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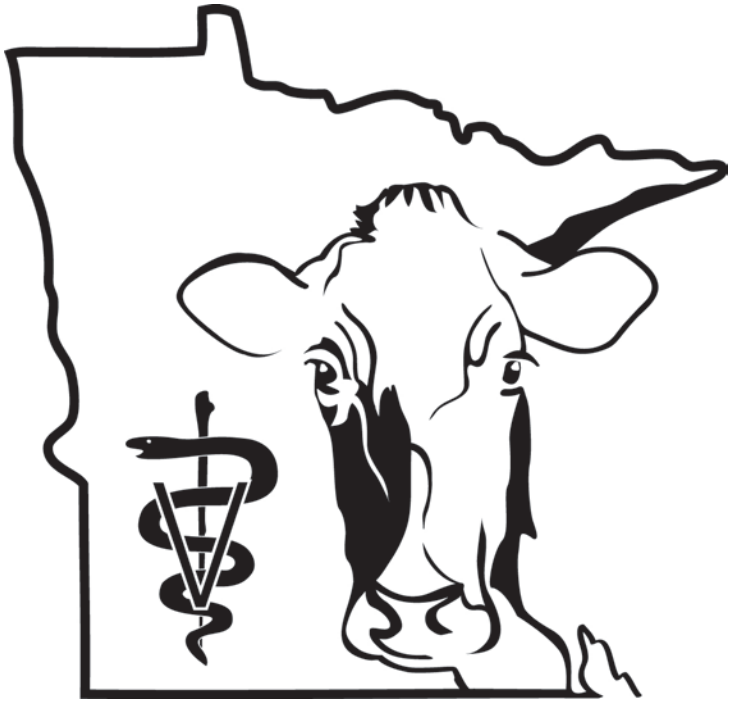

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Veterinarians and Antimicrobial Drug Use

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Introduction

Antimicrobial drugs have been a major weapon in the arsenal of the medical profession in the war against infectious disease for nearly 70 years. Sulfanilamide was first used to treat human patients in 1936.[1] Penicillin was first mass-produced and made available for clinical use in 1941.[1] However, it was quickly recognized that not all bacteria were sensitive to penicillin and resistant strains of *Staphylococcus aureus* were identified soon after the drug was introduced.[1] Antimicrobial drugs are used extensively around the world to treat and prevent disease in humans, animals, and plants.[2,3] These drugs are also used to improve productivity in animal agricultural, and have been found in food, soil, and water.[2] While little information is publicly available about the actual quantities of antimicrobial drugs produced and used, it has been suggested that 50 million lbs. of antimicrobial drugs are produced in the U.S. annually, and that 40% of these products are used in animal agriculture.[4]

Antimicrobial drugs exert their inhibitory or killing effects through a variety of mechanisms. Resistance mechanisms most likely originate from point mutations in the genome which allow bacteria to evade specific detrimental effects of these drugs. These mutations can be thought of as genetic accidents and these resistant organisms originate as a minority of bacterial populations. Mutations which confer antimicrobial resistance would probably not provide any survival advantage if bacterial populations were not exposed to antimicrobial drugs.[5,6] Bacteria with these mutations would therefore remain a minority of the bacterial population.[5,6] Exposure of bacterial populations to antimicrobial drugs inhibits proliferation of susceptible organisms. In theory, widespread, ongoing exposure of bacterial populations to antimicrobial drugs will cause increasing proportions of subsequent generations to be resistant.[5,6] To further complicate this problem, genetic material encoding resistance mechanisms can be spread to bacteria that have never been exposed to antimicrobial drugs.[2-6] Genetic sequences encoding resistance mechanisms can be located on chromosomal DNA, or extra-chromosomal DNA plasmids.[5,6] Both chromosomal and extra-chromosomal DNA are exchanged among bacteria (including bacteria of different genera and species) and this transmission of genetic material can sometimes confer antimicrobial resistance.[5-9]

In addition to the direct threat to animal health caused by resistant pathogens, human health experts are concerned about antimicrobial drug use in animals because resistance in animal-source bacteria could spread to bacteria of humans and affect human health. Theoretically, any

bacterium that could be transferred from animals to humans could be a source of resistance in humans. Veterinarians are responsible for overseeing the use of most antimicrobial drugs in the U.S. used for disease prevention and therapy in animals. Unfortunately, some public health organizations have suggested that veterinarians do not always meet this standard and their use practices significantly contribute to the problem of evolving resistance.[10,11] However, there is very little objective documentation of attitudes of veterinarians about the issue of antimicrobial drug resistance. Similarly, there are essentially no studies describing antimicrobial drug prescribing practices among veterinarians. This type of information is urgently needed to assist in science-based decision making as well as to provide a context for these decisions as U.S. regulatory agencies are poised to further restrict use of antimicrobial drugs by veterinarians.[12-14]

The financial cost to U.S. society from infections in people with resistant bacteria is now estimated to be $4-5 billion annually, and infections with resistant bacteria were estimated to have resulted in 19,000 human deaths in 1992.[14] Resistant strains appear to be increasingly prevalent among numerous bacteria including *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Neisseria gonorrhea*, *Pseudomonas aeruginosa*, *Streptococcus pneumonia*, *Campylobacter jejuni*, and *Salmonella*. Bacteria that were once highly susceptible to drugs commonly used to treat infections are becoming increasingly resistant, e.g., *S. pneumonia* and *S. aureus*. More than 90% of *S. aureus* strains currently isolated from humans in the U.S. are resistant to penicillin.[14] The most recent estimates suggest that foodborne illness affects 76 million people annually in the U.S.[15] According to this most recent CDC estimate, most (81%) of these illnesses have an unknown etiology. Among the disease with a known or attributed etiology (13.8 million cases), approximately 4.2 million cases are attributable to bacterial causes.[15] Some of these bacterial foodborne illnesses have been associated with agents that were phenotypically resistant to one or more antimicrobial agents. Trace-back investigations of these types of cases or outbreaks are extremely difficult for a variety of reasons including the complexity of the food distribution system, the complexity of the food processing system, the complexity of the animal production systems, and the time to diagnosis and recovery of an organism from human patients. In most cases the authors of these reports have demonstrated that foodborne transmission of pathogens can and does occur and that sometimes these pathogens possess antimicrobial resistance determinants. However, these authors have not been able to do more than speculate that the resistance determinant arose in the animal population because of antimicrobial drug exposure. They have often failed to consider other routes of exposure of animals to resistant organisms. The simple theory that antimicrobial use practices in animals could pose a public health risk, regardless of size of that risk, has been a stimulus to the agriculture producers and researchers to develop more data on this issue. Specifically, these groups are currently actively examining common production practices and their role in the amplification and spread of resistance in animal populations, as well as the ability to transfer resistant determinants through the food chain.

Researchers discovered long ago that feeding small doses of antimicrobial drugs to animals resulted in improved growth and feed efficiency. This use has been and probably remains the most controversial use of antimicrobial drugs in animals. Although the mechanism for this

enhanced production efficiency are still not understood, some proposed mechanisms include control of subclinical disease, stabilizing the gut flora, or selection of specific populations of gut flora. As bacterial isolates have been more commonly found to be resistant, and treatment failure of human patients has been recognized with increasing frequency, the debate about the appropriateness of various types of antimicrobial drug use in animals has been fueled. Numerous groups have debated the merits and potential adverse consequences of various antimicrobial uses in animals. The Swann committee from the U.K. in 1969 issued a report and called for the banning of certain antimicrobial growth promoters in animals.[16] The FDA in the U.S. proposed a ban of Tetracycline and Penicillin for growth promotion in 1972. This proposal was never accepted and resulted in the convening of a National Academy of Sciences group to evaluate the potential human health impacts of sub-therapeutic use of antimicrobial drugs for growth promotion in animals. They concluded that there was insufficient evidence to link the feeding sub-therapeutic doses of antimicrobial drugs to animals with adverse effects on human health.[17] Over the next 15 years many governmental groups have considered the issue of the public health impacts of antimicrobial use in animals with few definitive conclusions. More recently the emergence and epidemic spread in livestock of a multi-drug resistant form of *Salmonella* Typhimurium that was phage type (definitive type) DT104, and concerns about emerging fluoroquinolone-resistant *Campylobacter* spp. in poultry have brought the issue back into the center of interest.[18]

Since the first therapeutic application of penicillin G in 1940, bacteria have responded to the inherent selection pressure and developed diverse mechanisms of resistance to commonly used antimicrobial drugs.[5,6] Data indicate that resistant bacteria are being spreading internationally, that resistance is emerging in more bacterial species, and that more bacteria are becoming resistant to multiple drugs.[2] It is perhaps ironic that reliance upon the convenience and efficacy of antimicrobial drugs during the past 60 years is in some measure responsible for the current threat.

Actions to Address the Issue

There is agreement throughout the world's health officials that antimicrobial drugs must be used prudently if they are to maintain efficacy.[2] Infections caused by resistant bacteria may fail to respond to treatment resulting in prolonged illness and patient suffering, greater medical costs, and an increased risk of death.[19,20] Some believe that failure to contain the evolution of resistant bacteria will result in a medical catastrophe.[4,21] Considering the serious nature of this threat, it is not surprising that some human health experts have pointed to antimicrobial drug use in animals as an area that should be carefully scrutinized because of perceived abuse.[2,4,12-14] As a result of these concerns, several countries have banned use of antimicrobial drugs for certain purposes. For example, Sweden banned all non-prescription use of antimicrobial drugs in animal feed, and the European Union has banned the use of specific antimicrobial drugs used as additives in animal feed. The FDA is currently considering implementing restrictions on both therapeutic and subtherapeutic use of antimicrobial drugs in animals. In 1998, the FDA published a proposed framework for protecting public safety by imposing measures to assure that use of

antimicrobial drugs in food-producing animals would not negatively impact their efficacy in humans, and a draft guidance document has now been issued for public comment.[14] In 1999 and 2001, bills were introduced to the U.S. House of Representatives that if passed, would ban subtherapeutic use of antimicrobial drugs in food-producing animals unless within two years of enactment the manufacturers could submit data proving that continued use would pose "no harm to human health".[12,13]

The World Health Organization (WHO), in a 1997 report[21] recommended that practices of antimicrobial drug use in animals should be reviewed nationally, and antimicrobial use policies should be developed to reduce the risks of selection and dissemination of antimicrobial resistance. In their more recent 1999 report,[10] the WHO outlined eight factors thought to contribute to misuse of drugs and development of antimicrobial resistance. The most important factor identified was a general lack of knowledge among health professionals about antimicrobial resistance. In addition the following statements were specifically made regarding antimicrobial drug use in animals:

> *For prescribers and dispensers, education is lacking on antimicrobial resistance and appropriate antimicrobial therapy. In many countries, therapeutic antimicrobials are dispensed by inadequately trained individuals. By far the largest amount of antimicrobials is applied to animal flocks and herds through feed with inherent problems of accurate dosing and inevitable treatment of all animals irrespective of health status. Empiric treatment predominates because of the widespread lack of diagnostic services and may often be, from the producers' viewpoint, economically contraindicated. Sales of drugs constitute 40% of the income of veterinarians in some countries.*[10]

These comments suggest that in general veterinarians prescribing antimicrobial drugs are uninformed about this issue, unconcerned about the potential threat to human health, and that their motivation for using these drugs might be questioned. In truth, these comments are speculative generalizations as there are almost no published data about use of antimicrobial drugs by veterinarians in the U.S., or elsewhere.

While all health professionals should obviously be concerned about appropriate use of antimicrobial drugs, "white papers" such as these have often included inappropriate speculation about motivation and responsibility for using antimicrobial drugs in animals, or have inappropriately extrapolated information about antimicrobial drug use in humans to use practices in animals. Regardless, it appears that federal regulatory agencies are prepared to further restrict antimicrobial drug use in animals.[12-14]

Study Description

In 2001, investigators from Colorado State University performed a national mail survey of veterinarians engaged in private practice in the U.S. regarding their attitudes about antimicrobial resistance and about their use of in specific empirical used of antimicrobial drugs. An initial sampling frame of 13,144 veterinarians was obtained using the AVMA membership database. Responses were obtained from 35.3% of veterinarians that were sent surveys (4,639/13,144).

Veterinarians were categorized using their self-selected practice type (small animal exclusive, small animal predominate, mixed small and large animal, large animal predominate, large animal exclusive, equine, and other). The survey asked a series of questions regarding their attitude about the issue of antimicrobial resistance, their sources of information on the issue, areas of responsibility for the problem (veterinarians in similar practices, other veterinarians, physicians, agriculture, etc.). These data represent the first comprehensive study of veterinarians about the

attitudes on the subject of antimicrobial resistance, and should be of use and interest to veterinarians, legislators, and regulatory agencies.

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