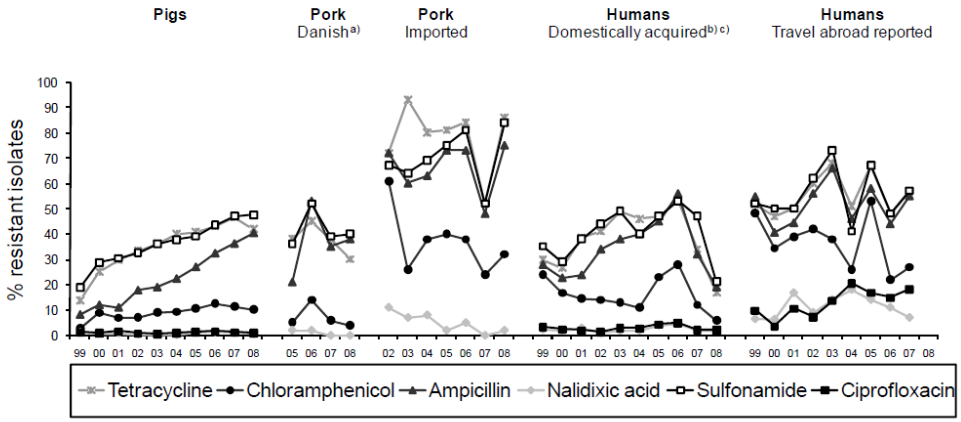


Figure 27. Trends in resistance to selected antimicrobials among Salmonella *Typhimurium isolated from pigs, pork and from human cases, Denmark*

Figure 28 from the 2008 DANMAP report (8), shown below, demonstrates increasing prevalences in antibiotic resistant *Campylobacter jejuni*, another important human pathogen.

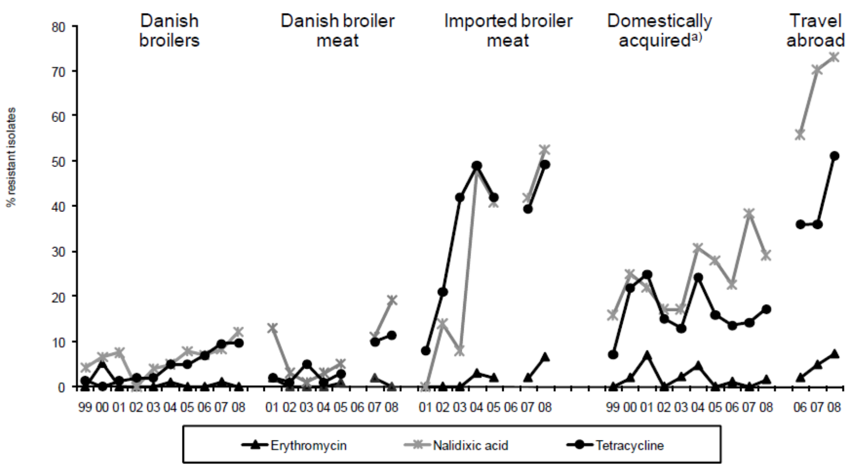


Figure 28, Trend C. jejuni. Trends in resistance to selected animicorbials among Campylobacter jejuni *isolates from broilers, broiler meat and human cases, Denmark*

Together, these figures demonstrate that the removal of antibiotics from animal production will not necessarily result in a decline in antibiotic resistance. Figures 9 and 10 from the 2008 DANMAP report (8), shown below, highlight a critical concern when setting antibiotic use policy. When the antibiotic administrations are recorded as the number of doses given to animals, the number of doses has steadily risen in Denmark since the ban of "production use" antibiotics. These Figures, when combined with Figure 2 from Aarestrup et al. as shown previously (2), clearly demonstrate that following the removal of the "production use"

antibiotics, considerably more therapeutic administrations were required. This is due to the increased animal illness that has been observed in Denmark since the ban.

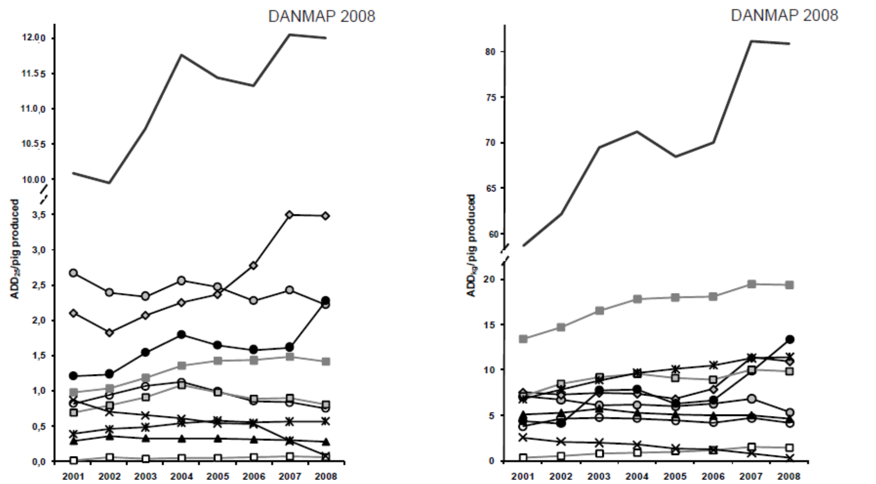
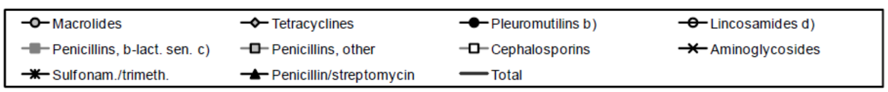


Figure 9. Trends in antimicrobial consumption (in ADD25 a)) in pigs, Denmark

Figure 10. Trends in antimicrobial consumption (in ADDkg) in sows and piglets;



Given that over ten years ago the removal of the "production use" antibiotics in Denmark was implemented to improve human health, one would expect to have seen human health improvements by this point in time. The major impacts that are cited are a reduction in resistant bacteria in animals and in people within the community; no clear-cut human health improvements (i.e. decreased incidence of disease caused by resistant bacteria) are even mentioned. As shown previously, even the reports of decreased antibiotic resistance in bacteria from animals and humans depends on which bacteria and which antibiotics are being considered.

On the contrary, the 2008 DANMAP report (8) documents the dramatic increase in multidrug-resistant *Klebsiella pneumoniae* isolates in hospitals. This bacterium can cause serious blood infections in people, and the multidrug-resistant strains are particularly difficult to treat. One hypothesis for the dramatic increase is the increased consumption of broad spectrum antibiotics, especially the 2nd and 3rd generation cephalosporins. Much of this consumption is occurring in human hospitals, but some of this consumption could also be occurring as a consequence of the increased use of therapeutic antibiotics on farms to treat the increasing numbers of ill animals.

How do we assess 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 (3). 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. Therefore, 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. The problem is that it is very difficult if not impossible to predict the negative unintended consequences associated with a precautionary measure (6).

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. Throughout many governmental and non-governmental reports, including those cited in FDA Draft Guidance #209 (28), there have been repeated calls for the use of risk assessment approaches. In 2003 the FDA Center for Veterinary Medicine (FDA-CVM), which uses a scientific approach to regulatory decisions, issued 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 (27). FDA Guidance Document #209 makes a clear distinction between the use of #152 in the pre-approval process of a new animal drug and a safety review of a currently-approved product. Regardless, the risk assessment approach is a science-based approach to evaluating the potential risks to human health associated with the use of antibiotics in animal agriculture. A major challenge to this approach, though, is related to the definition of risk and an acceptable level of risk. In FDA Guidance Document #209, it is stated on page 13 that "FDA considers an antimicrobial new animal drug to be "safe" if the agency concludes that there is "reasonable certainty of no harm to human health" from the proposed use of the drug in food-producing animals" (28). This is a vague definition that has traditionally been used for toxicological

assessments. With respect to antibiotic resistance, it is unclear what is implied by "reasonable certainty of no harm."

If the risk assessment approach is to be utilized, it should be expected that each antibiotic or class of antibiotic that is approved or that is seeking approval would be evaluated separately, and that an assessment would be conducted in each animal species separately. To assume that all antibiotics that are used in the same way pose the same risk to human health seems to defeat the purpose of a scientifically-sound risk assessment process. Performing a risk assessment that is drug-host-microbe specific is feasible, and there is at least one peer-reviewed and published risk assessment that did this while following the GFI #152 approach. The published model assessed the risk that the agricultural use of a family of antibiotics known as macrolide antibiotics poses to human health (14). 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. A semi-quantitative risk assessment model following the format of GFI #152 was developed and found that all macrolide antibiotic uses in animal agriculture in the U.S. pose a very low risk to human health. The Table below shows the results of the model. The risk is expressed as the probability that macrolide use in the animal species will result in macrolide resistance in a specific bacterium, that this bacterium will make it through the food chain and infect a person, that this person will seek medical care, and that treatment of the infection with macrolides will fail due to the macrolide resistance. 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.

Animal Product	Macrolide-Resistant Bacteria	Quantified Risk to Humans of Treatment Failure Due to a Resistant Infection
Beef	*Campylobacter*	< 1 in 236 million per person per yr
	E. faecium	< 1 in 29 billion per person per yr
Poultry	*Campylobacter*	< 1 in 14 million per person per yr
	E. faecium	< 1 in 3 billion per person per yr
Pork	*Campylobacter*	< 1 in 53 million per person per yr
	E. faecium	< 1 in 21 billion per person per yr

Results from Hurd et al., 2004, J Food Prot, 67:980-992

How can we manage the risks of antibiotic use in animal agriculture?

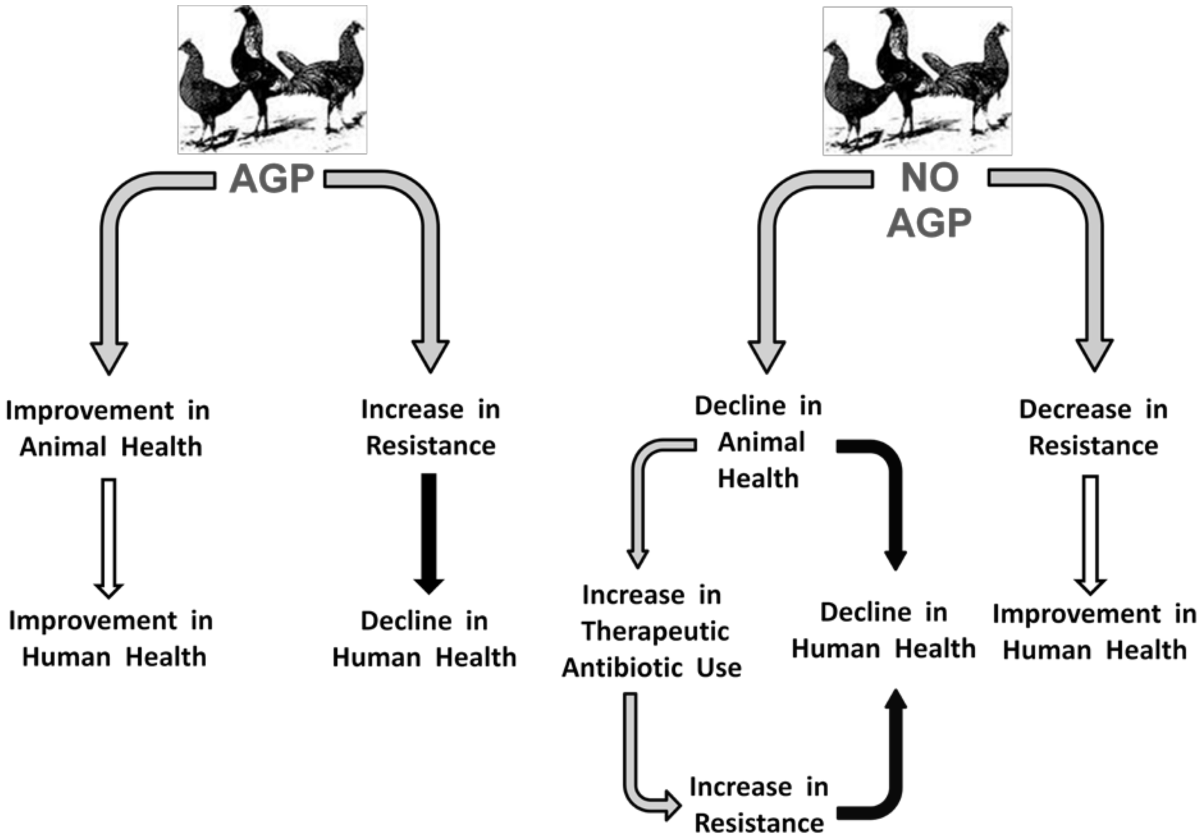
Most risk assessment models conducted to date in antibiotic resistance that have been used for regulatory purposes have not included specific interventions that can be implemented to reduce the human and animal health risks. Instead, the assessments seem to have been designed for the sole purpose of making the dichotomous decision of whether or not to withdraw an antibiotic from use. For risk assessments to be useful, they should 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 (4), 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.

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.

How does the *One Health* paradigm apply to antibiotic use in animal agriculture?

The health of humans, animals and the environment are intricately related. Many of the challenges we face today, including emerging infectious diseases, antibiotic resistance, food safety and security, and sustainable living exemplify this holistic view of health. The notion of *One Health* incorporates this holistic view and aims to bring a multidisciplinary approach to addressing these complex health issues. The issue of antibiotic resistance serves as an exemplary model for a *One Health* approach. We cannot possibly grasp how microbes are impacted by exposure to antibiotics without an understanding of the dynamics of microbes in the environment, animals, and people (25). Further, we cannot understand the implications of human exposure to bacteria carrying resistance genes without understanding how exposure occurs, how resistance develops, and what the risks of such exposure are.

When we consider the complex issue of antibiotic resistance, we must begin to take a more holistic view of health into consideration. Every action and every policy decision we make that is intended to slow or stop the development and spread of resistance has the potential to have serious unintended consequences. As an example, the removal of growth promoting antibiotics from use in food animals in Denmark resulted in an increased reliance on therapeutic doses of medically-important antibiotics to treat the ill animals. The Figure below shows a schematic of this relationship in which animals that are given antibiotics for growth or disease prevention are healthier, leading to a longer term improvement in animal health. This improvement leads to a safer food supply and therefore improved human health. However, these antibiotics can also select for resistance, which can lead to a decline in human health. If antibiotics used for growth or disease prevention are removed, there will be a decrease in antibiotic resistance, which could lead to improved human health. There will also be a decline in animal health, as seen in Denmark and other countries, which will then lead to an increased use of therapeutic antibiotics to treat the sick animals. This leads to increased antibiotic resistance and a decline in human health. Furthermore, a decline in animal health can lead to a decline in human health through more contaminated meat entering the food supply.



In this schematic, the solid black arrows denote negative impacts on human health while solid white arrows denote positive impacts on human health. AGP represents antibiotics used as for growth promotion, but because the effect of these antibiotics is also to improve animal health, AGP could be substituted with Disease Prevention doses.

The scenario described above has a basis in the published scientific literature. 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. Their gastrointestinal tracts can have weaker walls. 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 (13,22). A recent mathematical model was developed to address this relationship shown in the figure above (23). The model demonstrated 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. 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 (5,13,15).

Another example of a potential unintended consequence of antibiotic use policy relates to methicillin-resistant *Staphylococcus aureus* (MRSA). An observation was made that tetracycline resistance was among the resistance carried by MRSA isolates from animals. The concern was that any continued use of tetracycline was selecting for MRSA. A recent study from Denmark found that both MRSA and MSSA (susceptible strains) were resistant to tetracycline, but only the MRSA strains were resistant to zinc (1). Zinc chloride has been used in Denmark as a non-antibiotic alternative following the antibiotic bans, and now it appears that zinc compounds may have selected for the emergence and dissemination of MRSA strains in Denmark.

Summary

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. Even "production " uses of antibiotics, which have the unfortunate, decades-old label claim of improving feed efficiency and average daily weight gain, have the clear and documented effect of improving animal health. All uses of antibiotics may 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. A successful management strategy is one that will optimize human, animal and environmental health. Success should not be measured by implementation of the policy itself (21) but rather through documented health improvements.

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