

TESTIMONY OF

Christine Hoang, DVM, MPH, CPH

Assistant Director

American Veterinary Medical Association

Concerning

Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture

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Thank you, Mister Chairman and members of the Subcommittee on Health, for providing the American Veterinary Medical Association (AVMA) with the opportunity to speak about antimicrobial resistance and the use of antimicrobials in animal agriculture.

My name is Dr. Christine Hoang, and I am an Assistant Director in the Scientific Activities Division of the American Veterinary Medical Association. In addition to a doctorate in veterinary medicine, I also hold a master of public health degree with concentrations in veterinary public health policy, both national and international, as well as epidemiology^a and am additionally certified in public health. My work focuses upon science based policy for food safety, zoonotic disease^b, and antimicrobial resistance on behalf of the veterinary profession. Not only are these topics of public interest, but these are topics that require a great deal of intensive research and careful evaluation.

Established in 1863, the AVMA is a not for profit association representing more than 80,000 U.S. veterinarians engaged in every aspect of veterinary medicine and public health – private and corporate practice, government, industry, academia, and uniformed services. As veterinarians, our oath ethically charges us with promoting public health and protecting animal health and welfare. With that also comes the responsibility to be cognizant of the potential human impacts that may occur as a result of any decision we make. When a veterinarian makes the decision to use a drug, any drug, especially in a food animal, that person must consider the individual animal; other animals that may come into contact with that animal; humans who may come into contact with that animal; and if it is a food animal, we must ultimately consider the people who consume the end product. In today's world, the decisions of a veterinarian affect far beyond a single animal or person – it is an entire herd or flock and potentially hundreds or thousands of people affected by the many foods that are produced from a single animal. Therefore, as veterinarians, we carry a heavy burden, but we do so willingly with the knowledge, education, and ability to make the right decisions and to use the tools that are available to us appropriately and judiciously. With respect to antimicrobial resistance, our members share the same concerns as our human health counterparts. Yet, we also have additional concerns that must be considered such as negative impacts on animal health and welfare or even negative impacts on human health that are often unrealized.

Risk – Benefit Assessments and Human Health Impact

Two decades ago, at the request of the Food and Drug Administration (FDA), a committee of the National Research Council was charged with evaluating the effects of penicillin, chlortetracycline, and oxytetracycline at levels for growth promotion or disease prevention on human health. The committee concluded that human health hazards could not be proven or disproven because it is impossible to determine antimicrobial exposures of individual animal sources of meat products¹. The debate continues today for the very same reason. While there have been technological advances such as DNA fingerprinting that can identify clonal isolates, a direct epidemiologic investigation still cannot be completed. Therefore, antimicrobial resistance and the role of animal agriculture continue to be debated.

As the debate continues, it is important to understand that much of the varying opinions is due to differing levels of acceptable risks. For example, as an individual, a person may not accept any risks associated with food and yet be extremely tolerant of risks associated with driving at high speeds. As veterinarians, we must consider many risks – risks to the animal, risks to ourselves, risks to our clients, risks to public health, risks of action, and risks of inaction – and be accepting of some of those risks in order to minimize other risks.

^a Epidemiology is a medical discipline that is the study of the causes, distribution, and control of disease in populations and serves as the foundation and [logic](#) of interventions made in the interest of [public health](#) and [preventive medicine](#).

^b Zoonotic diseases are diseases that can be transmitted from animals to humans. CDC estimates at least 60 percent of all human diseases and 75 percent of all newly emerging diseases are zoonotic.

Whenever antimicrobials are used, there is some risk of resistance developing. Therefore, similar to human medicine, clinical infections do occur and resistance in food animals does develop. That resistance can be transmitted to humans, however multiple monitoring and surveillance systems are in place that can recognize impactful events and trigger further investigation to determine the level of associated risks. One of those systems is the FDA adverse event reporting system which should include treatment failure as a result of resistance. Another system is the National Antimicrobial Resistance Monitoring System (NARMS) that monitors resistance in foodborne human enteric pathogens as well as resistance in animals. The retail meat NARMS surveys and the animal arm of NARMS, provide a more comprehensive view of antimicrobial sub-populations than the NARMS human data that are collected. Furthermore, resistance is closely monitored through diagnostic samples and retail meats with an overrepresentation in sampling. The NARMS sample collection design ensures that resistant animal isolates are overrepresented.

Recognizing that food is the most likely route of transmission of resistance from food animals to humans², the AVMA supports the use of multidisciplinary and multi-hurdle^a approaches³ to safeguard our food supply and minimize the potential for any adverse impacts on human health. For instance, on the farm, we encourage the continued improvement of animal husbandry and management practices, the development of new technologies to advance animal health, and the continued availability and judicious use of antimicrobials. Post-harvest, we support the on-going improvements of Hazards Analysis and Critical Control Points (HACCP) based pathogen reduction programs – all of which to ensure a safe, healthy, and wholesome food supply. Some data suggest post harvest interventions, such as hyperthermia and disinfection can influence the survival of resistant bacteria, and should be further investigated.⁴

To minimize risks to human health, the FDA requires antimicrobial manufacturers to provide information to show that a proposed animal drug will not harm public health. The procedure ensures zero-risk for human safety because drugs that pose risks beyond “a reasonable certainty of no harm” to human health are rejected or the use of the antimicrobial may be limited in order to mitigate the adverse effect. Antimicrobials approved since the implementation of the FDA Guidance for Industry #152 (a risk analysis process) in 2003, have undergone a comprehensive, evidence-based approach to prevent the emergence and selection of antimicrobial resistant bacteria that may adversely affect human health. Because the extent-of-use limitations table in GFI #152 assigns a high ranking for intended administration to flocks or herds of animals, it is extremely difficult or impossible for FDA to approve antibiotics for use in feed or water for treatment of groups of animals, if those same antibiotics are also used in humans. Unfortunately, few new antimicrobials are currently being developed. While several drugs are developed and reserved for human use, only one new drug (tiamulin) has been made available for treating animal disease in recent years. Therefore, the antimicrobials that were approved decades ago (and in the same classes as some human use antimicrobials) may be the only antimicrobials available for use in herds and flocks to combat infectious diseases and safeguard the food supply.

Given the pre-approval safety measures taken by FDA, further action to restrict antimicrobial use in animals should only occur if there is an imminent threat to human health or if the data clearly show that there is a threat developing following an accurate scientific risk assessment. The risk assessment must be conducted to facilitate risk-based decisions concerning the appropriate and judicious use of antimicrobials. Risk analyses should continue to evaluate the risks and benefits to animal health and welfare, in addition to the risks and benefits to human health attributed to uses in food animals. Risk analyses include risk assessment, risk communication, and risk management actions that are commensurate with the level of risk that is determined through risk assessment. Following a risk assessment, the risk management action may simply be to allow continued availability of the product with no changes because the level of risk has been determined to be insignificant, or the action may be to withdraw approval of the drug product. Other actions by the FDA can also include review by the

^a The multi-hurdle concept refers to the interaction of factors that affect microbial behavior in foods. Under some circumstances these effects are additive. Under others, the implication is that synergistic interactions lead to a combined effect of greater magnitude than the sum of constraints applied individually.

Veterinary Medicine Advisory Committee or limitations of use such as use only for certain indications.

Several antimicrobial risk assessments have been performed demonstrating varying risks to humans depending on the drug and the specific use of the drug. This further emphasizes the need to ensure science based risk assessments on a drug by drug basis to fully inform the regulatory process. One of FDA's risk assessments concluded that an unacceptable level of risk (1 in 34,945 people estimated to be affected in 1998 and 1 in 32,912 in 1999) for fluroquinolone resistant *Campylobacter* as a result of poultry consumption due to the use of enrofloxacin in poultry⁵ resulting in withdrawal of the product in 2005. Yet, the desired outcome of minimizing fluoroquinolone resistant *Campylobacter* in humans remains questionable as human cases continue to rise⁶.

Another risk assessment by FDA in 2004⁷ could not form conclusions as to whether the use of streptogramins (virginiamycin, an antimicrobial growth promoter) in food animals contributes to the occurrence of streptogramin-resistant *E. faecium* (SREF) infections in humans via a foodborne pathway. In fact, the FDA found the different Minimum Inhibitory Concentration (MIC) distribution and the dissimilar pattern of resistance genes between animal and human isolates to be inconsistent with an attribution of human streptogramin resistance to animal sources, meaning the resistance did not come from an animal source. Regardless, if it were to occur, the average risk to a random member of the US population of having SREF and impaired Synercid[®] (a streptogramin used to treat bacterial infections in humans) therapy as a result of animal uses of virginiamycin ranges from 7 in 1 billion to 14 in 100 million per year. In Denmark, where virginiamycin has been banned since 1998, resistance to Synercid[®] is much greater than what is seen in the US.⁸

In 1987, at the request of the FDA, an Institute of Medicine study was conducted to evaluate the risks associated with penicillin and tetracyclines at growth promotion and prevention levels. The study estimated approximately 6 deaths per year attributable to the use of penicillin and/or tetracyclines for growth promotion and disease prevention. When only used for growth promotion, that number decreased to 2 deaths per year.⁹ When compared to estimated risks from the use of enrofloxacin for treatment¹⁰, this data is contrary to the assumption that growth promotion uses are inherently stronger drivers of resistance than treatment uses and therefore cause human health hazards.

Other risk assessments also demonstrate a very low risk to human health from the use of antimicrobials in food animals. With an approximate probability of less than 1 in 10 million per year for macrolide resistant *Campylobacter* infections and approximately 1 in 3 billion for *E. faecium* infections, a unique farm-to-patient risk assessment demonstrates that the use of tylosin and tilmicosin (macrolides) in food animals presents a very low risk of human treatment failure.¹¹

Another risk assessment examines the impact of the use of penicillin-based drugs in food animals on penicillin/ aminopenicillin resistant enterococcal infections. The conclusion indicated that no more than 0.04 - 0.18 excess mortalities per year would be prevented in the entire U.S. population by discontinuing current use of penicillin-based drugs in food animals. The true risk could be as low as zero.¹² This equates to one potentially preventable mortality in the U.S. population approximately every 7-25 years. Similarly, another risk assessment concluded that veterinary use of macrolides in Danish pigs resulted in a low risk to human health.¹³

Some of the models using a risks and benefits model predict an increased human health burden if the use is withdrawn. Utilizing that model, a risk assessment for virginiamycin evaluated benefits to humans in addition to the risks. That assessment found an increase of 0.27 cases per year of streptogramin-resistant and vancomycin-resistant *E. faecium* (VREF) potentially resulting from the use of virginiamycin. Yet, as a benefit of continued use, the assessment found a significant increased human health risk if virginiamycin use is withdrawn – an additional 6,660 cases of campylobacteriosis per year. The benefit of continued use and preventing those additional 6,660 cases per year of campylobacteriosis would far outweigh the minimal risks of an increased 0.27 cases per year of streptogramin-resistant and vancomycin-resistant *E. faecium* (VREF).¹⁴ Another risks and benefits assessment concluded that withdrawal of macrolide and fluoroquinolone use is estimated to cause significantly more illness days than

it would prevent.¹⁵

Others have estimated that risk management strategies focusing on eliminating resistance are expected to create < 1% of the public health benefit of strategies that focus on reducing microbial loads in animals or on foods.¹⁶ We must consider this information within the context of food safety, animal health and welfare benefits that are gained by focusing on pathogen reduction strategies, including judicious antimicrobial use. Another study agrees, concluding that, “antimicrobials that benefit animal health may benefit human health, while regulatory interventions that seek to reduce antimicrobial resistance in animals may unintentionally increase illness rates (and hence antimicrobial use and resistance rates) in humans...”¹⁷

Information derived from studies of organic or antibiotic-free production practices compared to traditional production practices is inconclusive, but there are indications that organically grown meat may have less-resistant organisms but greater prevalence and quantities of pathogens on the meat.^{18,19,20,21} Therefore, the greater risk of foodborne illness derived from these products must be weighed against the many other factors such as the likelihood of treatment failure if treatment is necessary.

The question of what the nature and magnitude of the risk to humans is can only be answered by performing systematic risk assessments. Such risk assessments must include identification of the endpoints of concern (e.g., increased illness or mortality caused by bacteria resistant to antibiotics used to treat the disease in humans), the nature of the treatment protocols in food animals, the potential routes of exposure, characterization of the population at risk, and the probability of occurrence. Furthermore, risk assessments that also consider benefits will provide a more balanced perspective and fully inform the decision making process.

Antibiotics as a tool to prevent and control disease in animals and humans

The use of drugs in animals is fundamental to animal health and well-being. Of the tools that are available to veterinarians, one of the most important tools that veterinarians use to protect human health and animal health is the judicious use of antimicrobials. Antibiotics are necessary to relieve pain and suffering associated with disease conditions in animals. For food animals, drugs additionally contribute to the public health by mitigating disease and thereby reducing the numbers of bacteria entering the food supply. Studies show that a reduction in the incidence of food animal illness will reduce bacterial contamination on meat, thereby reducing the risk of human illness.^{22,23,24,25,26,27,28,29} The continued availability of safe, effective antimicrobials for veterinary medicine, including the retention of currently approved drugs and future approvals of new drugs, are critical components of ensuring a safe food supply and essential to the improvement of animal health and welfare.

Just as in humans, resistant bacteria can and do develop in animals. However, many of the important details regarding the transfer of that resistant bacteria, or even resistance genes – to the environment or humans – still remains in question. Simply because resistance exists in animals, it does not necessarily equate to a significant human health risk. First, the bacteria or its resistance determinants may not effectively transfer to humans through the food chain. Secondly, the resistant pathogen may not colonize in humans to create disease. Third, if a disease does occur, antimicrobial therapy may not be indicated, and the disease resulting from the resistant bacteria is in effect no different than any other bacteria. In the vast majority of cases, antimicrobial therapy is not needed. Supportive therapy, such as fluids, is the only treatment that is needed for most *Salmonella*, *Campylobacter* and *E. coli* infections. For non-typhi *Salmonella*, antimicrobial therapy is generally not indicated because it has no effect on clinical illness and prolongs carriage and excretion of the organism. For *Campylobacter jejuni*, antimicrobial therapy is unlikely to provide benefit. Treatment of enterohemorrhagic *E. coli* (*E. coli* O157) may increase the risk of developing hemolytic uremic syndrome.³⁰ Lastly, if antimicrobial therapy is needed, even if the pathogen is resistant to one drug or multiple drugs, it may be still be susceptible to the drug of choice.

Routes of Transmission

There are several theorized mechanisms for the spread of resistance from animals to humans: 1) Via residues 2) Direct route - when an individual consumes resistant bacterium in food or by direct contact with an animal infected with a resistant organism 3) Indirect route - through a resistance reservoir where an individual acquires a resistance determinant from that resistance reservoir (the animal food product).

Residues

There is an extremely low risk of developing resistance as a result of antibiotic residues. Furthermore, that risk only exists if there are a series of flaws in the system that has been designed to protect the public from drug residues in food products. Whenever drugs are used to treat sick animals or prevent disease or when animals are exposed to chemicals in the environment, there is the potential for remnants to remain in the meat or other animal products (often known as residues). The FDA establishes tolerances for drug residues to insure food safety. The FDA also establishes “withdrawal times” or “withholding periods” which are times after drug treatment when milk and eggs are not to be used for food, and during which animals are not to be slaughtered. This allows time for the animals to metabolize and eliminate the drugs that had been used for treatment.

Maximum residue limits and tolerances for drug residues protect us from residues that may impact human health. If withdrawal times determined by the FDA are insufficient or are not adhered to, then there is the potential for violative residues. Also, if the tolerance levels are inadequate or ineffectively enforced, then again there is a possibility for a human health hazard. However, in addition to those systematic errors, two additional conditions must be met for the residue to pose a risk for the development of resistance: the drug residue must retain its efficacy through processing and/or cooking and remain as an active compound to affect human gut flora; and the drug residue remaining must be of a sufficient level to select for resistance in humans.

Direct Route

The direct route of transmission is also based on a series of events. There are many ways in which an animal can be infected with a resistant bacterium. Quantity of use is not necessarily the sole factor in selecting for resistance, nor is the dose or a particular purpose for antimicrobial use. Also of note, the use of a particular drug is not necessarily the cause of resistance to that same drug. The process of co-selection remains unclear and there is an increasing amount of evidence that resistance acquisition mechanisms are far more complex than previously thought. Resistance is mediated by certain genes and for many genes it is still unclear what causes the resistance gene expression or even development. Therefore, it is important to recognize that the use of a drug itself should not be a focus or rationale for restrictions on antimicrobials, but rather factual outcomes that are far more informative must be considered.

If an animal is infected with resistant bacteria at the time of slaughter and the carcass remains contaminated with the resistant bacteria through slaughter and processing, a sufficient microbial pathogen load must remain after processing and post harvest interventions (such as carcass rinses) to pose a threat to human health. The pathogen must then survive cooking in sufficient quantity to cause infection, or proper food hygiene procedures not followed. An individual must consume the contaminated food, become ill, seek medical attention, and in the worst case scenario, there is treatment failure as a result of the resistant pathogen. In most cases, medical attention is not sought and antimicrobial treatment is contraindicated.

As an example providing a comparative perspective on risk through a direct route of resistance transmission, a study on fluoroquinolone use in beef cattle had estimated the likelihood of a fluoroquinolone resistant *Campylobacter jejuni* infection causing a human death to be approximately a 1-in-250 million assuming the person had acquired the infection by eating contaminated ground beef.³¹ In

comparison with this risk that may be associated with the consumption of contaminated beef, a person is 567 times more likely to be killed in a plane crash and 14,284 times more likely to be killed in a car crash in any given year.³²

Indirect Route

The indirect route of transmission is theoretical, shown to be possible experimentally in vitro with no clear indication of what will occur in vivo. This route consists of many assumptions and a series of required events before a risk to human health can occur as a result of antimicrobial use in food producing animals. Resistance determinants are presumed to be present in a food producing animal as the resistance reservoir. Then the determinants must follow the same pathway as the direct route of transmission through the food chain: The animal food product must be contaminated with the determinant during slaughter; the determinant survives processing and cooking; is effectively transferred to an organism in the human; the human pathogen expresses the gene or passes it to yet another organism until there is gene expression; the organism causes human illness; the person seeks and needs medical attention; and in the worse case scenario, the person experiences treatment failure as a result of the resistance.

An example of the indirect route of transmission and concept of resistance reservoirs can be illustrated through the extended spectrum beta-lactamases (ESBLs). The concept of resistance reservoirs suggests that a pool of resistance genes is maintained within certain environments and poses a risk to public health. Scientists have detected similar, but not identical ESBL genes in both humans and animals in an isolated geographic region.³³ In Denmark, the initial cases of ESBL resistance had been detected in imported animals and food products prior to 2003. In 2005 and after, ESBL producing organisms were detected in domestic animals and animal products. In 2007, Denmark experienced the first major human outbreak with ESBLs. One interpretation of this series of events has been the application of the resistance reservoir concept. Based on the temporal sequence of events, many have theorized that animals, particularly those raised outside of Denmark with less stringent antimicrobial controls in animal agriculture, are serving as a reservoir for the ESBL resistance genes and transferring those mechanisms of resistance through the food chain. An alternative theory could suggest that ESBLs in animals and animal products have evolved and spread due to increased therapeutic antimicrobial use after the bans on growth-promoting antibiotics. Much of the increased use in animal agriculture has more often been in the same classes as human use antimicrobials and at greater doses. Since 1998, the consumption of β -lactams in food producing animals in Denmark has nearly doubled. Likewise, the development and spread of ESBL resistance genes in humans may be due to increased antimicrobial use in human medicine. Since 1998, human consumption of β -lactams in Denmark has nearly quadrupled. Some experts speculate that this increase in human use may be due to shortened hospital stays and increased perioperative prophylactic use.³⁴ Thus, it is plausible that ESBLs are transmitted through the food chain, but the probability, frequency, and efficiency of that transfer remains unknown.

Not all antimicrobials or all their uses are equal in their probability of developing resistance or creating a risk to human health, further elucidating the need for individual risk assessments. Based upon risk assessments conducted and epidemiological evidence obtained thus far, the risk to people of resistant infections from consuming animal products appears to be very low, as the use of antimicrobials in animals is only one of the many factors that can impact antimicrobial efficacy in treating these infections. In terms of animal agriculture, the main goal of mitigating risks to human health should be to decrease the spread of foodborne pathogens, rather than focusing upon what is presumed to be the source of antimicrobial resistance. Moreover, prior attempts to decrease use of antimicrobials in animals in other countries have not been shown to significantly decrease resistant infections in people. Thus, broad-based bans and other limitations on antimicrobial treatments in food animals cannot be expected to produce the desired result of enhancing human health. In addition, many antimicrobials used in food animals have no medically important counterpart in human medicine, so the concept of reducing these uses bears no impact at all on human infections.

AVMA's Efforts

The AVMA has maintained three primary objectives when considering antimicrobial use:

1. Safeguarding public health,
2. Safeguarding animal health, and the
3. Continued availability of effective therapeutic agents, including antimicrobials for veterinary medicine and the retention of currently approved, safe drugs and biologics as well as future approvals of new therapeutic agents.

The veterinary profession strives to promote optimal human health and public health through zoonotic disease prevention and control, which includes foodborne pathogens among other diseases. To achieve optimal animal health as well as animal welfare, and in turn, human health, the veterinary profession must practice the same fundamental principles of public health – prevention and control of disease in food animal medicine and population medicine^a. While the end goal is the same for all medical professionals – good health – veterinarians are severely limited in our tools for disease control and prevention. Regulations for drug approvals are more stringent for food animal drugs than human drugs, therapeutic agents can be more difficult to develop, and there are fewer treatments available. Thus, veterinarians must rely on their knowledge of clinical medicine to determine the best course of treatment. Given the numbers of food animal species, in addition to the diversity of disease conditions that affect animals, a relative scarcity of labeled indications accompanying FDA approved drugs exists. Although the FDA, the AVMA and others have made and continue to make significant strides in enhancing drug availability, including legislative initiatives (such as the Minor Use and Minor Species Act, and the Animal Drug Availability Act), the numbers of FDA approved drugs are inadequate to meet veterinary medical needs, placing both animal health and welfare – and, potentially, human health – at significant risk.

Other successes through collaborative efforts include a decline in foodborne illness from meat and poultry products³⁵ as well as a decline in the prevalence of foodborne pathogens (including Salmonella) associated with meat and poultry³⁶ and resistance of those organisms³⁷. These are all a result of improvements in animal health and the joint efforts of stakeholders.

The AVMA has also advocated for more research to support scientifically based therapeutic practices, such as epidemiological studies, that assess the effects of antimicrobial use. We support the scientifically valid and meaningful collection and review of data for all uses of antimicrobials and other pharmaceuticals used in humans and animals. We urge that such data be collected in concert with other data necessary to explain or inform fluctuations in use, e.g., disease prevalence, regional data, populations of animals, etc. An example is the USDA program, Collaboration for Animal Health, Food Safety and Epidemiology, that is attempting to study the use of antimicrobials on farms correlated with disease occurrence, and the effects of antimicrobial use on antimicrobial resistance as measured both on the farm and during processing of the meat from the specific farm. The AVMA also provided start-up funding for projects to create a nationally coordinated laboratory system to test for and report on resistance in animal pathogens and to create a decision support system to assist veterinarians when making antimicrobial use decisions. Unfortunately, while this project received follow-on funding by the FDA, it has not been sustained or completed.

^a Population medicine is a medical discipline focusing on the concepts of public health and epidemiology. In veterinary medicine, these concepts are incorporated to make strategic decisions to advance animal and herd health.

Veterinary Oversight, Judicious Use, and VCPRs

Since 1998, the AVMA has actively worked to mitigate the development of antimicrobial resistance related to the use of antimicrobials in food animals. The AVMA Guidelines for the Judicious Therapeutic Use of Antimicrobials were developed to safeguard public health by providing specific recommendations for responsible and prudent therapeutic use of antimicrobials. With support and input from the CDC, Infectious Diseases Society of America, the FDA, and the USDA, the guidelines were developed in collaboration with our species specific allied veterinary organizations. These guidelines were based upon carefully reviewed, scientifically sound research, and we believe that our members conscientiously adhere to the principles of judicious therapeutic use of antimicrobials to ensure the protection of human health, as well as animal health and welfare.

We have actively encouraged and assisted our allied veterinary organizations to use the AVMA general principles as a template to develop more detailed guidelines appropriate to each species, disease and type of client. The AVMA also worked with these groups to develop and deliver a continuing education program to raise awareness within the profession and to encourage utilization of the principles. Fundamentally, the guidelines encourage scientifically based therapeutic practices, the use of antimicrobials only when needed, and compliance with all existing regulatory requirements when antimicrobials are used. For example, the American Association of Avian Pathologists (AAAP) Guidelines to Judicious Therapeutic Use of Antimicrobials in Poultry states, “Antimicrobials in Class III used at labeled instructions should be considered first if farm history, in vitro sensitivity and clinical judgment warrants.” In the AAAP guidelines, Class III antimicrobials are identified individually and noted to be those of no or minimal importance to human medicine. The guideline further outlines disease specific diagnostics, non-antimicrobial interventions, and suggested antimicrobial interventions as a last resort.

Much of the discussion on antimicrobial use in animal agriculture revolves around a category commonly known as growth promotion or a group of antimicrobial uses that are poorly categorized as “non-therapeutic” or “sub therapeutic.” The terms “non-therapeutic,” and “sub-therapeutic,” have no consistent definition. The use of ill-defined or inconsistent definitions only serves to further confuse the issue. We caution against indiscriminate use of these terms. Alternatively, we advocate using the definitions of the Codex Alimentarius Commission (an organization of the World Health Organization and the Food and Agricultural Organization of the United Nations), the FDA, and AVMA. All three organizations classify treatment, prevention, and control of disease as therapeutic uses. Antimicrobials that are labeled for production uses such as increased rate of gain or feed efficiency are often referred to as growth promoters.

Additionally, it is important to recognize that veterinarians are the trained professionals who know when antimicrobials are indicated in animals and when they are not. While some production systems can provide benefits in meeting an animal's behavioral needs, the costs can often be an increase in risk of disease.³⁸ Even in pristine conditions, at certain life stages, and under certain stressful circumstances, disease outbreaks can be predictable. In some of these cases, a veterinarian may choose to recommend the use of antimicrobials during those predictable stages to strategically prevent or control disease. The ability of a trained medical professional to predict a disease outbreak and recommend appropriate therapy should not be considered injudicious nor banned as “routine use.”

There is little debate on the use of antimicrobials for treatment of disease in animals showing obvious clinical signs. However, few understand the importance of disease control and prevention, and even fewer have a clear understanding of growth promotants. Prevention and control of disease are key elements in the practice of veterinary medicine, particularly in animal agriculture, where the focus is on population health. This concept of disease prevention and control through herd health is analogous to public health efforts. If a disease is predictable and can be prevented, it is prudent for the veterinarian to recommend therapy to prevent animal pain and suffering that would occur associated with the disease condition. Likewise, if an infectious disease condition has been established in a herd or flock, it is incumbent upon the veterinarian to initiate appropriate therapy to minimize further disease spread and alleviate associated pain and suffering. Additionally, some of the growth promoting antimicrobials have

no human health equivalent and thus no human health impact. In fact, studies show a potential health benefit from the use of growth promoting antimicrobials.^{39,40,41,42,43,44,45,46}

While it may seem intuitive to some that healthy animals are critically important for safe food, there are few who understand the intricacies of why. As an example, it is fairly intuitive that an effective antibiotic will help decrease the bacterial load in food. What many do not understand is that it is extremely difficult to ascertain whether or not a particular animal is carrying certain bacteria. Animals can harbor types of bacteria in their intestinal tracts that have no effect on their health, but can cause illness in humans. Many bacteria such as *Salmonella*, are shed intermittently, can increase with physical stressors such as underlying infections, and cannot be easily detected by routine testing procedures. Thus, we must rely on the combination of many different types of interventions to protect our food supply. These interventions would range from prevention and control of disease before it occurs in animals, to post harvest interventions such as carcass rinsing to further minimize bacterial contamination in food.

Another concept that is often misunderstood or overlooked is how a seemingly unrelated illness, such as respiratory disease in a food animal, can affect the presence of enteric bacterial pathogens in the meat and therefore food safety. The example of air sacculitis, a respiratory disease that affects poultry, illustrates how food can be safer by treating an animal that does not exhibit obvious symptoms. Air sacculitis is a fairly common disease that can spread rapidly and often go undetected until slaughter. The disease causes tissues to become more friable^a and difficult to remove during food processing. The increased handling and difficulty in processing increases the potential for damaging the intestines and contaminating the carcass with enteric pathogens that can be harmful to humans⁴⁷. By controlling this disease through the use of antibiotics and/or other therapeutic agents, veterinarians assist producers in maintaining a healthy flock and a safe food supply. This example further illustrates the necessity to continually maintain and improve animal health in the preservation of food safety.

The AVMA also strongly encourages a veterinarian-client-patient relationship (VCPR) and veterinary consultation when implementing any treatment regimen. Dispensing or prescribing a prescription product (including antimicrobials) requires a VCPR. The VCPR is the basis for interaction among veterinarians, their clients, and their patients.

The veterinarian must have sufficient knowledge of the animal(s) to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s), or by medically appropriate and timely visits to the premises where the animal(s) are kept.

Veterinarians making treatment decisions must use sound clinical judgment and current medical information and must be in compliance with federal, state, and local laws and regulations. The veterinarian must also include consideration of: judicious use principles; food safety and public health; and producer education as a part of the treatment plan. After considerations have been made for animal, human, and the environmental health impact, veterinary authorization is required prior to dispensing of the prescription product.

There are older antimicrobials that are available in medicated feeds (over-the-counter or OTC drugs) that can be purchased without a veterinary prescription. However, this is not to say that these drugs are unregulated. In fact, there are greater restrictions on the use of antibiotics in animals than there are in humans. Feed mills that distribute medicated feeds are licensed to do so by the FDA. All FDA approved drug products are restricted to a very specific use, dose, and duration as indicated on the label. Veterinarians are strictly prohibited from using certain drugs in food animals. Veterinarians are also restricted by Extra Label Drug Use (ELDU) regulations. Therefore, if a drug is not used according to the label and FDA approved instructions or ELDU regulations, then it is illegal.

^a Friable is a term used in pathology to describe tissues that are brittle, fragile, and easily damaged.

To our knowledge, no new classes of antimicrobials have been approved by the FDA as an OTC drug since the 1980s. A newer category of drugs, the Veterinary Feed Directive (VFD) Drug category, was created by the Animal Drug Availability Act of 1996 to provide veterinary control for certain animal pharmaceuticals for use in feed that are not suitable for OTC status. Any animal feed bearing or containing a VFD drug shall be fed to animals only by or upon a lawful VFD issued by a licensed veterinarian in the course of the veterinarian's professional practice.

The AVMA recently convened the Antimicrobial Use Task Force to evaluate the veterinarians' role in all uses of antimicrobials. The Task Force concluded that veterinarians should be involved in the decision making process for the use of all antimicrobials in animals regardless of the distribution channel through which it was obtained. This would encompass prescription products, VFDs, and OTC antimicrobials.

In our unique role as the only profession that routinely operates at the interface of human and animal health, veterinarians must balance the need for animal health and welfare with the need of human health. Without exception, the AVMA is supportive of measures to mitigate risks to human health. Yet, we must emphasize the importance of science based risk analyses and risk management that is commensurate with the level of risk. Risk management measures can include any of the following: advisory committee review of an existing approval or application for a new animal drug approval; post-approval monitoring through systems such as the National Antimicrobial Resistance Monitoring System (NARMS); limitations on the extent of use (e.g., individual animals only for short duration of use); limited or broad extra-label use restrictions in some cases or all cases; and, finally, non-approval or withdrawal of a previously approved antimicrobial.

Although there are critical shortages in the veterinary workforce, particularly in food supply veterinary medicine and veterinary public health, veterinarians provide oversight and advice on the use of medications, including OTC antimicrobials, on a significant percentage of animal operations. *Feedlot '99* reports that all large operations and nearly all (96.5%) small operations used the services of a veterinarian. Large operations were more likely to use a veterinarian that made routine visits or employ a full-time veterinarian on staff than small operations. Conversely, small operations were more likely to use a veterinarian when the need for one arose. Veterinarian recommendations had strong or moderate influence on selection of an antimicrobial for nearly 100% of feedlots. Laboratory test results influenced 58.8% of feedlots strongly or moderately. Veterinarian recommendations and laboratory test results were more likely to strongly influence selection of antimicrobials on large feedlots than small feedlots. Almost three out of four feedlots provided formal training in areas related to antimicrobial use.⁴⁸

The *USDA Swine 2006* reports approximately seven of 10 sites (69.1%) used a veterinarian during the previous year. A higher percentage of large and medium sites (88.1 and 85.0%, respectively) used a veterinarian during the previous year compared to small sites (60.8%). Nearly 5 of 10 large sites (46.8%) used an on-staff veterinarian. A similar percentage of large sites (42.5%) used a local practitioner. Overall, approximately half of the sites (49.5%) used a local veterinarian during the previous 12 months. About one of four sites (24.7%) was visited by a veterinarian five or more times. Producers used the services of a veterinarian for many purposes during the previous 12 months. A higher percentage of large sites used a veterinarian for blood testing, production record analysis, employee education, and quality assurance compared to small sites. For sites that had at least one veterinary visit during the previous 12 months, the highest percentage of sites used a veterinarian to treat individual pigs (63.8%) and to provide drugs or vaccines (62.6%). These are followed by vaccination consultation (48.6%), quality assurance (47.9%), blood testing (47.6%), nutritional consultation (19.8%), environmental consultation (19.0%), and employee training/education (18.0%).⁴⁹

We believe that these numbers can be improved through the resolution of the critical shortage of the veterinary workforce by identifying resources and developing solutions in collaboration with key stakeholders to ensure that veterinary needs are met. Further studies and proposals should appropriately address the availability of veterinary services.

Data Collection and Review: Monitoring and Surveillance Systems

The AVMA believes that there is a critical need for improved, more robust monitoring and feedback systems for foodborne disease and antimicrobial resistance such as FoodNet and National Antimicrobial Resistance Monitoring System (NARMS). Since the mid-1990s, the FDA has coordinated the NARMS in cooperation with the CDC and the USDA. NARMS is a multi-agency program that includes monitoring for resistant bacteria in retail meats by the FDA, monitoring for resistant foodborne pathogens in humans by the CDC, and monitoring for resistant bacteria in animals on farms and animal products in slaughter and processing facilities by the USDA. The Foodborne Diseases Active Surveillance Network (FoodNet) is a collaborative project of the CDC, 10 states, the USDA, and the FDA to monitor trends of foodborne illness and attribute the illness to specific foods and settings. Veterinarians in both public and private practice actively participate in these national programs and AVMA has consistently advocated for funding to maintain and continually improve all of these programs.

We are pleased that in recent years reporting by NARMS has been timelier. Yet, we still find gaps in data collection, lack of clarity in the interpretation of trends, and uncertainty as to how the data may be used to determine action. We also note that there remains a disconnect between data collection systems. For example, FoodNet provides data on foodborne infections, including resistant bacterial infections, but does not specify the proportion or incidence of resistant foodborne illness. In fact, only 2 outbreaks of resistant foodborne bacteria have been reported in the past decade. One of which was as a result of raw milk cheese consumption. Yet, NARMS data incongruously provides resistance trends and specifies a relative proportion of resistant bacteria but does not indicate how or if it may relate to food and human infections. Therefore, there is a clear dissociation between resistant foodborne infections and the source. Lastly, and most importantly, there is no system for monitoring how or how much antimicrobials are being used in humans or animals. Without this critical piece of information, it is impossible to understand how various uses can impact the resistance trends.

The Netherlands

The MARAN 2008 report indicates an increase in total antibiotic use from 1998-2008. Part of the increase is attributed to an increase in therapeutic use as a substitution for growth promoters. Therapeutic use has doubled in 2007 when compared to 1999. Although therapeutic use in 2008 has declined compared to 2007, the report indicates the reduction is due to veterinarians stockpiling drugs at the end of 2007⁵⁰, a puzzling explanation that questions why the stockpiling occurred and the potential impact on data interpretation. Important data reported from MARAN indicates:

- Increase in ciprofloxacin resistant *Salmonella* infections in humans in 2008 compared to 2006/2007 with resistance attributed to DT104. The source of increased incidence is unknown but not a Dutch animal source.
- Fluoroquinolone resistant *Campylobacter* continued to increase in humans and animals in 2008
- Resistance rates in *E. coli* continue to increase in pigs, broiler chickens, and dairy cows
- Resistance levels of *Enterococcus* remain high or increases in all animal species

This data would suggest that the ban of antibiotic growth promoters in the Netherlands has not achieved a decrease in total use, a decrease in therapeutic use, or a decrease in resistance levels.

Danish Experience

The Danish experience has taught us that there can be serious negative consequences in animal health and welfare following the withdrawal of growth promoting antimicrobials and few, if any, improvements or positive human health impact.

In the late 1990s, Denmark instituted a voluntary ban on the use of antimicrobials for growth promotion (AGPs). A complete ban of AGPs was initiated in 2000 and completed by the start of 2002. The following has been observed as a result of the ban on the use of antibiotics for growth promotion in Denmark:

In animals –

- From 2001 to 2008, the overall consumption of antimicrobials in pigs increased by 19%.
 - Consumption of tetracyclines increased by 118% per pig from 2003-2008.
- Consumption of all antimicrobials in food animals has gradually increased 110% from 1998-2008, while the meat production has increased 32%.^a
- There has been increased death and disease in the swine herds, especially at the weaning stage (information inferred from DANMAP 2005 and other reports on pigs). According to published news reports, there was a relative increase of 25% in the number of pigs that died from illnesses from 1995 to 2005.
- Nearly double the quantity of antimicrobials is used for therapeutic purposes as compared to years before the ban. The antimicrobials now used are classes such as tetracyclines that are also used in humans.⁵¹
- Resistance to some antibiotics has decreased in some animals while resistance to other antibiotics has increased.

In humans –

- 35.6 % increase in Defined Daily Doses^b from 1999-2008
- Vancomycin, quinopristin/dalfopristin, avilamycin resistance still prevails more than a decade after banning the use of avoparcin, virginiamycin, and avilamycin for growth promotion.
- Resistance to virginiamycin (quinopristin/dalfopristin, e.g., Synercid) in humans had been steadily increasing (up to 25%) from 1997 to 2005 until the definition of resistance was changed in 2006⁵², bringing the level of resistance down to 0%.^c
 - When the definition of resistance is standardized to the United States definition used by CDC and the level of resistance in humans in Denmark to Synercid is compared to the United States, we find that the level is 10 times higher in Denmark in spite of the Danish ban in 1998 of use in animals and the continued use in the United States.

^aTrends in total consumption (kg active compound) of prescribed antimicrobials for production animals reported by DANMAP 2008; Table 5

^b Defined Daily Dose is a measure of antimicrobial use in human medicine in Denmark

^c The rationale for this change is unknown, but appears to introduce bias in reporting. DANMAP decided to use a preliminary European Committee on Antimicrobial Susceptibility Testing breakpoint instead of the previously used breakpoint established by the Clinical and Laboratory Standards Institute.

In humans and animals –

- A significant increasing trend of resistance to tetracycline, ampicillin, and sulfonamide in humans and pigs from 2001 – 2006 (2007 and 2008 decreases are related to an increase in outbreaks of sensitive strains)
- There is little evidence to demonstrate a general decline in antimicrobial resistance in humans and there is no evidence of an improvement in clinical outcomes of antimicrobial treatment of humans, the desired consequence of the antibiotic ban in livestock. The results have been mixed. In fact, resistance in humans to some of the banned drugs has increased dramatically.

This data indicates that the ban of antibiotic growth promoters in Denmark has not achieved a decrease in total use or a decrease in therapeutic use and mixed results in resistance levels in pigs (an increase in some resistance levels for some antibiotics and a decrease in resistance levels for others).

The ban on antibiotic growth promoters in Denmark has not resulted in a significant reduction of antibiotic resistance patterns in humans. It has, however, resulted in an increase in disease and death in the swine herds and an increase in the use of antimicrobials for therapeutic uses in swine herds that discontinued the use of antibiotic growth promoters.

Even though the results of the Danish experiment with antimicrobial growth promotant drug bans is very mixed, evidence shows that the Danish ban has caused animal health and welfare problems, without significantly improving human health.

Based on the results of the bans enacted in Denmark and the Netherlands, we do not believe the public would significantly benefit from such limitations on the use of antimicrobials. The loss of approved uses of antimicrobials will negatively impact animal health and welfare without significantly or predictably improving public health. Non-science based, broad bans of preventive uses of antimicrobials have the potential to harm public health, such as through increased foodborne disease.

Significant decisions regarding animal health need to be science- and risk-based decisions. Decisions made without the benefit of veterinary input as well as a thorough evaluation of risks and benefits have the potential to further divert resources away from more appropriate disease control measures.

NARMS

Important resistance trends^a reported by NARMS⁵³ (Isolates from humans with clinical disease) indicate substantial decreases in *Salmonella* resistance for some serotypes associated with animal sources and an increasing trend in resistance for the serotype associated with human reservoirs:

Salmonella spp. (non-Typhi) – more than twice as likely to be resistant in 1996 as compared to 2007

- a highly significant^b improvement in susceptibility^c (22.5% relative increase in susceptibility, from 66.2% in 1996 to 81.1% in 2007)

^a Odds ratios were calculated based upon available data from NARMS assuming the reported isolates were representative of the bacterial population.

^b “Marginally significant” indicates a p-value between 0.05 and 0.10; “significant” indicates a p-value between 0.01 and 0.05; “highly significant” indicates a p-value of less than 0.01

^c no resistance detected to any of 5 subclasses of antibiotics

Salmonella Typhimurium – more than twice as likely to be resistant in 1996 as compared to 2007

- a highly significant improvement in susceptibility (52% relative increase in susceptibility from 37.9% in 1996 to 57.6% in 2007)

Salmonella ser. Typhi (a human reservoir foodborne pathogen) - more than 4 times as likely to be resistant 2007 as compared to 1999

- a highly significant **decline** in susceptibility (50% relative increase in susceptibility from 71.3% in 1999 to 35.4% in 2007)

Most foodborne infections do not require treatment with antimicrobials. The data indicates that there is a decreasing trend of foodborne diseases, thereby decreasing the potential numbers of treatments.⁵⁴ NARMS⁵⁵ reports the following resistance percentages of non-typhi *Salmonella* to fluoroquinolone (ciprofloxacin) – 0.1%; third-generation cephalosporin (ceftriaxone) – 0.4%; ampicillin – 10.1%; and co-trimoxazole (trimethoprim-sulfamethoxazole) – 1.5%. These resistance levels do not indicate a public health crisis associated with foodborne *Salmonella*. Resistance patterns from *Campylobacter* and *E. coli* do not mirror *Salmonella* on a drug by drug basis, but do show overall increases or stability in susceptibility levels. Of note, *Campylobacter* resistance to ciprofloxacin (a fluoroquinolone) has continued to increase following the ban on enrofloxacin. The trends of decreasing resistance (increasing susceptibility) mean more successful treatments when needed. This information would suggest that there is not a public health crisis related to foodborne pathogens.

Conclusion

The American Veterinary Medical Association is committed to ensuring a safe and healthy abundant food supply. Among other things, our profession is dedicated to improving animal health, further safeguarding public health and food safety, and to maintaining the long-term effectiveness of antibiotics. The AVMA established a profession-wide initiative to create and implement judicious use guidelines for the therapeutic use of antimicrobials by veterinarians, and we launched an educational campaign to raise the awareness of the profession to the issue. Today, we continue to review and update those guidelines to reflect current practices and actively encourage compliance.

Foodborne illness and the spread of antibiotic resistance is a public and animal health concern. There is no question that the public demands a safe food supply and that the human medical profession is facing extreme challenges because of hospital- and community-acquired resistant human pathogens. The human medical problem with resistant nosocomial and community-acquired infections has increased the concern of development of resistant pathogens in animals that can be transferred to humans through the food supply or environment. Yet, we must not forget that animal health is food safety.

The AVMA shares the concerns of the human medical community, the public health community, governmental agencies, and the public regarding resistance developing in animals and then being transferred to humans. However, we emphasize the importance and primacy of using these medicines to prevent and treat diseases before they enter our food supply. Preemptive bans of veterinary antimicrobials before science-based studies and risk-based evaluations are performed can be detrimental to animal and human health. Simple solutions may not solve such complex problems. Inappropriate reactions could have unknown and unintended consequences that negatively affect animal health and welfare, and ultimately, could create other public health risks, such as increased foodborne illness.

The AVMA believes that a lack of availability of antimicrobials or other therapeutic agents in veterinary medicine and animal agriculture can put animal health and welfare and public health at risk. We encourage a regulatory strategy that is based on science, risks and benefits analyses, and cooperation with all relevant stakeholders.

An analysis that compared the regulatory strategy of the European Union to broadly ban or restrict animal antibiotic uses with the United States' approach of continued prudent use to prevent and control animal

infections, together with measures to improve food safety, has some pertinent conclusions. Among these, prudent use of animal antibiotics may actually improve human health, while bans on animal antibiotics, may inadvertently harm human health.⁵⁶ The AVMA supports the ongoing scientific efforts of monitoring and surveillance of foodborne disease and resistant foodborne pathogens; education; development of new antimicrobials, biologics, and other treatment options; and other research to better define the challenges presented by animal agriculture. Increased data collection and surveillance of disease, as well as continued veterinary input (including the appropriate use of pre- and post-harvest interventions, and compliance with judicious use guidelines for veterinarians and producers), may be sufficient to protect human health against the current small risks without compromising the health of food animals.

We also support adequate funding for all efforts to improve animal health and food safety, including efforts to combat antimicrobial resistance. These efforts were high-priority tasks in the 2001 version of the Public Health Action Plan to Combat Antimicrobial Resistance that was created by a Federal Interagency Task Force on Antimicrobial Resistance. Of the original 13 Top Priority Action Items, few actions have targeted animal health or yielded results that can mitigate antimicrobial resistance in animals, and therefore transmission to humans. The Action Plan reflected a broad-based consensus of federal agencies and stakeholders on actions needed to address antimicrobial resistance and provided a blueprint for specific, coordinated federal actions that included the full spectrum of antimicrobial use: human medicine, veterinary medicine and animal agriculture. We are disappointed that the Action Plan was not adequately funded and prioritized by Congress. We are also concerned that recent versions of the Action Plan do not appear to not be as collaborative, broad-based, or acceptable to the diverse community of stakeholders.

The AVMA is committed to working in concert with the CDC, FDA, and USDA to provide consumers – not only in the United States, but all over the world - with the safest food possible. The judicious use of antimicrobials is but one of the essential components of the process that enables animal agriculture to meet that demand. Other components include veterinary care, good management practices, biosecurity, proper nutrition and good husbandry.

Thank you for the opportunity to appear before you today and speak on behalf of our profession.

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