

TESTIMONY OF

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Concerning

Antimicrobial Resistance

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Thank you, Mister Chairman and members of the Committee, for giving the American Veterinary Medical Association the opportunity to speak about antimicrobial resistance.

I am Dr. Lyle Vogel, Assistant Executive Vice President of the American Veterinary Medical Association. The vast majority of my 41-year veterinary career has been engaged in the practice of protecting and advancing public health.

The AVMA represents more than 76,000 U.S. veterinarians engaged in every aspect of veterinary medicine and public health. Among other things, our members protect the health and welfare of our nation's animals, help ensure food safety, and protect animal and human health through prevention and control of zoonotic diseases.

As veterinarians, charged ethically with promoting public health in addition to protecting animal health and welfare, we have great interest in the prevention, control, and treatment of disease. Prevention and control of disease are key elements in the practice of veterinary medicine, particularly in animal agriculture, where the focus is on population medicine. This concept of disease prevention and control through herd health is analogous to public health efforts. The AVMA supports the use of multidisciplinary approaches to address issues affecting public health and food safety. In addition to our support of improved animal husbandry practices and the use of biologics, we also support the continued availability and use of antimicrobials to ensure that we are doing our best to safeguard the nation's food supply.

Antimicrobial resistance is a complex problem that is not going to be solved by simple solutions. The AVMA opposes seemingly simple bans on certain labeled uses of antimicrobials, such as growth promotion, feed efficiency, and disease prevention that are not science-based or risk-based. Not all antimicrobials nor all their uses are equal in their probability of developing resistance or creating a risk to human health. The European Union's Scientific Committee on Animal Nutrition has agreed that there is insufficient data to support such bans, yet *possible* theoretical human health concerns continue to be the focus while *probable* and scientifically based benefits to human and animal health are largely ignored.¹

Banning approved uses of antimicrobials will negatively impact animal health and welfare without significantly or predictably improving public health. Based on the results of a limited ban enacted in Denmark (i.e., the banning of growth promotants, not uses to prevent and control disease), we do not believe the public would benefit from such a ban. Non-science based, broad bans of preventive uses of antimicrobials have the potential to harm public health, such as through increased foodborne disease.

These significant decisions need to be science- and risk-based decisions. Decisions made without the benefit of a thorough evaluation of risks and benefits have the potential to further divert resources away from more appropriate disease control measures. Additionally, the AVMA believes that the judicious and regulated use of antimicrobials—through scientifically based FDA approvals and post approval review under Guidance for Industry #152 of previously approved antimicrobials—provides a sufficient safeguard for public health.

Actions Addressing Antimicrobial Resistance

AVMA's Efforts

The AVMA has acted with three objectives in mind:

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

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 emphasizing prudent and judicious therapeutic use of antimicrobials. With support and input from the Centers for Disease Control and Prevention, Infectious Disease Society of America, Food and Drug Administration, and the U.S. Department of Agriculture, 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 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.

The AVMA has also continually advocated for improved, more robust monitoring and feedback systems for foodborne disease and antimicrobial resistance such as FoodNet and the National Antimicrobial Resistance Monitoring System (NARMS). We have also advocated for more research to support scientifically based therapeutic practices, such as epidemiological studies that assess the effects of antimicrobial use. In addition, we advocate for increased resources for the FDA's Center for Veterinary Medicine so the agency can adequately implement its regulatory authority.

The AVMA 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 the latter project received follow-on funding by the FDA, neither project has been sustained or finished.

The FDA Role and Actions

The FDA approves antimicrobials for four purposes:

1. Treatment of disease,
2. Prevention of disease,
3. Control of disease, and
4. Growth promotion or feed efficiency.

The first three uses are classified as therapeutic uses by the FDA, AVMA, and Codex Alimentarius Commission (an organization of the World Health Organization and the Food and Agricultural Organization of the United Nations), and the fourth has also been shown to have health-promoting effects.

The FDA process for the evaluation of food animal antimicrobials is at least as stringent as, and often more stringent than, the approval process for human antimicrobials. In addition to the testing for efficacy and safety to the individual (human or animal) receiving the drug that is common to the human and animal drug approval process, each food animal antimicrobial undergoes an assessment for human and environmental safety as part of the review by the FDA. The FDA's Center for Veterinary Medicine (CVM) uses a very strict safety assessment approval process that requires sponsors to submit data proving the antibiotic is safe for both humans and animals. This is a zero-risk procedure for human safety – benefits to animals are not weighed to offset risks to humans, but rather, drugs that possess risks beyond "a reasonable certainty of no harm" to human health are rejected.

Another safety measure was instituted in 2003 (Guidance for Industry #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern,") that outlines a comprehensive, evidence-based approach to preventing the emergence and selection of antimicrobial resistant bacteria that may adversely affect human health. The Guidance requires antimicrobial manufacturers to provide information to the FDA showing that a proposed animal drug will not harm public health. The current FDA risk assessment on a drug-by-drug basis provides a scientifically sound process to protect human health. In the event that a determination is made that human health is jeopardized, FDA will not approve the antimicrobial or may limit the use of the antimicrobial in order to mitigate the adverse effect.

Since the mid-1990s, the FDA has coordinated the National Antimicrobial Resistance Monitoring System (NARMS) in cooperation with the Centers for Disease Control and Prevention and the United States Department of Agriculture. 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. NARMS has provided a great deal of useful information since 1996.

Therefore, the AVMA does not believe that The Food and Drug Administration needs new authority to regulate the human safety of animal drugs. Instead, the FDA needs additional resources to fulfill its existing mission. Some of those resources can be furnished through passage of the Animal Drug User Fee Act Amendments of 2008.

RESULTS

United States Monitoring/Surveillance Data

NARMS data, when combined with FoodNet data, demonstrates that the case rate of human infections with multidrug resistant *Salmonella* spp. has decreased 49% between the NARMS baseline years of 1996-98 and 2004 (the most current, publicly available human data from NARMS). In addition, there has been a 65% reduction in the case rate of penta-resistant *Salmonella* Typhimurium infections. The case rate for *Campylobacter* infections in humans that are resistant to ciprofloxacin have remained constant over that period.²

Additional important resistance trends^a reported by NARMS³ (Isolates from humans with clinical disease):

- *Salmonella* spp. (non-Typhi) – ½ as likely to be resistant in 2004 than in 1996
 - a highly significant^b improvement in susceptibility^c (20% relative increase in susceptibility, from 66.2% in 1996 to 79.6% in 2004)
- *Salmonella* Typhimurium – less than ½ as likely to be resistant in 2004 than in 1996
 - a highly significant^b improvement in susceptibility^c (60% relative increase in susceptibility from 37.9% in 1996 to 60.7% in 2004)
- *Campylobacter* – only 0.03 times more likely to be resistant in 2004 compared to 1997
 - a marginally significant^b decrease in susceptibility^c (2% relative decrease in susceptibility from 47% in 1997 to 46.1% in 2004)
 - However, campylobacter was significantly less likely to be resistant in 2003 when compared to 1997; there was a significant^b improvement in relative susceptibility^c (8.2% increase from 47% in 1997 to 50.9% in 2003)
- *Enterococcus faecium* – Decreased resistance to quinupristin/dalfopristin (Synercid) from 20.9% in 2001 to 3.7% in 2004
- *E. coli* O157 – 1/3 as likely to be resistant in 2004 compared to 1996
 - a highly significant^b improvement in susceptibility^c (10% relative increase in

^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

susceptibility)

In addition to trends of improved susceptibility, trends regarding multi-drug resistance^a also showed improvement:

- *Salmonella* spp. (non-Typhi) – nearly ½ as likely to be multi-drug resistant^a in 2004 when compared to 1996
 - a highly significant^b improvement (44% relative decrease) in multi-drug resistance^a (decreased from 27.0% in 1996 to 15.0% in 2004)

- *Salmonella* Typhimurium – nearly ½ as likely to be multi-drug resistant^a in 2004 when compared to 1996
 - a highly significant^b improvement (34% relative decrease) in multi-drug resistance^a (decreased from 56.2% in 1996 to 37.2% in 2004)

- *Campylobacter* – slightly less likely to be multi-drug resistant^a in 2004 when compared to 1997
 - a marginally significant^b improvement (10% relative decrease) in multi-drug resistance^a (decreased from 15.7% in 1997 to 14.1% in 2004)
 - However, when comparing 1997 to 2003, isolates were half as likely to be multi-drug resistant^a and there was a highly significant^b improvement (46% relative decrease) in multi-drug resistance^a (decreased from 15.7% in 1997 to 8.5% in 2003)

Most foodborne infections do not require treatment with antimicrobials. Information shows that there is a decreasing trend of foodborne diseases, thereby decreasing the potential numbers of treatments.⁴ The trends of increasing susceptibility/decreasing resistance mean more successful treatments when needed. This information indicates that there is not a public health crisis related to human pathogens that are thought to originate in animals.

Danish Experience

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.) The use of antimicrobials in feed and water for controlling and treating disease was not banned. The following has been observed as a result of the ban on the use of antibiotics for growth promotion in Denmark:

- 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

^a resistant to 2 or more antibiotic subclasses

^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

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.

- There has been increased death and disease in the swine herds, especially at the weaning stage (info 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.
- While the total quantity of antimicrobials used in food animals has decreased by 27%, the increase in disease has resulted in a 143% increase in the quantity of antimicrobials used for therapeutic purposes. And the antimicrobials now used are classes such as tetracyclines that are also used in humans.⁵
- Resistance to some antibiotics has decreased in some animals while resistance to other antibiotics has increased

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.

Some important resistance trends reported by DANMAP:

- *Salmonella* Typhimurium from human isolates^a has shown 34-49% *increase* in resistance to tetracycline, sulfonamides, and ampicillin from 1997-2006; increases in resistance to nalidixic acid and ciprofloxacin were 3.8% from 1997-2006
 - In contrast, during the same period of time, poultry isolates have shown only minimal increases (2-6%) in resistance to the same antimicrobials.
 - Isolates from pigs have also shown a lesser increase (25-27%) in resistance to tetracycline and ampicillin than human isolates during that time.
- *Campylobacter jejuni* from human isolates^a has shown 5-11% *increase* in resistance to tetracycline, nalidixic acid, and ciprofloxacin from 1997-2006.
 - In contrast, during the same period of time, poultry isolates have shown lesser increases (4-6%) in resistance to the same antimicrobials.
- *Enterococcus faecium* isolates from healthy human volunteers has shown no increase in resistance to vancomycin (the equivalent of avoparcin) from 1997- 2006, and remains at 0%.
 - However, resistance to virginiamycin (quinupristin/dalfopristin, e.g., Synercid) had been steadily increasing (up to 25%) from 1997 to 2005 until the definition of

^a domestically acquired clinical cases

- resistance was changed in 2006, bringing the level of resistance down to 0%.^a
- During the same period of time, *Enterococcus faecium* isolates from pigs and poultry has shown 8-20% decrease in resistance to avoparcin^b, virginiamycin, erythromycin and tetracycline from 1997- 2006 (using the same definition of resistance as the human isolates from 1997-2005)

Even though the results of the Danish experiment with antimicrobial growth promotant drug bans is very mixed, proposals within the United States go far beyond the Danish example by proposing to ban uses for the prevention and control of disease in addition to uses to promote growth and feed efficiency. Evidence shows that the Danish ban (and a ban in the United States, if instituted) will cause animal health and welfare problems.

Risk Assessments/ Human Health Impact

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. Antibiotics are needed for the relief of pain and suffering in animals. For food animals, drugs additionally contribute to the public health by helping keep animals healthy and thereby keeping bacteria from entering the food supply. The hypothesis, supported by scientific information, is that a reduction in the incidence of food animal illness will reduce bacterial contamination on meat, thereby reducing the risk of human illness.^{6,7,8,9,10,11,12,13}

Several risk assessments have been performed that demonstrate a very low risk to human health from the use of antimicrobials in food animals, and some of the models predict an increased human health burden if the use is withdrawn. The unique farm-to-patient risk assessment performed by Hurd demonstrates that the use of tylosin and tilmicosin in food animals presents a very low risk of human treatment failure because of macrolide resistance, with an approximate annual probability of less than 1 in 10 million with *Campylobacter* infections and approximately 1 in 3 billion *E. faecium* infections.¹⁴ Cox performed a quantitative human health risks and benefits assessment for virginiamycin and concluded that there would be a significant human health risk if virginiamycin use is withdrawn. There would be 6,660 excess cases per year of campylobacteriosis, which far outweighs the 0.27 per year reduction of cases of streptogramin-resistant and vancomycin-resistant *E. faecium* (VREF) resulting from the withdrawal.¹⁵ Cox also performed a risk assessment regarding macrolide and fluoroquinolone use and concluded that withdrawal is estimated to cause significantly more illness days than it would prevent.¹¹ Cox also examined the impact of the use of penicillin-based drugs in food animals on

^a 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.

^b avoparcin has never been approved for use in the United States

penicillin/aminopenicillin resistant enterococcal infections and concluded that not more than 0.04 excess mortalities per year (under conservative assumptions) to 0.18 excess mortalities per year (under very conservative assumptions) might be prevented in the whole U.S. population by discontinuing current use of penicillin-based drugs in food animals. The true risk could be as low as zero.¹⁶ This equates to one potentially preventable mortality in the U.S. population roughly every 7-25 years. Alban's risk assessment concluded that the risk associated with veterinary use of macrolides in Danish pigs resulted in a low risk to human health.¹⁷ Others have estimated that risk management strategies that focus 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.¹ In another paper, the authors concluded, "We came to some surprising conclusions that were robust to many uncertainties. Among these were 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. . . . In conclusion, our analysis suggests that the precautionary-principle approach to regulatory risk management may itself be too risky."¹⁸

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. So the greater risk of foodborne illness is somewhat offset by an increased likelihood of treatment success if treatment is necessary.^{2,19,20,21}

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.

Just because resistant bacteria may develop in animals that then are transferred to the environment or humans does not necessarily equate to a human health risk. First, the pathogen may not colonize in humans to create a foodborne disease. Second, if disease does occur, antimicrobial therapy may not be needed. In the majority of cases, treatment is not needed. Supportive therapy, such as fluids, is all that's needed for most *Salmonella*, *Campylobacter* and *E. coli* infections. In fact, antimicrobial therapy of *E. coli* O157 infections is contra-indicated because such treatment makes the effects of the disease worse. Thirdly, if antimicrobial therapy is needed, the pathogen may be susceptible to the drug of first choice. The Therapy Guidelines for Enteric Infections for non-typhi *Salmonella* are, "In uncomplicated infections antimicrobial therapy is not indicated because it has no effect on clinical illness and prolongs carriage and excretion of the organism. . . . Treatment recommended only for young infants (< or = 6 m) and immunocompromised individuals. Resistance is common. Agents that can be used include a fluoroquinolone or a third-generation cephalosporin such as ceftriaxone for 5-7 days. Ampicillin and co-trimoxazole can be used if the infecting organism remains susceptible."²² NARMS³ reports the following resistance percentages of non-typhi *Salmonella* to fluoroquinolone (ciprofloxacin) – 0.2%, third-generation cephalosporin (ceftriaxone) – 0.6%, ampicillin – 12.0%. and co-trimoxazole (trimethoprim-sulfamethoxazole) – 1.8%. These resistance levels do not

indicate a public health crisis associated with foodborne *Salmonella*.

Conclusion

The American Veterinary Medical Association is committed to ensuring judicious veterinary use of antimicrobials. To further safeguard public health and to maintain 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.

The spread of antibiotic resistance is a public and animal health concern. There is no question 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 possible development of resistant pathogens in animals that could be transferred to humans through the food supply or environment.

The AVMA shares the concerns of the human medical community, the public health community, governmental agencies and the public regarding the potential problem of resistant zoonotic pathogens 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. Passing legislation that would ban the use of these antibiotics before science-based studies and risk-based evaluations are done would be detrimental to animal and human health. Inappropriate reactions to the potential problem 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 disease.

The AVMA is committed to working in concert with 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.

The AVMA supports the ongoing scientific efforts of monitoring and surveillance of foodborne disease and resistant foodborne pathogens, education, development of new antimicrobials, and other research to better define the challenges presented by antimicrobial resistance. We also support adequate funding for such 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. 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 the new Action Plan under development appears to not be as collaborative, broad-based and acceptable to the diverse community of stakeholders.

The AVMA does not believe that additional legislation is needed to regulate the uses of antimicrobials in veterinary medicine and animal agriculture. Additional legislation can put animal health and welfare and public health at risk. FDA has adequate authority for oversight but lacks the resources to accomplish its many priorities.

An analysis that compared the regulatory strategy of the European Union to 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, intended to be precautionary, inadvertently may harm human health.¹⁰

Increased surveillance of resistance, as well as continued 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.

Thank you for the opportunity to appear before you today and speak about this important issue.

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⁴ CDC. FoodNet. Facts and Figures related to "Preliminary FoodNet Data on the Incidence of Infection with Pathogens Transmitted Commonly Through Food--10 States, United States, 2007" published in the *Morbidity and Mortality Weekly Report (MMWR)* on April 11, 2008. Available at <http://www.cdc.gov/foodnet/factsandfigures.htm>

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