Introduction

During the past decade, the threat of antimicrobial resistance has become increasingly real and its global dimensions have been increasingly recognized. Antimicrobial resistance is defined as a property of bacteria that confers the capacity to inactivate or exclude antibiotics, or a mechanism that blocks the inhibitory or killing effects of antibiotics, leading to survival despite exposure to antimicrobials (Institute of Medicine, 1998). Some bacteria become multi-resistant, i.e., resistant to different groups of antibiotics. Increasing reports of outbreaks of antimicrobial resistant bacteria, such as hospital outbreaks of vancomycin resistant enterococci (VRE), community outbreaks of antimicrobial resistant *Streptococcus pneumoniae* (Tenover, 1996) and human and animal outbreaks of multi-resistant *Salmonella* Typhimurium definitive type 104 (DT104) (Akkina et al., 1999), have heightened the concerns of the international public- and animal-health communities, medical and veterinary clinicians and the general public. Another reason for increased concern is the slowing of research and develoment of new antimicrobials due to the cost and time to develop new drugs as well as a focus by pharmaceutical companies on developing products for non-infectious disease.

Antimicrobial resistance issues have the potential to impact animal agriculture in a number of ways. Concern about the role of animal agriculture in antimicrobial resistance development and spread has recently prompted the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM), to propose a new "Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals", which may lead to new regulations on the approval process of antimicrobials for use in food-producing animals. In addition, the Center for Science in the Public Interest (CSPI) and other groups are petitioning the FDA to ban subtherapeutic or growth promotant use of antimicrobials that are currently used, or that may be used in the future for humans. In the Euopean Union (EU), four antimicrobials (bacitracin zinc, spiramycin, virginiamycin and tylosin phosphate) which are considered important in treating humans were banned for use in animal feed, effective July 1, 1999. Controversy over antimicrobial resistant pathogens and use of antimicrobials in food animals could impact future trade decisions.

One of the USDA/APHIS/Veterinary Services (VS) strategic principles for behavior and action outlined in the VS Strategic Plan, FY2000/2002, is to use its resources and act together with other partner agencies and the public to address food safety, public health, and natural resource issues of overlapping knowledge and concern. The issue of antimicrobial resistance is a good example of how the interaction of animal and human populations, and the environment, has become more complex and requires multidisciplinary attention and coordination from the public- and animal- health and agricultural sectors. The United States General Accounting Office, in their recent report (GAO/RCED-99-74) titled "Food Safety: The Agricultural Use of Antibiotics and Its Implication for Human Health", has recommended that the Secretaries of Agriculture and Health and Human Services develop and implement a plan that contains specific goals, time frames, and resources needed to evaluate the risks and benefits of existing and future use of antimicrobials in agriculture, including identifying and filling critical data gaps and research needs.

A coordinated effort between USDA, FDA, producers, practitioners and the pharmaceutical industry can assist in providing the scientific information needed to determine the prevalence and trends of antimicrobial resistance on the farm, identify risk factors for resistance development, develop and implement interventions to reduce antimicrobial resistance, and evaluate the effectiveness of interventions.

Objective

The purpose of this series of papers is to assist VS decision-makers in setting priorities and allocating resources for activities and research to address this threat to animal and public health, and to provide a knowledge base in antimicrobial resistance for VS personnel who want to educate themselves about antimicrobial drug resistance issues in animal agriculture. Although the document may benefit significantly a variety of readers, it is not intended for those who consider themselves, or are considered by others, to be experts in antimicrobial resistance issues. Nor is the document intended for those readers who do not have a basic background in veterinary medicine, epidemiology, microbiology, livestock production medicine, and related areas.

Background

An antimicrobial is an agent that kills bacteria or suppresses their multiplication or growth. Fleming discovered penicillin in 1928 and soon after other classes of antimicrobials were also identified. The first therapeutic use of penicillin however was not until 1940. Consequently, for more than 50 years the world has enjoyed a tremendous decrease in mortality and morbidity from bacterial diseases. Existence of resistance to antimicrobials was realized early. Also in 1940, Abraham and Chain described penicillinase, an enzyme that inactivates penicillin, in *Escherichia coli* (Tenover, 1996). The intrinsic ability of some organisms to resist antimicrobials was clearly present prior to the clinical use of antimicrobials. In addition, antimicrobial resistance can occur as a result of random genetic mutations in bacteria, leading to variation in susceptibility within any bacterial population. More commonly, resistance is not due to a chromosomal change event, but to the presence of extrachromosomal DNA (plasmid) which was acquired from another bacteria. Use of antimicrobials however, selects for these resistant organisms, leaving them to multiply more freely after the susceptible bacteria have been eliminated. This phenomenon is called selective pressure.

Antibiotic resistance is a complex global issue that should not be over simplified or over generalized. For example, antibiotic resistance does not always follow antibiotic use. *Streptococcus pyogenes* remains fully sensitive to penicillin despite selective pressure (Phillips, 1998). Conversely, the removal of selective pressure does not always lead to reversal of resistance. An example of this is the occurrence of chloramphenicol-resistant *E. coli* many years after chloramphenicol ceased to be used in Britain (Phillips, 1998). The presence or absence of resistance applies for a specific microbial isolate in relation to one or more specific antimicrobial(s), and therefore is often geographically specific as well. It is not only resistant pathogens that are of concern. Resistance factors (genes) present in commensal (non-pathogenic) intestinal bacteria can be transferred to pathogenic bacteria.

The development of a resistant microorganism and its subsequent transmission in the human or animal population is often a multifactorial and multistep process. One major factor in the increasing problem of resistance in human pathogens is the overuse and injudicious use of antimicrobials in the hospital and community environments. There is also concern that antimicrobial use in food animals can lead to the selection of antimicrobial resistant zoonotic enteric pathogens which may then be transferred to people by the consumption of contaminated food or by direct animal contact. Though instances of resistance transfer, either direct or indirect, from animals to humans have been described, (Wegener et al., 1999; Spika et al., 1987; Institute of Medicine, 1998), the true magnitude of the medical impact from antimicrobial resistant bacteria originating from food animals or companion animals (pets and horses), is mostly unknown. Many reviews are available in the literature regarding the relationship between antibiotic resistance in humans and resistance in animals, with the conclusions varying widely from minimal impact to a substantial impact (Threlfall et al., 1992; Shah, 1993; Wiedmann, 1993; National Research Council, 1999). Another concern is resistant bacteria excreted in the feces of animals who have received antimicrobials, which contributes to the reservoir of resistant bacteria in the environment (Levy, 1998; National Research Council, 1999). Antimicrobials are used in plant agriculture and in aquaculture to destroy and prevent fungal and bacterial pests. This use may also contribute to the environmental reservoir of resistant microbes. In addition, the contribution of companion animals, i.e., pets and horses, to resistance in humans is unknown.

There are many other factors which contribute to the rising incidence of resistance in human pathogens. These factors include liberal availability of antimicrobials in some countries and societal factors such as the increasing number of immunocompromised individuals, unnecessary antimicrobial use caused by patient demands for antimicrobial treatment of viral infections, the changing population age structure, and an increase in institutional care environments such as day care centers, nursing homes and hospitals (Livermore, 1998). In these environments large numbers of susceptible persons in close contact, and with high incidence of antibiotic use, promote transmission of resistant microbes and/or factors. Similarly in animal agriculture, the current trend in developed countries toward more concentrated livestock production, with fewer farms and more animals per farm, places large numbers of susceptible animals in close physical contact. In addition, increasing international travel and trade allows resistant organisms to quickly disseminate globally.

Implications of Antimicrobial Resistance for Human Health

Antimicrobial resistant infections in humans lead to increased morbidity, mortality, and longer hospitalizations. Increased health care costs are associated particularly with longer hospital stays and use of more expensive antimicrobials necessary to fight resistant pathogens. Often the antimicrobials used to combat resistant organisms are more toxic, with more serious side effects. Other associated costs to society include lost work days and value of lives lost due to deaths.

The cost of antimicrobial resistant hospital acquired infections was estimated by the National Foundation for Infectious Disease to be as high as four billion dollars annually. In 1995, the Office of Technology Assessment (OTA) produced a minimum estimate of 1.3 billion (1992 dollars) yearly in-hospital costs related specifically to six species of antibiotic resistant bacteria and only one antibiotic (Institute of Medicine, 1998).

Antimicrobial Use in Animal Agriculture

Antimicrobials are used in animal agriculture to improve:

1) the health and welfare of the animal, through treatment of disease

2) carcass quality

3) the economic efficiency of growth and production

4) public health, through decreased shedding of zoonotic pathogens which may contaminate both the environment and food animal products (National Research Council, 1999).

Clearly, the use of antimicrobials in animal agriculture has many important benefits. Antimicrobials are an integral component in the treatment of livestock disease and in livestock production in the U.S. The loss of efficacious antimicrobials, either due to development of resistance or due to limiting availability or use, could potentially have serious consequences. Consequences include areas such as changes in the makeup of the food supply, food cost changes, impacts on producers, impacts on animals, and overall impacts on food quality.

Actions by the public- and animal- health communities to manage antimicrobial resistance must be based on sound science. The following series of reports provide a brief review of some of the scientific aspects of antimicrobial resistance issues and animal agriculture.

Executive Summaries

Understanding the Biology of Antimicrobial Resistance

Summary

To make science-based decisions about priorities, activities, and resource allocation to address the issue of antimicrobial resistance, a working knowledge of the biology of resistance is necessary. This section reviews the basics of antimicrobial mechanisms of action and the development and spread of microbial mechanisms to resist antibiotics. Antimicrobial susceptibility testing of microbial isolates is an important tool for clinical use and for monitoring the prevalence of antimicrobial resistance. The broth microdilution method and the disk diffusion method are described and discussed.

Antibiotic Use in U.S. Livestock Production

Summary

Antibiotics are used in livestock production as therapeutics, prophylactics, and growth promoters. These drugs assist in sustaining livestock production and in controlling bacterial pathogens that may be transferred to humans. The scientific community is increasingly concerned about the transfer of antibiotic resistance and/or antibiotic resistance determinants from animals to humans. These concerns may lead to increased restrictions on the use of antibiotics in animal agriculture as well as to decreased exports. This report lists many of the antibiotics approved for use in livestock production in the U.S., the EU, and the UK. The report also describes the purposes and prevalence of antibiotic use in the U.S. livestock population, based on several different studies by the National Animal Health Monitoring System (NAHMS) between 1990 and 1997. Antibiotics were used in most phases of swine production and were administered via injection, feed, water and orally. Antibiotic use increased in swine production between 1990 and 1995. Approximately 25 percent of small cattle feedlot operations and 70 percent of large feedlot operations used antibiotics. Similarly, approximately 31 percent of cattle on small feedlot operations and 57 percent of cattle on large feedlot operations were exposed to antibiotics. Tetracycline and derivatives of tetracycline were some of the most frequently used in-feed additives on feedlot operations. Varying percentages of dairy operations and varying percentages of dairy cows on these operations were exposed to antibiotics during lactation and the dry period. Only a few antibiotics have been approved for use in catfish production. Romet was used to manage enteric septicemia of catfish on 41 percent of affected operations. Increased restrictions on the use of antibiotics could have significant implications for animal health. Therefore, developing economically feasible, chemotherapeutic and non-chemotherapeutic alternatives to antibiotics (e.g., management strategies) may become vital to maintain the health of U.S. livestock and to maintain viable export markets.

Prevalence of Salmonella and *Escherichia coli* On U.S. Livestock Operations

Summary

Salmonella and *Escherichia coli* (*E. coli*) cause significant morbidity and mortality in livestock and therefore are two of the most economically significant pathogens of livestock. In humans, *Salmonella* and *E. coli* are important causes of food-borne illness. The Centers for Disease Control and Prevention (CDC) estimates 1.4 million *Salmonella* cases with 600 deaths occur each year. Morbidity and mortality from *Salmonella* leads to significant economic loss to the population through medical expenses and productivity lost. Since antimicrobials are used in livestock to control these two pathogens, there is concern about antibiotic resistance development in these pathogens and subsequent transfer to humans through contaminated food. The prevalence of these two pathogens in livestock therefore may impact the level of antibiotic use, antibiotic resistance development and human food-borne disease. This concern provides impetus for thoroughly understanding the ecology and epidemiology of *Salmonella* and *E. coli* infections in animals.

The objective of this report is to provide an abbreviated review of *Salmonella* and *E. coli* infections, and present the descriptive results of several national studies by the USDA's National Animal Health Monitoring System (NAHMS) of *Salmonella* and *E. coli* on U.S. livestock operations. *Salmonella* were found in animals on dairy, feedlot cattle, and swine operations. None of the *Salmonella* serotypes from feedlot cattle were on the CDC's list of the top 5 *Salmonella* isolates from humans in 1991. However, three of the serotypes from swine were on the CDC's list of the top 5 *Salmonella* isolates from humans in 1994. *E. coli* O157:H7 was detected in dairy calves and feedlot cattle, but the prevalence generally was low in comparison to the prevalence of some other pathogens. *E. coli* O157:H7 was not found in a 1995 survey of U.S. swine operations. Diseases in swine that may be caused by other serotypes of *E. coli* were reported to have been an important cause of morbidity and mortality on swine operations.

Epidemiology of Antimicrobial Resistance in *Salmonella* , *Escherichia coli*

And Other Selected Pathogens in Livestock

Summary

This report summarizes the descriptive epidemiology of antimicrobial resistance in animals in different countries, as presented at the WHO conference on "The Medical Impact of the Use of Antimicrobials in Food Animals" in October, 1997 (World Health Organization, 1998). This brief description of the epidemiology of antimicrobial resistance in livestock focuses primarily on two important zoonotic pathogens, *Salmonella* and *Escherichia coli.* In addition, the epidemiology of antimicrobial resistance in livestock is discussed briefly for the following pathogens: *Staphylococcus aureus*, *Serpulina hyodysenteriae*, *Campylobacte*r, *Salmonella* Typhimurium DT104, and respiratory pathogens. Finally, resistance to several antimicrobials including vancomycin, streptogramins, and quinolones, is discussed.

Widespread resistance to old and recently developed antimicrobial drugs is occurring in several pathogens that are commonly associated with diseases in animals and humans. In general, long-term trends in the prevalences of resistance were not available from many countries because many surveillance systems were organized only recently. Where available, data indicates that the prevalence of resistance of some infectious agents in animals to some antimicrobial drugs used in livestock production is increasing, and it is already high in some situations.

Strategies to Reduce Antimicrobial Resistance in Food Animal Agriculture

Summary

Limiting availability of antimicrobials, enhanced surveillance, and on-farm interventions (including prudent antimicrobial use and management practices) have been proposed as key strategies to reduce antimicrobial resistance in food animal agriculture. Improved, rapid diagnostic methods and accelerated development and approval of new antimicrobial drugs can also play an important role in preventing and controlling antimicrobial resistance. This report describes the essential characteristics of a surveillance system for antimicrobial resistance and briefly reviews recently organized surveillance systems in the U. S., France, and Sweden. In addition, management practices that can decrease the need for antimicrobial use on the farm are explored. Examples of management practices that decrease the need for antimicrobials are the use of vaccines, probiotics, immune enhancers, good husbandry practices, and biosecurity. According to data from the USDA's National Animal Health Monitoring System (NAHMS), appropriate use of health management practices could be pivotal to an on-farm intervention strategy to reduce antimicrobial resistance on U.S. swine, dairy, and beef operations. Some specific results of NAHMS' health management data were: (1) Only 32% of calves received the recommended volume of colostrum during the first feeding. (2) The immunoglobulin concentration was less than ideal in approximately 67% of the 2,177 dairy calves sampled. (3) Proper protection against respiratory pathogens may have been inadequate in as many as 86% of beef calves in the U.S. at the time of sale in 1997, based on the frequency of vaccination. Educating animal producers and veterinarians concerning these strategies to prevent and control antimicrobial resistance is essential to their success.

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