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Report to Congressional Requesters

April 2004

ANTIBIOTIC RESISTANCE

Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals

GAO-04-490

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Highlights

Highlights of GAO-04-490, a report to congressional requesters

Why GAO Did This Study

Antibiotic resistance is a growing public health concern; antibiotics used in animals raised for human consumption contributes to this problem. Three federal agencies address this issue—the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC), and the Department of Agriculture (USDA). GAO examined (1) scientific evidence on the transference of antibiotic resistance from animals to humans and extent of potential harm to human health, (2) agencies' efforts to assess and address these risks, (3) the types of data needed to support research on these risks and extent to which the agencies collect these data, (4) use of antibiotics in animals in the United States compared with its key agricultural trading partners and competitors, and (5) information on how use has affected trade.

What GAO Recommends

GAO recommends that (1) FDA expedite its risk assessments of drugs used in animals that are critical for human health and (2) USDA and HHS develop and implement a plan to collect data on antibiotic use in animals. USDA and HHS generally agreed with GAO's findings. With respect to the recommendations, HHS agreed that it is important to review animal drugs that are critical to human health and both agencies discussed ways to better collect antibiotic use data.

www.gao.gov/cgi-bin/getrpt?GAO-04-490.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Anu Mittal at (202) 512-3841 or Marcia Crosse at (202) 512-7119.

What GAO Found

Scientific evidence has shown that certain bacteria that are resistant to antibiotics are transferred from animals to humans through the consumption or handling of meat that contains antibiotic-resistant bacteria. However, researchers disagree about the extent of harm to human health from this transference. Many studies have found that the use of antibiotics in animals poses significant risks for human health, but a small number of studies contend that the health risks of the transference are minimal.

Federal agencies have expanded their efforts to assess the extent of antibiotic resistance, but the effectiveness of their efforts to reduce human health risk is not yet known. FDA, CDC, and USDA have increased their surveillance activities related to antibiotic resistance. In addition, FDA has taken administrative action to prohibit the use of a fluroquinolone in poultry. FDA has identified animal drugs that are critically important for human health and begun reviewing currently approved drugs using a risk assessment framework that it recently issued for determining the human health risks of animal antibiotics. However, because FDA's initial reviews of approved animal drugs using this framework have focused on other drugs and have taken at least 2 years, FDA's reviews of critically important drugs may not be completed for some time.

Although federal agencies have made some progress in monitoring antibiotic resistance, they lack important data on antibiotic use in animals to support research on human health risks. These data, such as the type and quantity of antibiotics and purpose for their use by species, are needed to determine the linkages between antibiotic use in animals and emerging resistant bacteria. In addition, these data can help assess human health risks from this use and develop and evaluate strategies for mitigating resistance.

The United States and several of its key agricultural trading partners and competitors differ in their use of antibiotics in animals in two important areas: the specific antibiotics allowed for growth promotion and availability of antibiotics to producers (by prescription or over the counter). For example, the United States and Canada allow some antibiotics important in human medicine to be used for growth promotion, but the European Union (EU) and New Zealand do not. Regarding over the counter sales of antibiotics, the United States is generally less restrictive than the EU.

Antibiotic use in animals has not yet been a significant factor affecting U.S. international trade in meat and poultry, although the presence of antibiotic residues in meat has had some impact, according to government and industry officials. Instead, countries raise other food safety issues, such as hormone use and animal diseases. However, according to these officials, antibiotic use in animals may emerge as a factor in the future. They particularly noted that the EU could object to U.S. use of antibiotics for growth promotion as its member countries are phasing out that use.

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Abbreviations

ADG	average daily weight gain
ADP	antibiotics used for disease prevention
AGP	antibiotics used for growth promotion
CAHFSE	Collaboration in Animal Health, Food Safety, and Epidemiology
CDC	Centers for Disease Control and Prevention
DT	definitive type
DNA	deoxyribonucleic acid
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FAS	Foreign Agricultural Service
FCR	feed conversion ratio
FDA	Food and Drug Administration
FoodNet	Foodborne Diseases Active Surveillance Network
HIV	human immunodeficiency virus
HHS	Department of Health and Human Services
MR	mortality rate
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System—Enteric Bacteria
NRC	National Research Council
OIE	Office International des Epizooties
Q/D	quinupristin/dalfopristin
USDA	U.S. Department of Agriculture
WHO	World Health Organization
WTO	World Trade Organization

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United States General Accounting Office
Washington, D.C. 20548

April 22, 2004

The Honorable Olympia J. Snowe
Chair, Committee on Small Business and Entrepreneurship
United States Senate

The Honorable Tom Harkin
Ranking Democratic Member
Committee on Agriculture, Nutrition, and Forestry
United States Senate

The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Health, Education, Labor, and Pensions
United States Senate

Antibiotic resistance is a serious and growing public health problem.[1] As resistance to antibiotics develops in disease-producing bacteria, it can become difficult to treat diseases that were formerly treatable with antibiotics, and this can have deadly consequences. Treating antibiotic-resistant infections often requires the use of more expensive drugs and can result in longer hospital stays. According to Institute of Medicine estimates, the annual cost of treating antibiotic-resistant infections may be as high as $3 billion. Experts cite the widespread use of antibiotics in human medicine as the principal cause of resistance, but they identify the use of antibiotics in animals raised for human consumption as contributing to antibiotic resistance in humans. It is generally agreed that a large proportion of the antibiotics used in the United States is administered to animals raised for human consumption.

While antibiotic use in animals poses potential human health risks, it also reduces the cost of producing these animals, which in turn helps reduce the prices consumers pay for food. Antibiotics are an integral part of animal production in the United States and many other countries where large numbers of livestock and poultry are raised in confined facilities, which increases the likelihood of disease. Antibiotics are used to treat animal

[1]Antibiotics are substances that destroy microorganisms or inhibit their growth. They are used extensively to treat bacterial infectious diseases in plants, animals, and humans. Some scientists refer to synthetic antibiotics as antimicrobials. In this report, we use the term antibiotics to mean both natural and synthetic types.

diseases; to prevent the spread of diseases that are known to occur during those phases of production when animals are at a high risk of disease (e.g., when animals have been transported to a new location); and to increase animals' growth rate. Consumer groups argue that antibiotic use would be reduced if different animal production methods were used. Public health officials are particularly concerned about the use of antibiotics in animals to promote growth because antibiotics used for growth promotion are administered in low doses over long periods of time to large groups of animals that are not sick. This practice can allow animals to become reservoirs of antibiotic-resistant bacteria. If a person becomes ill from handling or ingesting meat or poultry contaminated with antibiotic-resistant bacteria, the infection may be resistant to treatment not only with the antibiotic of choice for that infection but also with other antibiotics in the same class of drugs. Use of antibiotics in animals also may lead to the transference of resistance from one type of bacteria to another type.

Three federal agencies are primarily responsible for protecting Americans from the health risk associated with the transfer of antibiotic-resistant bacteria from meat and poultry to the humans who handle or consume these products. The Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) approves for sale and regulates the manufacture and distribution of antibiotics used in animals. HHS's Centers for Disease Control and Prevention (CDC) conducts surveillance and other research to assess the extent of antibiotic resistance in humans from animals. The U.S. Department of Agriculture (USDA) gathers data on antibiotic resistance in animals, conducts surveillance, and funds epidemiologic and other research on antibiotic resistance in humans, animals, and the environment. In addition, internationally, the World Health Organization (WHO) and the Office International des Epizooties (OIE) have been examining these issues.[2]

[2]The Office International des Epizooties is also known as the World Organization for Animal Health and, among other things, helps ensure the safety of foods produced from animals.

In 1999, we reported that the development and spread of antibiotic-resistant bacteria is a worldwide phenomenon and that the widespread use of various antibiotics has created the potential for U.S. public health costs to increase.[3] We further reported that the extent to which the agricultural use of antibiotics contributes to antibiotic-resistant bacteria in humans is uncertain and recommended that HHS and USDA work together to develop and implement a plan with specific goals, time frames, and resources needed for determining the safe use of antibiotics in agriculture.[4] In response, in January 2001, the federal Interagency Task Force on Antimicrobial Resistance, which is composed of FDA, CDC, and USDA, and several other agencies,[5] issued an action plan to address antibiotic resistance issues, including those associated with antibiotic use in animals. Subsequently, in June 2003, the task force issued a status report that described the agencies' progress in implementing the activities outlined in the action plan.

You asked us to examine the (1) scientific evidence regarding the transference of antibiotic resistance from animals to humans through consuming or handling contaminated meat and poultry and the extent of potential harm to human health, (2) progress federal agencies have made in assessing and addressing the human health risk of antibiotic use in animals, (3) types of data that federal agencies need to support research on the human health risk of antibiotic use in animals and the extent to which these data are collected, (4) use of antibiotics in animals in the United States compared with antibiotic use by its key agricultural trading partners and competitors, and (5) information that is available on the degree to which antibiotic use in animals has affected U.S. trade.

For the purpose of this report, the term "animal" refers to animals raised for human consumption, such as cattle, sheep, swine, chickens, and

[3]U.S. General Accounting Office, *Antimicrobial Resistance: Data to Assess Public Health Threat from Resistant Bacteria Are Limited*, GAO/HEHS/NSIAD/RCED-99-132 (Washington, D.C.: Apr. 28, 1999).

[4]U.S. General Accounting Office, *Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health*, GAO/RCED-99-74 (Washington, D.C.: Apr. 28, 1999).

[5]The other task force agencies are the National Institutes of Health, the Agency for Healthcare Research and Quality, the Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, the Department of Defense, the Department of Veterans Affairs, the Environmental Protection Agency, and since 2001, the U.S. Agency for International Development.

turkeys; the term "meat" refers to beef, lamb, pork, chicken, and turkey; and the term "contaminated meat" refers to meat that contains antibiotic-resistant bacteria. We limited the scope of our work to the transference of antibiotic-resistant bacteria from animals to humans through the consumption or handling of meat. Specifically, we looked at the evidence for transference of antibiotic-resistant foodborne intestinal pathogens from these animals to humans. We did not examine issues related to antibiotics used on plants and seafood, antibiotic residues in animals, or the effects of antibiotics present in the environment because of the application of animal waste to agricultural lands.

To identify scientific literature on the transmission of antibiotic-resistant bacteria from animals to humans, we searched medical, social science, and agricultural databases, which included HHS's National Institutes of Health's National Library of Medicine, for studies published in professional journals. We identified articles published since the 1970s on antibiotic use and resistance in animals and humans, as well as articles on antibiotic-resistant foodborne illnesses.

To examine federal agencies' progress in assessing and addressing the human health risk of antibiotic use in animals, we examined documents from FDA, CDC, and USDA. These documents include reports on results from the federal government's antibiotic resistance surveillance program and on the progress of the federal Interagency Task Force on Antimicrobial Resistance, documents presented in an FDA administrative proceeding concerning the agency's proposal to withdraw the approval of the use of a certain antibiotic used in poultry that is also an important antibiotic in human medicine, and FDA's framework to assess the human health risk of antibiotic use in animals.

To examine the types of data that federal agencies need on antibiotic use in animals to support research on the human health risk and the extent to which these data are collected, we reviewed federal agencies' documents and reports and interviewed FDA, CDC, and USDA officials. We reviewed foreign government reports to determine how other countries use data on antibiotic use for research and international reports from WHO and OIE, which provide guidelines on the types of antibiotic use data that countries should collect. We also interviewed officials from Denmark, which collects extensive data on antibiotic use in animals, and from Canada, which plans to implement a data collection system. We discussed the availability of data on U.S. antibiotic use in animals with officials from pharmaceutical

companies, industry associations, state veterinary offices, firms that collect data on antibiotic use in animals, and public health advocacy groups.

To compare the United States' use of antibiotics in animal production with that of its key trading partners and competitors, we reviewed information on antibiotic use in animals for these countries. We reviewed FDA regulations on antibiotic use in animals in the United States and visited livestock and poultry farms in Georgia, Maryland, and Pennsylvania. Using international trade data, we identified the European Union (EU) and 11 countries—Australia, Brazil, Canada, China, Denmark,[6] Hong Kong, Japan, Mexico, New Zealand, Russia, and South Korea—as key U.S. trading partners or competitors. We identified relevant documents on these countries' policies concerning antibiotic use in animals and obtained further information through discussions with USDA's Foreign Agricultural Service officials, as well as through a questionnaire we sent to the agency's attachés stationed in those countries. We examined these policies and identified the similarities and differences between countries. In addition, we discussed antibiotic use and policies with government officials from Canada, a leading U.S. trading partner and competitor, and Denmark, a leading U.S. trading partner and competitor that took significant actions to curtail antibiotic use in animals during the late 1990s. We also reviewed USDA and other reports on antibiotic use in animal production. We did not independently verify the information we received in response to our questionnaire; other documents, including laws and regulations from the foreign countries; or other reports on antibiotic use in the United States.

To examine the available information on the degree to which antibiotic use in animals has affected U.S. trade, we examined USDA records on foreign countries' meat import standards and reviewed reports by USDA and international food safety organizations on international trade issues related to food safety. In addition, we discussed international trade issues with officials from the Office of the U.S. Trade Representative, USDA's Foreign Agricultural Service, and meat industry trade associations.

We discussed the matters in this report with government officials, public interest groups, pharmaceutical manufacturers, and international and academic experts. Appendix I provides additional information on our scope and methodology. We conducted our work from May 2003 through

[6]Although Denmark is an EU member, we included it in addition to the EU because it is a major U.S. competitor in pork exports.

April 2004 in accordance with generally accepted government auditing standards.

Results in Brief

Antibiotic-resistant bacteria have been transferred from animals to humans, and many of the studies we reviewed found that this transference poses significant risks for human health. Studies have shown two types of evidence related to the transfer of antibiotic-resistant bacteria from animals to humans. First, some studies have provided evidence of associations between changes in antibiotic use in animals and resistance to antibiotics in humans. For example, researchers have found that antibiotic-resistant *Escherichia coli* (*E. coli)* and campylobacter bacteria increased in humans as use of the antibiotics commonly used to treat infections caused by those bacteria has increased in animals. Second, studies that have examined the genetic makeup of the bacteria have provided evidence of a stronger link and have established that antibiotic-resistant campylobacter and salmonella bacteria are transferred from animals to humans. In those studies, strains of antibiotic-resistant bacteria infecting humans were indistinguishable from those found in animals, leading the researchers to conclude that the animals were the source of infection. Researchers disagree about the extent of the human health risk caused by this transference. Many studies have found that the use of antibiotics in animals poses significant risks for human health. However, a small number of studies contend that health risks of the transference are minimal.

Federal agencies have expanded their surveillance of antibiotic resistance from the use of antibiotics in animals to assess the risk to human health, but it is too early to determine the effectiveness of their efforts to reduce this risk. FDA, CDC, and USDA have increased their surveillance activities related to antibiotic resistance in animals, humans, and retail meat by studying more types of bacteria, increasing the geographic areas studied, and adding new programs. In addition, all three agencies have funded or conducted research on antibiotic resistance in animals. As the regulatory agency responsible for animal drugs, FDA has determined that antibiotic resistance in humans resulting from the use of antibiotics in animals is an unacceptable risk to the public health and has taken a variety of recent actions. For example, FDA has taken action to prohibit the use of the fluoroquinolone antibiotic enrofloxacin in poultry because of what the agency asserts is strong evidence that the use of these antibiotics has led to the transference of antibiotic-resistant bacterial diseases from poultry to humans. A challenge from the drug's manufacturer has led to administrative proceedings that have lasted more than 3 years, and the

product remains on the market pending the final outcome of this case. In addition, FDA has issued guidance recommending a risk assessment framework for determining the human health risk of animal antibiotics and has begun to apply this framework in its reviews of manufacturers' applications for approval of new animal drugs. FDA has also begun reviewing currently approved animal antibiotics using this same framework. However, the approved drugs that it has reviewed to date using this approach have not included those that FDA identified in its guidance as critically important to human health, and the reviews have taken at least 2 years to complete. Therefore it may be some time before FDA completes its reviews of critically important drugs in order to determine if enforcement action to protect human health is warranted.

Although they have made some progress in monitoring antibiotic resistance, federal agencies do not collect the critical data on antibiotic use in animals that they need to support research on the human health risk. The data that could help this research include the types and quantities of antibiotics sold for use in animals, the purpose of their use (such as disease treatment or growth promotion), the species in which they are used, and the method used to administer them. These types of data are needed to study the linkages between antibiotic use in animals and the human risk from antibiotic resistance and to develop and evaluate strategies for mitigating resistance. Such data could also help researchers assess the human risk from using antibiotics in animals. At this time, FDA is not collecting data on antibiotic use in animals, and USDA's data collection activities are limited to a few swine farms. In Denmark, where detailed data on antibiotic use are collected, scientists have been able to research the effects of antibiotic use in animals on the development of resistant bacteria in animals, food, and humans and to develop mitigation strategies that minimize the potential human health risk.

The United States and several of its key trading partners and competitors, such as the EU, Canada, Australia, South Korea, and New Zealand, differ in their use of antibiotics in animals in two key areas: the specific antibiotics that can be used for growth promotion and the availability of antibiotics to producers (by prescription or over the counter). For example, the United States and Canada allow some antibiotics important in human medicine to be used for growth promotion. In contrast, New Zealand and the EU have banned this use in feed for those antibiotics that are important in human medicine. The EU has also issued a regulation requiring that member nations prohibit the use of all other antibiotics in feed for growth promotion by 2006. With regard to the availability of antibiotics to

producers, the United States allows older antibiotics to be sold over the counter but requires a veterinarian's prescription for newer antibiotics, such as fluoroquinolones. Some other countries, including Canada, also allow certain antibiotics to be sold over the counter. In contrast, Danish producers need prescriptions for all antibiotics, while other EU countries generally require prescriptions.

To date, antibiotic use in animals has not been a significant factor affecting the United States' international trade in meat products, although the presence of antibiotic residues in meat has had some impact, according to officials from USDA, the Office of the U.S. Trade Representative, and industry. In addition, these officials told us, foreign governments have raised other food safety concerns as trade issues, including hormone use in animals and animal diseases, such as bovine spongiform encephalopathy (commonly known as mad cow disease) and avian influenza. However, according to government officials, a USDA report, and a Canadian government report, antibiotic use in animals may emerge as a factor in U.S. trade negotiations in the future. The officials particularly noted that the EU could object to the United States' use of antibiotics for growth promotion because member countries are phasing out that use.

We are making recommendations to federal agencies to better focus their efforts to reduce the risk to human health from the transfer of antibiotic-resistant bacteria from meat. We recommend that FDA expedite its risk assessments of the antibiotics used in animals that are critically important to human health to determine if regulatory action is necessary. We also recommend that the Secretaries of Agriculture and of Health and Human Services develop and implement a plan to collect data on antibiotic use in animals that will adequately (1) support research on the relationship between this kind of antibiotic use and emerging resistant bacteria, (2) help assess the human health risk related to antibiotic use in animals, and (3) help the agencies develop and evaluate strategies to mitigate antibiotic resistance.

In commenting on a draft of this report, USDA and HHS generally agreed with our findings. With respect to our recommendations, HHS agreed that it is important to review animal drugs that are critical for human health, and both agencies discussed ways to better collect antibiotic use data.

Background

For over 50 years, antibiotics have been widely prescribed to treat bacterial infections in humans. Many antibiotics commonly used in humans have

also been used in animals for therapeutic and other purposes, including growth promotion. Resistance to penicillin, which was the first broadly used antibiotic, started to emerge soon after its widespread introduction. Since that time, resistance to other antibiotics has emerged, and antibiotic resistance has become an increasing public health problem worldwide.

Development of Antibiotic Resistance

Antibiotics kill most, if not all, of the susceptible bacteria that are causing an infection, but leave behind—or select, in biologic terms—the bacteria that have developed resistance, which can then multiply and thrive. Infection-causing bacteria that were formerly susceptible to an antibiotic can develop resistance through changes in their genetic material, or deoxyribonucleic acid (DNA). These changes can include the transfer of DNA from resistant bacteria, as well as spontaneous changes, or mutations, in a bacterium's own DNA. The DNA coding for antibiotic resistance is located on the chromosome or plasmid of a bacterium.[7] Plasmid-based resistance is transferred more readily than chromosomal-based resistance. Once acquired, the genetically determined antibiotic resistance is passed on to future generations and sometimes to other bacterial species. The dose of antibiotic and length of time bacteria are exposed to the antibiotic are major factors affecting whether the resistant bacteria population will dominate. Low doses of antibiotics administered over long periods of time to large groups of animals, such as doses used for growth promotion in animals, favor the emergence of resistant bacteria.[8]

Investigating the Impact of Antibiotic Resistance on Human Health

To investigate the impact on human health of antibiotic use in animals, researchers have used both epidemiologic studies alone and epidemiologic studies combined with molecular subtyping of bacterial isolates.[9] Epidemiologic studies examine patterns of health or disease in a population and the factors that influence these patterns. These studies help to identify the cause of a disease and the factors that influence a person's

[7]Chromosomes are linear threads made of DNA in the nucleus of a cell. Plasmids are circular pieces of DNA that are smaller than chromosomes and are often called extra- or mini-chromosomes.

[8]Stuart B. Levy, "Multidrug Resistance—A Sign of the Times," *New England Journal of Medicine*, vol. 338, no. 19 (1998): 1376-1378.

[9]A bacterial isolate is a population of organisms that come from a sample, such as diseased tissue from animals or humans.

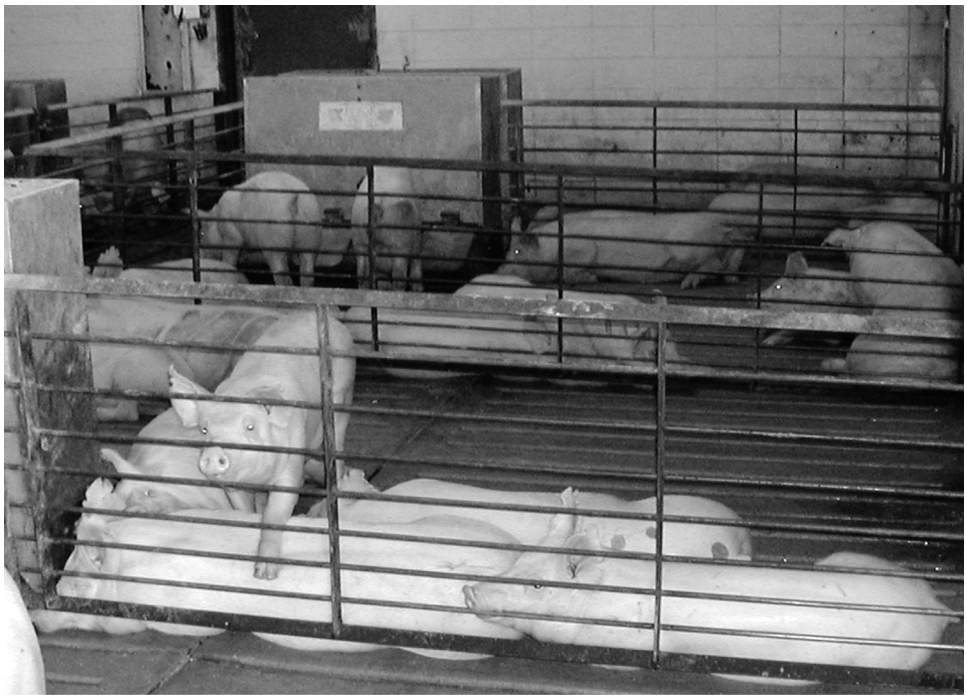
risk of infection. Many studies investigating antibiotic-resistant bacteria and their impact on human health combine epidemiologic studies with molecular subtyping—also called "DNA fingerprinting"—a technique that translates bacteria's genetic material into a "bar code" that can be used to identify specific pathogens and link them with disease outbreaks. For example, following an outbreak of a diarrheal disease among people in a community, an epidemiologic study would determine all the common exposures among the people with the disease, and molecular subtyping of bacterial isolates could determine what pathogens were responsible for the disease.

Use of Antibiotics in Animals

While the use of antibiotics in animals poses potential human health risk, it is also an integral part of intensive animal production in which large numbers of poultry, swine, and cattle are raised in confinement facilities. (See fig. 1.) Antibiotics are used in animals to treat disease; to control the spread of a disease in a group of animals when disease is present in some of the animals; to prevent diseases that are known to occur during high-risk periods, such as after transport, when the animals are stressed; and to promote growth—that is, to allow animals to grow at a faster rate while requiring less feed per pound of weight gain.[10] This use of antibiotics is commonly referred to as growth promotion and generally entails using low doses of antibiotics over long periods of time in large groups of animals. Many animal producers believe the use of antibiotics for growth promotion also prevents disease. Antibiotics are generally administered by injection to individual animals and in feed or water to groups of animals.

[10]Although scientists do not fully understand how antibiotics promote growth in animals, they believe antibiotics work through mechanisms such as increasing the absorption of nutrients in feed and suppressing subclinical bacterial infections.

Figure 1: Swine Confinement Facility



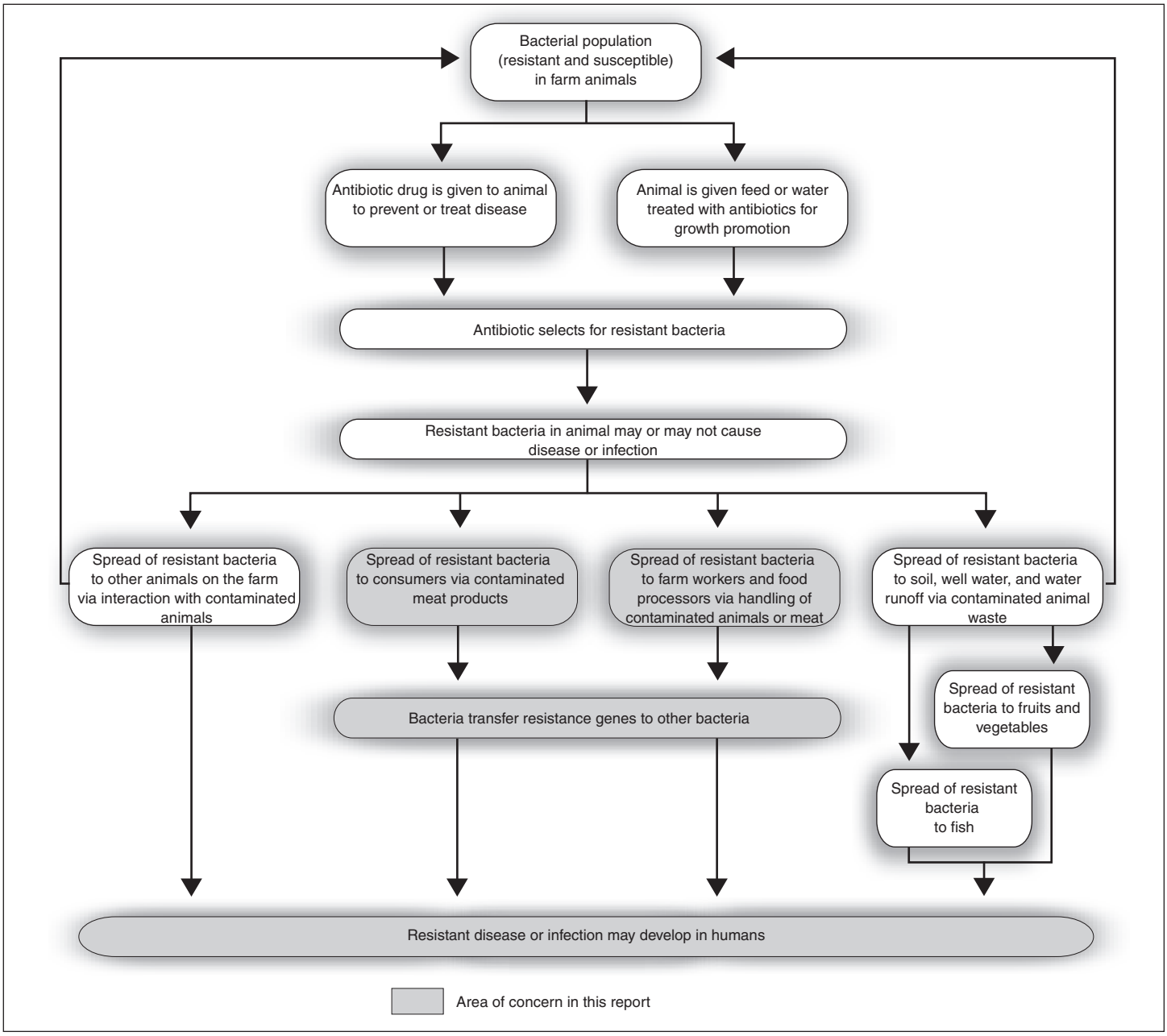
Source: GAO.

Possible Spread of Antibiotic-Resistant Bacteria from Animals to Humans

Figure 2 shows how antibiotic-resistant bacteria that develop in animals can possibly be transferred to humans, who may then develop a foodborne illness, such as a salmonella infection, that is resistant to antibiotic treatment.[11] Once the resistant bacteria develop in animals, they may be passed to humans through the consumption or handling of contaminated meat. An animal or human may carry antibiotic-resistant bacteria but show no signs or symptoms of an illness. Resistant bacteria may also be spread to fruits, vegetables, and fish products through soil, well water, and water runoff contaminated by waste material from animals harboring these bacteria, although such routes are beyond the focus of this report.

[11]Foodborne illnesses generally cause gastrointestinal symptoms, such as nausea, vomiting, abdominal cramps, and diarrhea. There are more than 250 foodborne diseases, and most are caused by bacteria, viruses, and parasites.

Figure 2: Possible Spread of Antibiotic-Resistant Bacteria from Animals to Humans



Source: GAO.

Debate Regarding Public Health Impact of Use of Antibiotics in Agriculture

Researchers in human medicine have debated the public health impact of antibiotic use in agriculture for many years. In the United States the debate intensified before FDA approved the first fluoroquinolone antibiotic for use in animals in 1995. At that time, drugs from the fluoroquinolone class had already been used for humans for nearly a decade. Debate focused on whether development of resistance to the drug approved for use in animals could, through cross-resistance,[12] compromise the effectiveness of other drugs in the fluoroquinolone class that were valuable in treating human diseases.

Efforts have been made to address the spread of antibiotic resistance by providing education to change behaviors of physicians and the public, but researchers differ on whether changes in agricultural practices are also needed. CDC has undertaken educational efforts aimed at physicians and the public. CDC is encouraging physicians to reduce prescribing antibiotics for infections commonly caused by viruses, such as ear and sinus infections. Patients are being taught that antibiotics are only for bacterial infections, not viral infections. Many researchers contend that efforts to reduce the use of antibiotics in animals are also needed to preserve the effectiveness of antibiotics necessary for treatment of bacterial diseases in humans and animals and to decrease the pool of resistant bacteria in the environment. However, agricultural industry officials argue that antibiotic use in animals is essential to maintaining the health of animals and therefore the safety of food.

[12]Cross-resistance is the phenomenon in which a microbe, such as a bacterium, that has acquired resistance to one drug through direct exposure, also turns out to have resistance to one or more other drugs, typically in the same drug class, to which it has not been exposed.

Professional organizations and associations differ on the use of antibiotics in animals. Many professional organizations that have studied the human health implications of antibiotic use in animals—including WHO and, in the United States, the Institute of Medicine of the National Academy of Sciences and the Alliance for the Prudent Use of Antibiotics—have recommended either limiting or discontinuing the use of antibiotic growth promoters.[13] Many of the professional associations for human medicine—such as the American Medical Association, the American College of Preventive Medicine, the American Public Health Association, and the Council of State and Territorial Epidemiologists—have position statements for limiting antibiotic use in animals for nontherapeutic purposes, such as growth promotion, for antibiotics that are important for both human and animal health. Many of the professional associations for veterinary medicine—such as the American Veterinary Medical Association and the American Association of Swine Practitioners—agree on the goal of reducing the use of antibiotics in animals but differ on the means to achieve this goal. These associations are calling for veterinarians to work with owners of animals to implement judicious use guidelines.

While limiting the use of antibiotics in animals for growth promotion may reduce the human health risk associated with antibiotic-resistant bacteria, such restrictions also may increase the cost of producing animals and the prices consumers pay for animal products. For example, a 1999 economic study estimated that a hypothetical ban on all antibiotic use in feed in swine production would increase U.S. consumers' costs by more than $700 million per year.[14,15] However, the increase in consumer costs would be much smaller if—as the Institute of Medicine proposed in 2003—producers were allowed to continue to use some antibiotics for growth promotion and

[13]World Health Organization, Department of Communicable Disease Surveillance and Response, *WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food* (Geneva, Switzerland, 2000); Alliance for the Prudent Use of Antibiotics, "The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences." *Clinical Infectious Diseases*, vol. 34, suppl. 3 (2002): S76-S77; and Institute of Medicine of the National Academies of Sciences, *Microbial Threats to Health: Emergence, Detection, and Response* (Washington, D.C., 2003): 16-17.

[14]Dermot J. Hayes, Helen H. Jensen, Lennart Backstrom, and Jay Fabiosa, "Economic Impact of a Ban on the Use of Over-the-Counter Antibiotics," Staff Report 99-SR 90, Center for Agricultural and Rural Development, Iowa State University, Ames, Iowa, December 1999.

[15]However, FDA's authority to withdraw a currently approved animal antibiotic use is generally limited to human health considerations and does not concern the economic impacts of such a withdrawal. *See* 21 U.S.C. §360b(e)(2000).

only antibiotics that are used in humans were banned for growth promotion. Moreover, in other animal species, such as beef cattle or chickens, the economic impacts of growth promotion restrictions would likely be smaller than in swine because antibiotic use for growth promotion is less prevalent in the production of these other species. Appendix II summarizes studies of the economic effects of banning antibiotic use for growth promotion and other proposed restrictions on antibiotic uses in animals.

Federal Agency Responsibilities and Authority

The three federal agencies responsible for protecting Americans from health risk associated with drug use in animals are FDA, CDC, and USDA. These agencies have a variety of responsibilities related to surveillance, research, and regulation. All three agencies collaborate on surveillance activities, such as the National Antimicrobial Resistance Monitoring System—Enteric Bacteria (NARMS), which was initiated in 1996 because of public health concerns associated with the use of antibiotics in animals. In addition, FDA's primary responsibilities as a regulatory body focus on human health and animal drug safety. CDC primarily conducts research and education that focus on human health. USDA oversees the retail meat trade, including related farm and slaughter operations. USDA activities may include studies of healthy farm animals, evaluations of diagnostic data involving sick animals, and biological sampling from slaughter and meat processing plants. USDA also conducts research and education related to antibiotic resistance.

In addition, FDA approves for sale and regulates the manufacture and distribution of drugs used in veterinary medicine, including drugs given to animals from which human foods are derived. Prior to approving a new animal drug application, FDA must determine that the drug is safe and effective for its intended use in the animal. It must also determine that the new drug intended for animals is safe with regard to human health. FDA considers a new animal antibiotic to be safe if it concludes that there is reasonable certainty of no harm to human health from the proposed use of the drug in animals. FDA may also take action to withdraw an animal drug from the market when the drug is no longer shown to be safe.[16]

[16]21 U.S.C. §360b(e)(1)(2000).

These three agencies also participate in the federal Interagency Task Force on Antimicrobial Resistance. Task force activities focus on antibiotic resistance from use of antibiotics in animals, as well as the human use of antibiotics. In January 2001, the task force developed an action plan based on advice from consultants from state and local health agencies, universities, professional societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups, and other members of the public. The action plan includes 84 action items, 13 of which have been designated as top-priority items and cover issues of surveillance, prevention and control, research, and product development.[17] A federal agency (or agencies) is designated as the lead for each action item.

International Trade Issues

The United States is one of the world's leading exporters of meat. In 2002, U.S. meat exports accounted for about $7 billion. The World Trade Organization (WTO), of which the United States is a member, provides the institutional framework for conducting international trade, including trade in meat products. WTO member countries agree to a series of rights and obligations that are designed to facilitate global trade. When a country regulates imports, including imported meat, WTO guidelines stipulate that member countries have the right to determine their own "appropriate levels of protection" in their regulations to protect, among other things, human and animal health. Member countries must have a scientific basis to have levels of protection that are higher than international guidelines. To encourage member countries to apply science-based measures in their regulations, WTO relies on the international standards, guidelines, and recommendations that its member countries develop within international organizations, such as the Codex Alimentarius Commission for food safety and the OIE for animal health and the safety of animal products for human consumption.

While ensuring that food products are safe and of high quality usually promotes trade, one country's food safety regulations could be interpreted by another country as a barrier to trade. It is difficult, however, to distinguish between a legitimate regulation that protects consumers but incidentally restricts trade from a regulation that is intended to restrict

[17]See http://www.cdc.gov/drugresistance/actionplan/ (downloaded Apr. 11, 2003).

trade and protect local producers, unless that regulation is scientifically documented.

Antibiotic-Resistant Bacteria Have Been Transferred from Animals to Humans, but Researchers Disagree About the Extent of Potential Harm to Human Health

Research has shown that antibiotic-resistant bacteria have been transferred from animals to humans, but the extent of potential harm to human health is uncertain. Evidence from epidemiologic studies suggests associations between patterns of antibiotic resistance in humans and changes in antibiotic use in animals. Further, evidence from epidemiologic studies that include molecular subtyping to identify specific pathogens has established that antibiotic-resistant campylobacter and salmonella bacteria are transferred from animals to humans. Many of the studies we reviewed found that this transference poses significant risks for human health. Researchers disagree, however, about the extent of potential harm to human health from the transference of antibiotic-resistant bacteria.

Antibiotic-Resistant Bacteria Have Been Transferred from Animals to Humans

Antibiotic-resistant bacteria have been transferred from animals to humans. Evidence that suggests that this transference has taken place is found in epidemiologic studies showing that antibiotic-resistant *E. coli* and campylobacter bacteria in humans increase as use of the antibiotics increases in animals. Evidence that establishes transference of antibiotic-resistant bacteria is found in epidemiologic studies that include molecular subtyping. These studies have demonstrated that antibiotic-resistant campylobacter and salmonella bacteria have been transferred from animals to humans through the consumption or handling of contaminated meat. That is, strains of antibiotic-resistant bacteria infecting humans were indistinguishable from those found in animals, and the researchers concluded that the animals were the source of infection.

Epidemiologic Evidence Suggests That Patterns of Antibiotic Resistance in Humans Are Associated with Changes in Antibiotic Use in Animals

Evidence from epidemiologic studies that do not include molecular subtyping indicates that patterns of antibiotic resistance in humans are associated with changes in the use of particular antibiotics in animals. For example, work conducted in the United States in the 1970s showed an association between the use of antibiotic-supplemented animal feed in a farm environment and the development of antibiotic-resistant *E. coli* in the intestinal tracts of humans and animals.[18] In the study, isolates from chickens on the farm and from people who lived on or near the farm were tested and found to have low initial levels of tetracycline-resistant *E. coli* bacteria. The chickens were then fed tetracycline-supplemented feed, and within 2 weeks 90 percent of them were excreting essentially all tetracycline-resistant *E. coli* bacteria. Within 6 months, 7 of the 11 people who lived on or near the farm were excreting high numbers of resistant *E. coli* bacteria. Six months after the tetracycline-supplemented feed was removed, no detectable tetracycline-resistant organisms were found in 8 of the 10 people who lived on or near the farm when they were retested. Another study,[19] based on human isolates of *Campylobacter jejuni* submitted to the Minnesota Department of Health, reported that the percentage of *Campylobacter jejuni* in the isolates that were resistant to quinolone increased from approximately 0.8 percent in 1996 to approximately 3 percent in 1998.[20]

[18]Stuart B. Levy, George B. Fitzgerald, and Ann B. Macone, "Spread of Antibiotic-Resistant Plasmids from Chicken to Chicken and from Chicken to Man," *Nature*, vol. 260, no. 5546 (1976): 40-42; and Stuart B. Levy, George B. Fitgerald, and Ann B. Macone, "Changes in Intestinal Flora of Farm Personnel after Introduction of a Tetracycline-Supplemented Feed on a Farm," *New England Journal of Medicine*, vol. 295 (1976): 583-588.

[19]Kirk E. Smith, John M. Besser, Craig W. Hedberg, Fe T. Leano, Jeffrey B. Bender, Julie H. Wicklund, Brian P. Johnson, Kristine A. Moore, Michael T. Osterholm, and the investigation team, "Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992-1998," *New England Journal of Medicine*, vol. 340, no. 20 (1999).

[20]These percentages are from isolates from people who acquired the infections in the United States. There was a greater increase in the number of quinolone-resistant human isolates when infections acquired from foreign travel and from people who took fluoroquinolones prior to the collection of stool samples were included. Noting this, the percentage change between 1996 and 1998 of the domestically acquired infections was found to be statistically significant. FDA approved the use of fluoroquinolones in animals in 1995.

There is also evidence to suggest that antibiotic-resistant enterococcus has developed from the use of antibiotics in animals. Vancomycin[21] resistance is common in intestinal enterococci of both exposed animals and nonhospitalized humans only in countries that use or have previously used avoparcin (an antibiotic similar to vancomycin)[22] as an antibiotic growth promoter in animal agriculture.[23] Since the EU banned the use of avoparcin as a growth promoter, several European countries have observed a significant decrease in the prevalence of vancomycin-resistant enterococci in meat and fecal samples of animals and humans.

Evidence Shows That Antibiotic-Resistant Campylobacter and Salmonella Bacteria Have Been Transferred to Humans

Epidemiologic studies that include molecular subtyping have demonstrated that antibiotic-resistant campylobacter and salmonella bacteria have been transferred from animals to humans through the consumption or handling of contaminated meat. That is, strains of antibiotic-resistant bacteria infecting humans were indistinguishable from those found in animals, and the authors of the studies concluded that the animals were the source of infection.

Campylobacter Bacteria

The strongest evidence for the transfer of antibiotic-resistant bacteria from animals to humans is found in the case of fluoroquinolone-resistant campylobacter bacteria. Campylobacter is one of the most commonly identified bacterial causes of diarrheal illness in humans. The strength of the evidence is derived in part from the fact that the particular way fluoroquinolone resistance develops for campylobacter bacteria makes it easier to identify the potential source of the resistance. Most chickens are colonized with campylobacter bacteria, which they harbor in their intestines, but which do not make them sick. Fluoroquinolones are given to flocks of chickens when some birds are found to have certain infections caused by *E. coli*. In addition to targeting the bacteria causing the infection, treatment of these infections with fluoroquinolones almost always replaces susceptible campylobacter bacteria with fluoroquinolone-resistant campylobacter bacteria. Because fluoroquinolone resistance is located on

[21]The antibiotic vancomycin has been reserved to treat infections, such as enterococcus infections, in humans that are resistant to antibiotics normally used for treatment.

[22]Avoparcin has never been approved for food animal use in the United States.

[23]Anthony E. van den Bogaard and Ellen E. Stobberingh, "Epidemiology of Resistance to Antibiotics Links between Animals and Humans," *International Journal of Antimicrobial Agents*, vol. 14 (2000): 327-335.

the chromosome of campylobacter, the resistance is generally not transferred to other species of bacteria. Therefore when fluoroquinolone-resistant campylobacter bacteria are detected in human isolates, the source is likely to be other reservoirs of campylobacter bacteria, including animals. In some cases, molecular subtyping techniques have shown that fluoroquinolone-resistant isolates of campylobacter from food, humans, and animals are similar.

Fluoroquinolone-resistant *Campylobacter jejuni* in humans has increased in the United States and has been linked with fluoroquinolone use in animals. CDC reported that in the United States the percentage of *Campylobacter jejuni* in human isolates that were resistant to fluoroquinolones increased from 13 percent in 1997 to 19 percent in 2001.[24] A study in Minnesota found that fluoroquinolone-resistant *Campylobacter jejuni* was isolated from 14 percent of 91 chicken products obtained from retail markets in 1997.[25] Through molecular subtyping, the strains isolated from the chicken products were shown to be the same as those isolated from nearby residents, thereby bolstering the case that the chickens were the source of the antibiotic resistance.

During the 1980s, the resistance of campylobacter bacteria to fluoroquinolones increased in Europe. European investigators hypothesized that there was a causal relationship between the use of fluoroquinolones in animals and the increase in fluoroquinolone-resistant campylobacter infections in humans. For example, an epidemologic study that included molecular subtyping in the Netherlands found that among different strains of campylobacter bacteria, the percentage of fluoroquinolone-resistant strains in isolates tested had risen from 0 percent in both human and animal isolates in 1982 to 11 percent in human isolates and 14 percent in poultry isolates by 1989.[26] The authors concluded that the

[24]Centers for Disease Control and Prevention, *National Antimicrobial Resistance Monitoring System: Enteric Bacteria 2001 Annual Report* (2003): 10.

[25]Kirk E. Smith, John M. Besser, Craig W. Hedberg, Fe T. Leano, Jeffrey B. Bender, Julie H. Wicklund, Brian P. Johnson, Kristine A. Moore, Michael T. Osterholm, and the investigation team, "Quinolone-resistant *Campylobacter jejuni* Infections in Minnesota, 1992-1998," *New England Journal of Medicine*, vol. 340, no. 20 (1999).

[26]Hubert Ph. Endtz, Gijs J. Ruijs, Bert van Klingeren, Wim H. Jansen, Tanny van der Reyden, and R. Peter Mouton, "Quinolone Resistance in Campylobacter Isolated from Man and Poultry Following the Introduction of Fluoroquinolones in Veterinary Medicine," *Journal of Antimicrobial Chemotherapy*, vol. 27 (1991): 199-208.

use of two new fluoroquinolones, one in humans in 1985 and one in animals in 1987, was responsible for the quinolone-resistant strains. The authors asserted that the extensive use of fluoroquinolones in poultry and the common route of campylobacter infection from chickens to humans suggest that the resistance was mainly due to the use of fluoroquinolones in poultry.

Salmonella Bacteria

Several epidemiologic studies using molecular subtyping have linked antibiotic-resistant salmonella infections in humans, another common foodborne illness, to animals. For example, in 1998 bacteria resistant to ceftriaxone were isolated from a 12-year-old boy who lived on a cattle farm in Nebraska.[27] Molecular subtyping revealed that an isolate from the boy was indistinguishable from one of the isolates from the cattle on the farm. No additional ceftriaxone-resistant salmonella infections were reported in that state or adjoining states that could have been the cause of the infection. Similarly, an epidemiologic study in Poland from 1995 to 1997 using molecular subtyping found identical profiles for ceftriaxone-resistant salmonella bacteria in isolates from poultry, feed, and humans.[28] The researchers concluded that the salmonella infections were introduced in the poultry through the feed and reached humans through consumption of the poultry. Researchers in Taiwan also found that *Salmonella enterica* serotype choleraesuis bacteria that were resistant to ciprofloxacin in isolates collected from humans and swine were closely related and, following epidemiologic studies, concluded that the bacteria were transferred from swine to humans.[29]

[27]Paul D. Fey, Thomas J. Safranek, Mark E. Rupp, Eileen F. Dunne, Efrain Ribot, Peter C. Iwen, Patricia A. Bradford, Frederick J. Angulo, and Steven H. Hinrichs, "Ceftriaxone-Resistant Salmonella Infection Acquired by a Child from Cattle," *New England Journal of Medicine*, vol. 342 (2000): 1242-1249.

[28]Andrzej Hoszowski and Dariusz Wasyl, "Typing of *Salmonella enterica* subsp. *enterica* serovar Mbandaka Isolates," *Veterinary Microbiology,* vol. 80 (2001): 139-148.

[29]Po-Ren Hsueh, Lee-Jene Teng, Sung-Pin Tseng, Chao-Fu Chang, Jen-Hsien Wan, Jing-Jou Yan, Chun-Ming Lee, Yin-Ching Chuang, Wen-Kuei Huang, Dine Yang, Jainn-Ming Shyr, Kwok-Woon Yu, Li-Shin Wang, Jang-Jih Lu, Wen-Chien Ko, Jiunn-Jong Wu, Feng-Yee Chang, Yi-Chueh Yang, Yeu-Jun Lau, Yung-Ching Liu, Cheng-Yi Liu, Shen-Wu Ho, and Kwen-Tay Luh, "Ciprofloxacin-Resistant *Salmonella enterica* Typhimurium and Choleraesuis from Pigs to Humans, Taiwan," *Emerging Infectious Diseases*, vol. 10, no. 1 (2004): 60-68.

Researchers have also documented human infections caused by multidrug-resistant strains of salmonella linked to animals. In 1982, researchers used molecular subtyping to show that human isolates of multidrug-resistant salmonella bacteria were often identical or nearly identical to isolates from animals.[30] In the mid-1990s, NARMS data showed a rapid growth of multidrug resistance in *Salmonella enterica* serotype Typhimurium definitive type (DT) 104 among humans.[31] Molecular subtyping found that human isolates with this strain of multidrug resistance in *Salmonella enterica* serotype Typhimurium DT104 in 1995 were indistinguishable from human isolates with this strain tested in 1985 and 1990. These results indicated that the widespread emergence of multidrug resistance in *Salmonella enterica* serotype Typhimurium DT104 may have been due to dissemination of a strain already present in the United States. Because food animals are the reservoir for most domestically acquired salmonella infections and transmission from animals to humans occurs through the food supply, the researchers concluded that the human infections were likely from the animals.

Recently, there has been an emergence of multidrug-resistant *Salmonella enterica* serotype Newport infections that include resistance to cephalosporins,[32] such as cefoxitin.[33] Based on molecular subtyping, multidrug-resistant salmonella isolates from cattle on dairy farms were found to be indistinguishable from human isolates. An epidemiologic study found that the infections in humans were associated with direct exposure

[30]Thomas F. O'Brien, John D. Hopkins, Elaine S. Gilleece, Antone A. Medeiros, Ralph L. Kent, Billie O. Blackburn, Marion B. Holmes, Joseph P. Reardon, James M. Vergeront, Wendy L. Schell, Eleanor Christenson, Marjorie L. Bissett, and Erskine V. Morse, "Molecular Epidemiology of Antibiotic Resistance in Salmonella from Animals and Human Beings in the United States," *New England Journal of Medicine*, vol. 307, no. 1 (1982): 1-6.

[31]Efrain M. Ribot, Rachel K. Wierzba, Frederick J. Angulo, and Timothy J. Barrett, "*Salmonella enterica* serotype Typhimurium DT104 Isolated from Humans, United States, 1985, 1990, and 1995," *Emerging Infectious Diseases*, vol. 8, no. 4 (2002): 387-391.

[32]Cephalosporins are antibiotics that are commonly used, especially in children, to treat severe salmonella infections.

[33]Amita Gupta, John Fontana, Colleen Crowe, Barbara Bolstorff, Alison Stout, Susan Van Duyne, Mike P. Hoekstra, Jean M. Whichard, Timothy J. Barrett, Frederick J. Angulo, for the National Antimicrobial Resistance Monitoring System PulseNet Working Group, "Emergence of Multidrug-Resistant *Salmonella enterica* Serotype Newport Infections Resistant to Expanded-Spectrum Cephalosporins in the United States," *Journal of Infectious Diseases*, vol. 188 (2003): 1707-1716.

to a dairy farm, and the authors hypothesized that the infections were associated with handling or consuming the contaminated foods.

Many Studies Have Found That Transference of Antibiotic-Resistant Bacteria from Animals to Humans Is a Human Health Risk, but Researchers Disagree About the Extent of Risk

The extent of harm to human health from the transference of antibiotic-resistant bacteria from animals is uncertain. Many studies have found that the use of antibiotics in animals poses significant risks for human health, and some researchers contend that the potential risk of the transference is great for vulnerable populations. However, a small number of studies contend that the health risks of the transference are minimal.

Many Researchers Contend That Antibiotic Use in Animals Poses Significant Risk for Human Health

Some studies have sought to determine the human health impacts of the transference of antibiotic resistance from animals to humans. For example, the Food and Agriculture Organization of the United Nations (FAO), OIE, and WHO recently released a joint report based on the scientific assessment of antibiotic use in animals and agriculture and the current and potential public health consequences.[34] The report states that use of antibiotics in humans and animals alters the composition of microorganism populations in the intestinal tract, thereby placing individuals at increased risk for infections that would otherwise not have occurred. The report also states that use of antibiotics in humans and animals can also lead to increases in treatment failures and in the severity of infection.

Similarly, a recent review of studies regarding increased illnesses due to antibiotic-resistant bacteria found significant differences in treatment outcomes of patients with antibiotic-resistant bacterial infections and patients with antibiotic-susceptible bacterial infections.[35] For example, one study found that hospitalization rates of patients with nontyphoidal salmonella infections were 35 percent for antibiotic-resistant infections and 27 percent for antibiotic-susceptible infections. That study also found

[34]Food and Agriculture Organization of the United Nations, Office International des Epizooties, and World Health Organization, *Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment* (Geneva, Switzerland, Dec. 1-5, 2003).

[35]Karin Travers and Michael Barza, "Morbidity of Infections Caused by Antimicrobial-Resistant Bacteria," *Clinical Infectious Diseases*, vol. 34, suppl. 3 (2002): S131-S134.

that the length of illness was 10 days for antibiotic-resistant infections versus 8 days for antibiotic-susceptible infections. Another study found diarrhea from *Campylobacter jejuni* infections lasted 12 days for antibiotic-resistant infections versus 6 days for susceptible infections. Also, based on this review, the authors estimated that fluoroquinolone resistance likely acquired through animals leads to at least 400,000 more days of diarrhea in the United States per year than would occur if all infections were antibiotic-susceptible. The authors estimated that antibiotic resistance from nontyphoidal salmonella infections mainly arising from animals could account for about 8,700 additional days of hospitalization per year.

Experts are especially concerned about safeguarding the effectiveness of antibiotics such as vancomycin that are considered the "drugs of last resort" for many infections in humans. Evidence suggests that use of the antibiotic avoparcin in animals as a growth promoter may increase numbers of enterococci that are resistant to the similar antibiotic vancomycin. A particular concern is the possibility that vancomycin-resistant enterococci could transfer resistance to other bacteria. Some *Staphylococcus aureus* infections found in hospitals are resistant to all antibiotics except vancomycin, and human health can be adversely affected, as treatment could be difficult, if not impossible, if these strains develop resistance to vancomycin, too. Recently, two human isolates of *Staphylococcus aureus* were found to be resistant to vancomycin.

With the increase in infections that are resistant to vancomycin, the streptogramin antibiotic quinupristin/dalfopristin (Q/D, also known as Synercid) has become an important therapeutic for life-threatening vancomycin-resistant enterococcus infections.[36] Virginiamycin, which is similar to Q/D, has been used in animals since 1974, and Q/D was approved for human use in 1999. NARMS data from 1998 to 2000 indicate that Q/D-resistant *Enterococcus faecium* has been found in chicken and ground pork purchased in grocery stores, as well as in human stools.[37] Experts hypothesize that use of virginiamycin in poultry production has led to Q/D-resistant bacteria in humans because the antibiotics are very similar, but the human health consequences of this have not been quantified.[38]

Experts are also concerned about risks to vulnerable populations such as individuals with compromised immune systems or chronic diseases, who are more susceptible to infections, including antibiotic-resistant infections. For example, salmonella infections are more likely to be severe, recurrent, or persistent in persons with human immunodeficiency virus (HIV). Another concern is that people with resistant bacteria could inadvertently spread those bacteria to hospitalized patients, including those with weakened immune systems.

[36]Vancomycin-resistant enterococcus infections are easily transmitted in health care settings and are difficult to treat.

[37]J. McClellan, K. Joyce, S. Rossiter, T. Barrett, F. J. Angulo, and the NARMS Enterococci Working Group, "High-Level Gentamicin Resistant Enterococci and Quinupristin/Dalfopristin Resistant *E. faecium* from Ground Pork Purchased from Grocery Stores" (paper presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy annual meeting, Chicago, Ill., 2001), and K. Gay, K. Joyce, J. Stevenson, F. Angulo, T. Barrett, and the NARMS Working Group, "Quinupristin/Dalfopristin-Resistant *Enterococcus faecium* Isolated from Human Stools, Retail Chicken, and Retail Pork: EIP Enterococci Project" (paper presented at the International Conference on Emerging Infectious Diseases, Atlanta, Ga., March 2002).

[38]Joshua R. Hayes, Angela C. McIntosh, Sadaf Qaiyumi, Judith A. Johnson, Linda L. English, Lewis E. Carr, David D. Wagner, and Sam W. Joseph, "High-Frequency Recovery of Quinupristin-Dalfopristin-Resistant *Enterococcus faecium* Isolates from the Poultry Production Environment," *Journal of Clinical Microbiology*, vol. 39, no. 6 (2001): 2298-2299; and D. L. Smith, J. A. Johnson, A. D. Harris, J. P. Furuno, E. N. Perencevich, and J. G. Morris Jr., "Assessing Risks for a Pre-Emergent Pathogen: Virginiamycin Use and the Emergence of Streptogramin Resistance in *Enterococcus faecium*," *The Lancet Infectious Diseases*, vol. 3 (2003): 241-249.

Other Researchers Contend That Evidence of Human Health Risk from Antibiotic Use in Animals Is Lacking

Although it is generally agreed that transference is possible, some researchers contend that the health risks of the transference are minimal.[39] Proponents of this view note that not all studies have shown an increase in antibiotic-resistant bacteria. For example, one study conducted between 1997 and 2001 found no clear trend toward greater antibiotic resistance in salmonella bacteria.[40]

Proponents of this view also assert that restricting the use of antibiotics in animal agriculture could lead to greater levels of salmonella and campylobacter bacteria reaching humans through meat, thus increasing the risk of human infections. Conversely, some of these researchers also argue that the risk to humans of acquiring these infections from animals can be eliminated if meat is properly handled and cooked. They also cite a few studies that have concluded that the documented human health consequences are small. For example, they noted that one study estimated that banning the use of virginiamycin in animals in the U.S. would lower the number of human deaths by less than one over 5 years.[41]

[39]I. Phillips, M. Casewell, T. Cox, B. De Groot, C. Friis, R. Jones, C. Nightingale, R. Preston, and J. Waddell, "Does the Use of Antibiotics in Food Animals Pose a Risk to Human Health? A Critical Review of Published Data," *Journal of Antimicrobial Chemotherapy*, vol. 53, no. 1 (2004): 28-52.

[40]Jennifer M. Stephen, Mark A. Toleman, Timothy R. Walsh, Ronald N. Jones, and the SENTRY Program Participants Group, "*Salmonella* Bloodstream Infections: Report from the SENTRY Antimicrobial Surveillance Program (1997-2001)," *International Journal of Antimicrobial Agents*, vol. 22 (2003): 395-405.

[41]I. Phillips, M. Casewell, T. Cox, B. De Groot, C. Friis, R. Jones, C. Nightingale, R. Preston, and J. Waddell, "Does the Use of Antibiotics in Food Animals Pose a Risk to Human Health? A Critical Review of Published Data," *Journal of Antimicrobial Chemotherapy*, vol. 53, no. 1 (2004): 42.

Federal Agencies Have Increased Surveillance of Antibiotic Resistance from Animals to Assess Human Health Risk; Effectiveness of Risk Reduction Efforts Is Not Yet Known

FDA, CDC, and USDA have increased their surveillance activities related to antibiotic resistance in animals, humans, and retail meat since beginning these activities in 1996. New programs have been added, the number of bacteria being studied has increased, and the geographic coverage of the sampling has been expanded. In addition, all three agencies have sponsored research on the human health risk from antibiotic resistance in animals. FDA has taken several recent actions to minimize the human health risk of antibiotic resistance from animals, but the effectiveness of its actions is not yet known. These activities include administrative action to prohibit the use of the fluoroquinolone enrofloxacin (Baytril) for poultry and the development of a recommended framework for conducting qualitative risk assessments of all new and currently approved animal drug applications with respect to antibiotic resistance and human health risk.

Federal Surveillance Activities for Antibiotic Resistance in Animals and Humans Have Increased

FDA, CDC, and USDA have six surveillance activities ongoing to identify and assess the prevalence of resistant bacteria in humans, animals, or retail meat. (See table 1.) Since 1996, these activities have expanded to include additional bacteria, greater geographic coverage, and new activities. Two of these activities—NARMS and Collaboration in Animal Health, Food Safety and Epidemiology (CAHFSE)—focus on antibiotic resistance from animals. The other four activities—Foodborne Diseases Active Surveillance Network (FoodNet), PulseNet, PulseVet, and National Animal Health Monitoring System (NAHMS)—focus on foodborne disease or animal health in general, not antibiotic resistance, but are nevertheless relevant to issues of antibiotic resistance. Figure 3 shows how these different surveillance activities provide data about various aspects of antibiotic resistance.

Table 1: Federal Surveillance Activities Related to Antibiotic Resistance and Foodborne Disease or Animal Health

Activity	Purpose	Lead agency	Bacteria	Source of bacteria isolates
Focus on antibiotic resistance				
National Antimicrobial Resistance Monitoring System—Enteric Bacteria (NARMS)	To monitor antimicrobial resistance among foodborne bacteria isolated from humans, animals, and retail foods and perform research to further evaluate resistance, including molecular analysis, and develop special projects to better understand resistance. Implement response activities to mitigate the resistance and perform epidemiologic studies.	CDC (Human NARMS)	• *Salmonella* Typhi • non-Typhi *Salmonella* • *Campylobacter* • *E. coli* O157:H7 • *Enterococcus* • *Shigella*	Humans
		USDA (Animal NARMS)	• Non-Typhi *Salmonella* • *Campylobacter* • generic *E. coli* • *Enterococcus*	Animals: on farm, diagnostic, slaughter/ processing
		FDA (Retail Meat NARMS)	• Non-Typhi *Salmonella* • *Campylobacter* • generic *E. coli* • *Enterococcus*	Retail samples of ground beef, ground turkey, pork chops, chicken breasts[a]
Collaboration in Animal Health, Food Safety and Epidemiology (CAHFSE)	To assess the presence of bacteria, relate the onset and duration of infection with antibiotic use patterns in animals, and describe on-farm trends in the prevalence of bacteria.	USDA	• *Salmonella* • *Campylobacter* • generic *E. coli* • *Enterococcus*	Swine (on farm), expanding to include slaughter/processing
Focus on foodborne disease or animal health				
Foodborne Diseases Active Surveillance Network (FoodNet)	To determine the incidence of foodborne diseases, monitor foodborne disease trends, and determine the proportion of foodborne diseases attributable to specific foods and settings.	CDC	• *Salmonella* • *Campylobacter* • Shigatoxin-producing *E. coli* (e.g., *E. coli* O157:H7) • *Shigella* • *Listeria* • *Vibrio* • *Yersinia* • *Cryptosporidium* • *Cyclospora*	Humans
PulseNet	To provide data on the extent and relatedness of outbreaks and individual isolates of foodborne disease.	CDC	• Non-Typhi *Salmonella* • *E. coli* O157:H7 • *Listeria* • *Shigella* • *Campylobacter*	Humans and food[b]
PulseVet	To conduct DNA fingerprinting of animal bacteria.	USDA	• *Salmonella*	Animals from slaughter/processing

(Continued From Previous Page)

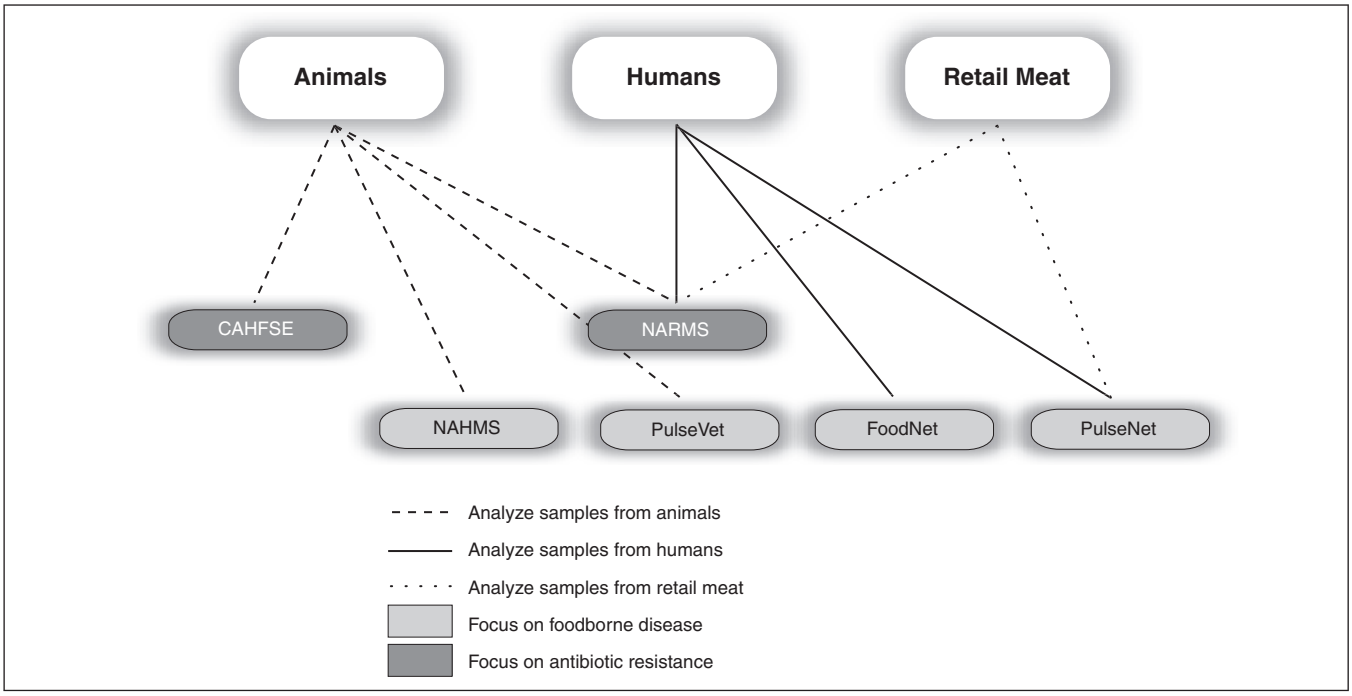
Activity	Purpose	Lead agency	Bacteria	Source of bacteria isolates
National Animal Health Monitoring System (NAHMS)	To collect, analyze, and disseminate data on animal health, management, and productivity.	USDA	• *Salmonella*	Animals on farm

Source: GAO.

[a]The retail meat program of NARMS, with USDA, will also look at susceptibilities of recovered *E. coli* and salmonella bacteria obtained from their produce surveys.

[b]PulseNet includes any type of food, not just retail meat.

Figure 3: Sources of Data from Surveillance Activities about Antibiotic Resistance and Foodborne Disease or Animal Health



Source: GAO.

Note: CAHFSE = Collaboration in Animal Health, Food Safety and Epidemiology; NARMS = National Antimicrobial Resistance Monitoring System—Enteric Bacteria; NAHMS = National Animal Health Monitoring System; FoodNet = Foodborne Diseases Active Surveillance Network.

NARMS and CAHFSE Focus on Antibiotic Resistance

NARMS monitors changes in susceptibilities of bacteria in humans and animals to antibiotics. To assess the extent of changes in levels of resistance, NARMS collects animal and human isolates of six different bacteria, specifically non-Typhi *Salmonella*, *Campylobacter*, *E. coli*, *Enterococcus*, *Salmonella* Typhi, and *Shigella*.[42] These activities are conducted under three independent, yet coordinated, programs, with FDA serving as the funding and coordinating agency. The human program gathers isolates from humans and is led by CDC. The animal program, led by USDA, gathers isolates from animals on farms, from slaughter and processing plants, and from diagnostic laboratories. The retail meat program gathers samples of meat purchased at grocery stores and is run by FDA. The agencies work together to standardize results through ongoing quality control efforts.

NARMS has expanded in three major ways—range of bacteria tested, geographic coverage, and number of programs—since it was established in 1996. For example, human NARMS started by looking at two bacteria and now studies six bacteria.[43] Further, NARMS also assessed the potential of other bacteria to become sources of resistance by collecting and assessing listeria and vibrio isolates in pilot studies.[44] With regard to geographic coverage, the number of participating health departments has increased from 14 state and local health departments in 1996 to all 50 states and Washington, D.C., in 2003.[45] Finally, the retail meat program was added in 2002. Initially, 5 states participated in the retail meat program, but by 2004, 10 states were participating. Despite this recent expansion, all of NARMS experienced budget cuts in fiscal year 2004, calling into question future expansion efforts. For example, the USDA budget for the animal program was cut 17.6 percent for 2004.

[42]Two of the bacteria studied in NARMS—*Salmonella* Typhi and *Shigella*—do not occur in food animals but are acquired by humans as a result of poor hygiene. As a result, they are not tested in the animal or retail meat programs of NARMS.

[43]NARMS began testing human non-Typhi salmonella and *E. coli* O157:H7 isolates. As of early 2004, NARMS tests *Salmonella* Typhi, non-Typhi salmonella, *E. coli*, campylobacter, enterococcus, and shigella isolates.

[44]Because little antibiotic resistance was found in these isolates, these bacteria are no longer tested for antibiotic susceptibility.

[45]In 1999, testing of campylobacter isolates was limited to seven of these departments. By 2003, 10 states were participating in campylobacter testing.

NARMS has also produced collaborative research efforts among FDA, CDC, and USDA and helped further scientific understanding of antibiotic resistance. For example, data from NARMS led CDC to conclude that the proportion of campylobacter isolates resistant to ciprofloxacin in 2001 was 2.4 times higher than in 1997.[46] Similarly, FDA and CDC officials reported that NARMS data were used to evaluate antibiotic resistance to fluoroquinolones, and CDC officials told us that after NARMS data showed an increased number of cases of *Salmonella* Newport infections in humans, researchers at CDC and USDA shared human and animal isolates to determine whether the same pattern existed in animals.

CAHFSE, established by USDA in 2003, collects samples from animals on farms to identify changes in antimicrobial resistance over time. The first animals that are being tested in the program are swine. USDA conducts quarterly sampling of 40 fecal and 60 blood samples from animals from farms in four states. As of March 2004, 40 farms were participating in CAHFSE. In addition to the laboratory analyses, there are plans for risk analyses, epidemiologic studies, and field investigations, as well as analysis of samples collected at slaughter, and the addition of more species, funding permitted.

Other Activities Focus on Foodborne Disease or Animal Health

FoodNet, PulseNet, PulseVet, and NAHMS focus on foodborne disease or animal health rather than antibiotic resistance. FoodNet, the principal foodborne disease component of CDC's Emerging Infections Program, is a collaborative project with 10 states (referred to as FoodNet sites), USDA, and FDA.[47] The goals of FoodNet are to determine the incidence of foodborne diseases, monitor foodborne disease trends, and determine the proportion of foodborne diseases attributable to specific foods and settings. FoodNet data are derived from specimens collected from patients. Isolates from these specimens are sent to NARMS for susceptibility testing. CDC officials reported that one of every 20 patients with a specimen in FoodNet also has an isolate in NARMS.

A recent development has been the linking of the NARMS and FoodNet data systems. For example, FoodNet data can be used to determine

[46]CDC, *National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): 2001 Annual Report*, Atlanta, Ga: HHS, CDC, 2003.

[47]CDC officials reported that USDA and FDA provide one-third of the funding for FoodNet, and the agencies and states each have representatives on FoodNet's steering committee.

whether an individual was hospitalized, and NARMS data can reveal whether the bacteria that infected the person were resistant to antibiotics. CDC officials reported that because of the linked databases, they were able to determine whether, for example, someone with an antibiotic-resistant salmonella infection was more likely to be hospitalized than someone with an antibiotic-susceptible salmonella infection. FoodNet also has a role in the retail meat program of NARMS. The FoodNet sites purchase the meat samples from grocery stores, examine the samples for the prevalence or frequency of bacterial contamination, and forward isolates of the bacteria to FDA for susceptibility testing for antibiotic resistance.

PulseNet is CDC's early warning system for outbreaks of foodborne disease. USDA recently established a similar animal program, called PulseVet. PulseNet studies isolates from humans and suspected food, and PulseVet studies isolates from animals.[48] Both PulseNet and PulseVet conduct DNA fingerprinting of bacteria[49] and compare those patterns to other samples in order to identify related strains. The PulseNet and PulseVet isolates are tested for antibiotic resistance at CDC and USDA, respectively. FDA also performs DNA fingerprinting on salmonella and campylobacter isolates obtained from the retail meat program of NARMS and submits these data to PulseNet.

NAHMS, which focuses on healthy animals, was initiated by USDA in 1983 to collect, analyze, and disseminate data on animal health, management, and productivity across the United States. Since 1990, USDA has annually conducted studies on animal health, including information about antibiotic use, through NAHMS. Each study focuses on different animals, including swine, cattle (both dairy and beef), and sheep. NAHMS provides only a snapshot of a particular species or commodity; it does not track changes over time. While NAHMS contributes information about healthy animals, a USDA official told us that it also includes information about antibiotics used and may include information on the route of administration and the reason for treatment, which can be useful in further understanding NARMS findings. In addition, researchers and veterinarians are able to access the NAHMS database for studies of disease incidence, risk assessment, and

[48]PulseNet fingerprints salmonella, *E. coli*, listeria, and shigella isolates, and PulseVet fingerprints salmonella and plans to include, as funding allows, campylobacter, enterococcus, and generic *E. coli* isolates.

[49]DNA fingerprinting is performed through genetic relatedness studies using pulsed-field gel electrophoresis.

preventive treatment techniques. Further, bacteria samples obtained from NAHMS have been added to the NARMS database.

Federally Funded Research Is Under Way to Study the Human Health Risk of Antibiotic Resistance in Food Animals

Under the federal Interagency Task Force on Antimicrobial Resistance action plan, FDA, CDC, and USDA have initiated a number of research efforts that are relevant to antibiotic use in animals and human health. These ongoing research efforts focus on defining the effects of using various animal drugs on the emergence of antibiotic-resistant bacteria and identifying risk factors and preventive measures. Through CDC, FDA currently has cooperative agreements with four veterinary schools to study ways to reduce antibiotic-resistant bacteria in animals and is assessing the prevalence of antibiotic-resistant DNA in feed ingredients.[50] In addition, FDA annually issues a 3-year research plan that describes research focusing on, among other things, antibiotic resistance in animals and its consequences for human health. Current studies include efforts to examine the consequences of antibiotic use in animals, the transmission of antibiotic resistance, and the processes underlying the spread of antibiotic resistance. In total, CDC has funded three projects under its Antimicrobial Resistance Applied Research extramural grant program. One of these grants, for example, is to study the prevalence of antibiotic-resistant *E. coli* in chicken and ground beef products, examine the risk factors for human colonization with a resistant strain of *E. coli*, and compare characteristics of antibiotic-susceptible and antibiotic-resistant isolates from meat with those of antibiotic-susceptible and antibiotic-resistant isolates from humans. Similarly, USDA has funded studies of antibiotic resistance in chicken, turkey, pork, and dairy products. These studies have provided additional sources of isolates to FDA for risk assessment purposes. Also, USDA's Cooperative State Research, Education, and Extension Service has funded over 30 studies related to antibiotic resistance since 2000 and awarded an additional $8 million in grants in 1999 and 2000. Funded research includes studies on the prevalence, development, and possible transmission of antibiotic resistance; the epidemiology of antibiotic resistance; and the evaluation of management practices and potential prevention/intervention strategies for antibiotic resistance.

[50]Animal feeds may include animal products or parts which have DNA. For example, cattle feed, may include blood and blood products, among others. *See* 21 C.F.R. §§ 589.2000(a)(1),(7),(b)(2003).

FDA Has Taken Action to Minimize the Potential Human Health Risk of Antibiotic Resistance from Animals, but It Is Too Early to Determine Effectiveness

FDA has taken a variety of actions to minimize the risk to the public health of antibiotic resistance in humans resulting from the use of antibiotics in animals, although it is still too early to determine the effectiveness of these actions. First, FDA has taken action to prohibit the use of an already approved animal drug for poultry because of concerns about human health risk. Second, the agency developed a recommended framework for reviewing all new animal antibiotic applications with respect to antibiotic resistance and human health risk. Third, FDA has begun reviewing antibiotics currently approved for use in animals according to its new framework to determine whether FDA needs to act to ensure that the drugs are safe. It is too early to determine the effectiveness of FDA's review of currently marketed drugs. FDA has not made drugs used in animals that are critically important for human health its top priority for review, and any remedial actions pursued by the agency may take years to complete.

FDA Has Initiated Action to Prohibit the Use of Enrofloxacin in Poultry, but Proceedings Not Yet Complete

On October 31, 2000, FDA proposed withdrawing the approval of enrofloxacin (Baytril), a fluoroquinolone drug used in poultry,[51] after human health risks associated with the use of the drug in chickens and turkeys were documented by, among others, NARMS. Enrofloxacin is administered to flocks of poultry in their water supply to control mortality associated with *E. coli* and *Pasteurella multocida* organisms. FDA had found that new evidence, when evaluated with information available when the application was approved, demonstrated that enrofloxacin used with poultry flocks has not been shown to be safe for humans. Specifically, FDA determined that the use of enrofloxacin in poultry causes the development of a fluoroquinolone-resistant strain of campylobacter in poultry, which, when transferred to humans, is a significant cause of fluoroquinolone-resistant campylobacter infections in humans.

Before proceeding with formal efforts to withdraw approval for use of enrofloxacin with poultry flocks, FDA considered a number of alternative actions. For example, the agency determined that changing the label to limit use to the treatment of individual birds and limiting use to one time or one treatment per individual bird were impractical. The agency also considered and rejected the establishment of a registry that would require veterinarians to demonstrate the need for the drug. FDA proceeded with its efforts to withdraw approval of enrofloxacin for use in poultry because

[51] 65 *Fed. Reg.* 64954 (Oct. 31, 2000). There were two fluoroquinolones approved at that time: sarafloxacin hydrochloride and enrofloxacin.

FDA knew that there were alternative effective drugs for treating these illnesses in poultry.

In February 2002, FDA announced that a hearing would be held on the proposal to withdraw approval of enrofloxacin.[52] Since FDA's proposed action to ban the use of enrofloxacin in poultry, representatives of both FDA and Bayer, the manufacturer of Baytril, as well as numerous experts, have provided testimony on the question of its safety. Submission of written testimony was due in December 2002, and cross-examination of witnesses took place from late April 2003 through early May 2003. The final posthearing briefs and responses were delivered in July and August 2003. On March 16, 2004, an FDA administrative law judge issued an initial decision withdrawing the approval of the new animal drug application for Baytril. This decision will become final unless it is appealed to the FDA Commissioner by Bayer or another participant in the case or the Commissioner chooses to review it on his own initiative.[53] If the Commissioner reviews and upholds the initial decision, Bayer or another participant may choose to appeal in court.[54]

Effectiveness of FDA's Framework for Reviewing New Animal Drugs Is Not Yet Known

FDA has determined that the human health risk from antibiotic use in animals is not acceptable, and the agency may initiate risk management strategies to contain such risk. In October 2003, as part of its efforts to approve and regulate animal drugs, FDA issued Guidance for Industry #152. The guidance outlines a framework for determining the likelihood that an antibiotic used to treat an animal would cause an antibiotic resistance problem in humans who consume meat or other food products from animals. The guidance's risk assessment framework is based on three factors—the probability that resistant bacteria are present in the target animal, the probability that humans would ingest the bacteria in question from the relevant food commodity, and the probability that human exposure to resistant bacteria would result in an adverse health consequence. The resulting overall risk estimate is ranked as high, medium, or low.

[52]After the original notice of FDA's plans to withdraw approval of enrofloxacin for poultry, the only other manufacturer of an approved fluoroquinolone for poultry, Abbott Laboratories, voluntarily requested withdrawal of the approval for its drug sarafloxacin hydrochloride (SaraFlox).

[53]The only other participant in the case is the Animal Health Institute.

[54]*See* 21 C.F.R. §§ 12.120-12.140(2003).

Because the guidance is new, it is not yet known how the results of a risk assessment conducted according to the guidance will influence FDA's decisions to approve new drug applications. Agency officials told us that FDA has never denied a new or supplemental animal drug application because of evidence that the drug caused antibiotic resistance in humans. In addition, the risk assessment guidance states that drugs with high risk may still be approved, though with specific use restrictions, if there is a reasonable certainty of no harm to human health when the drug is approved. These restrictions might include availability only by prescription, restrictions on uses not specified on the label (known as extralabel use), limitations for use in individual animals (versus groups of animals) for fewer than 21 days, and requirements for postapproval monitoring. FDA has previously used these kinds of restrictions with some drugs. While agency officials told us that the extralabel use prohibitions for animal drugs have generally reduced unauthorized use, such use restrictions may not prevent human health risk. For example, while FDA had earlier limited fluoroquinolones to use by or under the order of a veterinarian and prohibited the extralabel use of fluoroquinolones, the agency has now concluded that a human health risk exists despite these restrictive measures.

FDA officials reported that the agency has reviewed about seven new drug applications using the risk assessment framework in Guidance for Industry #152. Some of those drugs have been approved. Other drugs have been approved but with label claims different from those requested in the application. FDA officials have not denied approval to any of these new drug applications.

Timing and Effectiveness of FDA Plans to Review Currently Marketed Animal Antibiotics for Human Health Risk Are Uncertain

To determine whether future regulatory actions may be necessary, FDA is conducting risk assessments for drugs currently used in animal agriculture that are also important for human medicine. FDA began with two quantitative risk assessments for drugs ranked as critically important for human health at the time the assessments were initiated. FDA completed the assessment for fluoroquinolones in October 2000 and expects to complete the assessment for virginiamycin, a streptogramin drug related to Synercid, its counterpart for humans, in 2004.[55] The quantitative risk assessments calculate estimates of the number of cases of infection. Agency officials told us that they had hoped that the quantitative risk assessment approach would provide a template for future risk assessments. However, FDA decided that it did not.

FDA officials told us that as a result, the agency plans to review other currently marketed antibiotics using the qualitative risk assessment framework outlined in Guidance for Industry #152, which uses broad categories to assess risk. An FDA official reported that if the information necessary to complete any section of the qualitative risk assessment were unavailable, the agency would assign a higher score to the product, to err on the side of caution. After outlining possible risk management steps, if any, the agency would allow a drug's sponsor (generally pharmaceutical firms) to provide additional information to help FDA reconsider its risk estimate. Generally, these qualitative risk assessments are considered to be a starting point for examining human health risk for some drugs.

[55]Virginiamycin is no longer considered a critically important drug. Synercid, was the first antibiotic approved for the treatment of vancomycin-resistant *Enterococcus faecium* bacteremia and was the only drug available for treatment when the risk assessment began. Since that time, other drugs have been developed, and the status of virginiamycin has been reduced from critically important to highly important for human health.

FDA has not made drugs that are critically important for human health its top priority for review.[56] (See app. III for more detail on evaluating the importance of an animal drug for human health.) Instead, the agency focused its first qualitative risk assessments on subtherapeutic penicillin and tetracycline drugs.[57] These assessments are expected to be completed by April 2004. FDA officials told us that the agency will then conduct qualitative risk assessments for therapeutic penicillin and tetracycline drugs, followed by assessments for those drugs that are defined in Guidance for Industry #152 as critically important for human health. As of March 2004, there were four such categories of drugs.[58]

For a number of reasons, it is not known whether FDA's new framework for reviewing currently approved and marketed animal drugs will be able to effectively identify and reduce any human health risk. First, under this plan, it may take years for FDA to identify and reduce any human risk of acquiring antibiotic resistance from meat. FDA has not developed a schedule for conducting the qualitative risk assessments on the currently approved drugs, and the assessments may take a significant amount of time to complete. For example, based on the current schedule, FDA officials told us they expect the qualitative risk assessment of subtherapeutic penicillins and tetracyclines, which were begun in 2002, to take nearly 2 years to complete. Second, FDA officials told us that the risk estimation from the qualitative risk assessments will only use data already available in the original new drug application and any supplemental drug applications, rather than actively seeking new evidence. However, FDA told us that new evidence was an important factor in its risk assessment of fluoroquinolones. Finally, while FDA can pursue a number of enforcement options if its reviews uncover a human health risk, it is not known if they will be effective or how long it will take for such changes to take effect. As the enrofloxacin case demonstrates, risk management strategies may not mitigate human health risk, and administrative proceedings can extend for

[56]FDA has rated classes of animal drugs as critically important, highly important, or important to human health.

[57]Subtherapeutic drugs are typically used to enhance growth rates or improve feed efficiency.

[58]Categories of drugs identified in Guidance for Industry #152 as critically important for human health include third-generation cephalosporins, fluoroquinolones, macrolides, and trimethoprim/sulfamethoxazole.

several years after FDA decides to take enforcement action.[59] An FDA official also told us that if the drug sponsor voluntarily cooperates in implementing risk management strategies, lengthy administrative proceedings may be avoided.

Federal Agencies Do Not Collect Data Needed to Address the Risk of Antibiotic Resistance Associated with Use in Animals

Although they have made some progress in monitoring antibiotic resistance associated with antibiotic use in animals, federal agencies do not collect data on antibiotic use in animals that are critical to supporting research on the human health risk. Data on antibiotic use would allow agencies to link use to the emergence of antibiotic-resistant bacteria, help assess the risk to human health, and develop strategies to mitigate resistance. FDA and USDA do not collect these data because of costs to the industry and other factors. Countries that collect antibiotic use data, depending on the amount and type of data collected, have been able to conduct more extensive research than U.S. agencies.

Federal Agencies Do Not Collect Needed Data

According to FDA, CDC, and USDA, more data are needed on antibiotic use in animals in order to conduct further research on antibiotic resistance associated with this use. In particular, FDA has stated that it needs information on the total quantity of antibiotics used in animals, by class; the species they are used in; the purpose of the use, such as disease treatment or growth promotion; and the method used to administer the antibiotic. WHO and OIE have also recommended that countries collect such data. This information could be used for the following:

- *To link antibiotic use to emerging strains of antibiotic-resistant bacteria.* Antibiotic use information would clarify the relationship between resistance trends in NARMS and the actual use of antibiotics. For example, detailed on-farm data on antibiotic use and other production practices that are linked to bacteria samples from animals could help identify the conditions under which resistant bacteria develop.

[59]By law, the Secretary of HHS can also determine that there is an imminent hazard from an animal drug. In such cases, the authority to market the drug could be immediately suspended pending challenges from the manufacturer. 21 U.S.C. §360b(e)(2000).

- *To help assess risk to human health.* Information on antibiotic use would help assess the likelihood that humans could be exposed to antibiotic-resistant bacteria from animals. This potential exposure is important in determining the risk that antibiotic use in animals may pose to human health.

- *To develop and evaluate strategies to mitigate resistance.* Data on antibiotic use would help researchers develop strategies for mitigating increased levels of resistant bacteria in animals, according to CDC officials. Strategies could be developed based on such factors as the way the drug is administered, dosage levels, or use in a particular species. In addition, unless data are available for monitoring the effects of these interventions, researchers cannot assess the strategies' effectiveness.

FDA recognizes that additional data on antibiotic use in animal production would facilitate research on the linkages to human resistance. To that end, FDA had considered a plan that would have required pharmaceutical companies to provide more detailed information on antibiotics distributed for use in animals.[60] This information would have been reported as a part of FDA's ongoing monitoring of these antibiotics after their approval. However, according to FDA officials, this more detailed reporting would have resulted in significant costs to the pharmaceutical industry.[61] Consequently, FDA is analyzing other options to minimize the burden to the industry.

In addition, the information that USDA collects through NAHMS is of limited use for supporting research on the relationship between antibiotic use in animals and emerging antibiotic-resistant bacteria. NAHMS was not designed to collect antibiotic use data; instead, as previously discussed, its main goal is to provide information on U.S. animal health, management, and productivity. Through NAHMS, USDA does collect some data on

[60]In addition, the Animal Health Institute—a trade association representing veterinary pharmaceutical manufacturers—publishes yearly information on the total quantity of animal antibiotics sold by its members. The Animal Health Institute's members account for about 85 percent of animal drug sales in the United States. Its reports present the data by antibiotic class and groups certain classes together. The data include amounts sold for both livestock and pets and are not separated by species.

[61]According to Animal Health Institute officials, many manufacturers sell antibiotics to wholesale distributors or feed mills and cannot provide the details on the end use of their products. In addition, certain antibiotics are authorized for use in multiple species and for multiple purposes.

antibiotic use, but only periodically and only for certain species. For example, it has studied the swine industry every 5 years since 1990 but has not yet studied broiler chickens—the most common type of poultry Americans consume.

USDA's Collaboration in Animal Health, Food Safety and Epidemiology (CAHFSE) is a new program designed to enhance understanding of bacteria that pose a food safety risk. USDA plans to monitor, over time, the prevalence of foodborne and other bacteria, as well as their resistance to antibiotics on farms and in processing plants. These data are expected to facilitate research on the link between agricultural practices, such as the use of antibiotics, and emerging resistant bacteria. Currently, however, CAHFSE does not provide information on the impact of antibiotic use for species such as poultry and cattle and for a significant portion of the swine industry. According to USDA, CAHFSE funding comes primarily from a limited amount of funding that is redirected from other USDA programs, and the program would need additional funding before it could expand to cover processing plants, more swine operations, or other species. USDA officials told us they plan to coordinate data collection and analysis efforts for CAHFSE with NARMS activities at FDA and CDC.

According to the officials we spoke with at market research firms, private companies also collect some data on antibiotic use, but this information is developed for commercial purposes and is not always available for public research. These companies collect information on animal production practices, including antibiotic use, and sell this information to producers, who use it to compare their production costs and practices with those of other producers. They also sell these data to pharmaceutical companies, which use the information to estimate the future demand for their products. In any case, the market research firms do not design their data collection efforts to assist research on antibiotic resistance.

Other Countries Collect Data That Are Useful for Conducting Research on Antibiotic Use and Developing Strategies to Mitigate Antibiotic Resistance

Unlike the United States, other countries, such as Denmark, New Zealand, and the United Kingdom, collect more extensive data on antibiotic use in animals. Among the countries we examined, Denmark collects the most comprehensive and detailed data, including information on the quantities of antibiotics used in different animal species by age group and method of administration. According to Danish researchers, these data have allowed them to take the following actions:

- *Link antibiotic use in animals to emerging strains of antibiotic-resistant bacteria*. Danish researchers have been able to determine how changes in the consumption of antibiotics in animals affect the occurrence of antibiotic-resistant bacteria. In addition, researchers began collecting additional data on antibiotic-resistant bacteria in humans in 2002, allowing them to explore the relationship between levels of antibiotic-resistant bacteria in animals, food, and humans.

- *Develop strategies to mitigate resistance*. By monitoring trends in antibiotic use and levels of antibiotic-resistant bacteria, Denmark has been able to adjust national veterinary use guidelines and revised regulations to minimize potential risk to human health.

Other countries, such as New Zealand and the United Kingdom, have data collection systems that are not as comprehensive as Denmark's. Nevertheless, these nations collect data on total sales for antibiotics used in animals by class of antibiotic. The United Kingdom is also working to more accurately track the sales of antibiotics for use in different species. These data show trends in use over time and identify the importance of different antibiotic classes for the production of livestock and poultry. According to the official responsible for the United Kingdom's data collection system, collecting these data requires few resources. In addition, Canadian officials told us Canada is collecting some data on antibiotic use on farms and expects to collect data on sales of antibiotics used in animals. Canada also plans to develop comprehensive methods to collect use data and integrate these data into its antibiotic resistance surveillance system. According to Canada's first annual report on antibiotic resistance, issued in March 2004, its next annual report will include some information on antibiotic use in animals. See appendix IV for information on other countries' data collection systems.

The United States and Its Key Trading Partners and Competitors Differ in the Restrictions They Place on the Use of Antibiotics in Animals

The United States and several of its key trading partners, such as Canada and South Korea, and its competitors, such as the EU, differ in their use of antibiotics in animals in two important areas: the specific antibiotics that can be used for growth promotion and the availability of antibiotics to producers (by prescription or over the counter).[62]

With respect to growth promotion in animals, the United States, as well as Australia, Canada, Japan, and South Korea, allow the use of some antibiotics from classes important in human medicine.[63] However, the United States and Australia are currently conducting risk assessments to determine whether to continue to allow the use of some of these antibiotics for growth promotion. Canada plans to conduct similar risk assessments, and Japan is reviewing the use of antibiotics for growth promotion if those antibiotics are from classes used in humans. In contrast, New Zealand has completed its risk assessments of antibiotics used for growth promotion and no longer allows the use of any antibiotics for growth promotion that are also related to antibiotics used in human medicine. Similarly, the EU has prohibited its member countries from using antibiotics in feed for growth promotion if those antibiotics are from antibiotic classes used in human medicine. In addition, the EU has issued a regulation that will prohibit the use of all other antibiotics in feed for growth promotion by 2006.[64]

We found differences among the United States' and other countries' use of antibiotics for growth promotion in the following four antibiotic classes that FDA has ranked as critically or highly important in human medicine:

- *Macrolides*. The United States, Canada, and South Korea allow antibiotics from the macrolide class for growth promotion, but the EU

[62]With regard to trade in meat, the key U.S. trading partners on which we obtained information were the EU, Australia, Canada, China, Denmark, Hong Kong, Japan, Mexico, New Zealand, Russia, and South Korea; the key U.S. competitors were the EU, Australia, Brazil, Canada, and Denmark. We did not independently verify the information in foreign government documents, which included laws and regulations.

[63]China, Hong Kong, and Mexico allow the use of antibiotics for growth promotion. We did not obtain information on whether these include antibiotics from classes important in human medicine.

[64]The EU will still allow the use of coccidiostat and histomonostat drugs as feed additives for growth promotion. These drugs control parasites, and many coccidiostat and histomonostat drugs are not used in humans.

and New Zealand do not.[65] In the United States, tylosin, a member of this class, is among the most commonly used antibiotics for growth promotion in swine. As of March 2003, Australia allowed antibiotics from the macrolide class for growth promotion, but it had a review under way on some antibiotics in this class, including tylosin, to determine if growth promotion use should continue.

- *Penicillins and tetracyclines*. The United States, Canada, and South Korea allow certain antibiotics from these two classes to be used for growth promotion, but Australia, the EU, Japan, and New Zealand do not. Furthermore, as mentioned earlier, the United States is currently conducting risk assessments on these two classes to determine whether to continue allowing their use for growth promotion.

- *Streptogramins*. The United States, Canada, and South Korea allow the use of virginiamycin, an antibiotic from this class, for growth promotion, but the EU and New Zealand do not. The United States is conducting a risk assessment on the use of virginiamycin for growth promotion and disease prevention. As of April 2003, Australia permitted virginiamycin for growth promotion, but the Australian agency that regulates antibiotic use in animals has recommended that approval of this use be withdrawn.

Appendix V lists antibiotics—including antibiotics from the above classes—that are frequently used in U.S. animal production.

With regard to the availability of antibiotics to livestock and poultry producers, public health experts advocate requiring a veterinarian's prescription for the sale of antibiotics. They believe that this requirement may help reduce inappropriate antibiotic use that could contribute to the emergence of antibiotic-resistant bacteria in animals and the human health risk associated with these resistant bacteria.

The United States and Canada permit many antibiotics to be sold over the counter, without a veterinarian's prescription, while the EU countries and New Zealand are more restrictive regarding over-the-counter sales.[66] The

[65]The United States has not started a risk assessment for any antibiotic in this class.

[66]Australia, Brazil, China, Hong Kong, Japan, Mexico, Russia, and South Korea permit the sale of some antibiotics over the counter. We did not obtain more detailed information on which antibiotics these countries allow to be sold in this manner.

United States and Canada generally allow older antibiotics, such as sulfamethazine, to be sold over the counter, but they require a prescription for newer antibiotics, such as fluoroquinolones. In addition, with regard to the availability of antibiotics from antibiotic classes that are important in human medicine, the United States and Canada allow livestock and poultry producers to purchase several antibiotics over the counter, including penicillins, tetracyclines, tylosin, and virginiamycin. However, Canada is considering changing its rules to require prescriptions for antibiotics used in animals for all antibiotic uses except growth promotion.

In contrast, the EU countries and New Zealand are more restrictive regarding over-the-counter sales of antibiotics for use in animals. Unlike the United States and Canada, the EU does not allow penicillins, tetracyclines, tylosin, and virginiamycin to be sold over the counter and will end all over-the-counter sales by 2006. Denmark, an EU member, already prohibits all over-the-counter sales. Similarly, New Zealand requires producers to have a veterinarian's prescription for antibiotics that it has determined are associated with the development of resistant bacteria in humans.

Appendix IV contains additional information on the key U.S. trading partners and competitors discussed in this section, including, as previously mentioned, their systems for collecting data on antibiotic use.

Antibiotic Use in Animals Has Not Significantly Affected U.S. Trade but Could Be an Issue in the Future

To date, antibiotic resistance associated with use in animals has not been a significant factor affecting U.S. trade in meat products,[67] according to officials of USDA's Foreign Agricultural Service, the Office of the U.S. Trade Representative, the U.S. Meat Export Federation, and the U.S. Poultry and Egg Export Council. However, the presence of antibiotic residues in meat has had some impact on trade.[68] In particular, Russia has previously banned U.S. poultry because of the presence of tetracycline residues. Furthermore, these officials indicated that other issues have been more prevalent in trade discussions, including the use of hormones in beef cattle and animal

[67]Information obtained in the course of this study identified only Ukraine as having import requirements banning fresh or frozen poultry products that were treated with antibiotics for growth promotion. However, Ukraine is not a significant market for U.S. poultry.

[68]Antibiotic residues in meat may occur when antibiotics are improperly used. Traces of the antibiotic can remain in the meat tissue, which may affect human health when the meat is consumed.

diseases such as bovine spongiform encephalopathy (commonly referred to as mad cow disease) and avian influenza. For example, the EU currently bans U.S. beef produced with hormones. Many other nations ban the import of U.S. beef because of the recent discovery of an animal in the United States with mad cow disease.

Although federal government and industry officials stated that antibiotic use in animals has not significantly affected U.S. trade to date, we found some indication that this issue might become a factor in the future. As USDA reported in 2003,[69] antibiotic use in animals could become a trade issue if certain countries apply their regulations on antibiotic use in animals to their imports. For example, according to some government and industry officials, the United States' use of antibiotics could become a trade issue with the EU as it phases out its use of all antibiotics for growth promotion by 2006. However, the EU is not currently a significant market for U.S. meat because of trade restrictions, such as its hormone ban that effectively disallows U.S. beef. Similarly, a Canadian task force reported in June 2002 that the issue of antibiotic resistance and differences in antibiotic use policies could become a basis for countries to place trade restrictions on exports of meat from countries that have less stringent use policies.[70]

The issue of antibiotic use in animals and of the potential human health risk associated with antibiotic-resistant bacteria have also received international attention. For example, in 2003, the Codex Alimentarius Commission, an international organization within which countries develop food safety standards, guidelines, and recommendations, issued draft guidance for addressing the risk of antibiotic resistance in animals. Codex also requested that a group of experts assess the risk associated with antibiotic use in animals and recommend future risk management options. In December 2003, these experts concluded that the risk associated with antibiotic-resistant bacteria in food represents a significantly more

[69]U.S. Department of Agriculture, Economic Research Service, *International Trade and Food Safety: Economic Theory and Case Studies (*Washington, D.C.: 2003).

[70]Report of the Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health. *Uses of Antimicrobials in Food Animals in Canada: Impact on Resistance and Human Health*. A special report prepared at the request of the Veterinary Drugs Directorate, Health Canada. June 2002.

important human health risk than antibiotic residues—an issue that countries have already raised as a trade concern.[71]

Conclusions

Antibiotics have been widely prescribed to treat bacterial infections in humans, as well as for therapeutic and other purposes in animals. Resistance to antibiotics is an increasing public health problem in the United States and worldwide. Published research results have shown that antibiotic-resistant bacteria have been transferred from animals to humans. In evaluating the safety of animal drugs, FDA considers their effect on human health. Such drugs are safe in this regard if there is reasonable certainty of no harm to humans when the drug is used as approved. Using this critieria, FDA has determined that the potential health risk from transference of antibiotic resistance from animals to humans is unacceptable and must be a part of FDA's regulation of animal antibiotics.

FDA, CDC, and USDA have made progress in their efforts to assess the extent of antibiotic resistance from the use of antibiotics in animals through both individual and collaborative efforts, including work through the Interagency Task Force. However, the effectiveness of these efforts remains unknown. FDA has developed guidance to evaluate antibiotics used in animals and intends to review all new drug applications and antibiotics currently approved for use with animals for this risk to determine if it needs to act to ensure that the drugs are safe. Although FDA has recently begun the reviews using this approach, its initial reviews have been for drugs other than those that are critically important for human health. FDA officials do not know how long each review will require. In addition, it is not yet known what actions FDA would take if concerns became evident. Although the agency has the authority to deny or withdraw approval of new or approved animal antibiotics that pose such a risk, FDA also has a variety of other options available. However, FDA action to prohibit the use of fluoroquinolone antibiotics in poultry has continued for more than 3 years.

Finally, researchers and federal agencies still do not have critical data on antibiotic use in animals that would help them more definitively determine

[71]Food and Agriculture Organization of the United Nations, Office International des Epizooties, and World Health Organization. *Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment.* December 2003.

any linkage between use in animals and emerging resistant bacteria, assess the relative contribution of this use to antibiotic resistance in humans, and develop strategies to mitigate antibiotic resistance. The experience of countries such as Denmark indicates that data collection efforts are helpful when making risk-based decisions about antibiotic use in animals. While we recognize that there are costs associated with collecting additional data on antibiotic use in animals, options exist for collecting these data that are not cost-prohibitive. For example, the United Kingdom's efforts to collect national sales data on antibiotic use in animals use relatively few resources. In addition, existing federal programs, such as FDA's ongoing monitoring of approved antibiotics and USDA's CAHFSE, can provide a data collection framework that can be expanded to begin collecting the needed data. FDA, CDC, and USDA recognize the importance of such information and have taken some steps to collect data, although they have not yet developed an overall collection strategy. Until the agencies have implemented a plan to collect critical data on antibiotic use in animals, researchers will be hampered in their efforts to better understand how this use affects the emergence of antibiotic-resistant bacteria in humans, and agencies will be hampered in their efforts to mitigate any adverse effects.

Recommendations for Executive Action

Because of the emerging public health problems associated with antibiotic resistance in humans and the scientific evidence indicating that antibiotic-resistant bacteria are passed from animals to humans, we recommend that the Commissioner of FDA expedite FDA's risk assessments of the antibiotics used in animals that the agency has identified as critically important to human health to determine if action is necessary to restrict or prohibit animal uses in order to safeguard human health.

Additionally, because more data on antibiotic use in animals—such as the total quantity used, by class; the species in which they are used; the purpose of the use, such as disease treatment or growth promotion; and the method used to administer—are needed to further address the risk of antibiotic resistance, we also recommend that the Secretaries of Agriculture and of Health and Human Services jointly develop and implement a plan for collecting data on antibiotic use in animals that will adequately (1) support research on the relationship between this use and emerging antibiotic-resistant bacteria, (2) help assess the human health risk related to antibiotic use in animals, and (3) help the agencies develop strategies to mitigate antibiotic resistance.

Agency Comments and Our Response

We provided USDA and HHS with a draft of this report for review and comment. We also provided segments of the draft related to trade matters to the Department of State and the Office of the U.S. Trade Representative. In their written comments, USDA and HHS generally agreed with the report and provided comments on certain aspects of our findings.

USDA stated that our report recognized the many issues and complexities of efforts to address the risk to humans from antibiotic use in animals. The department also provided information on the extent of research related to antibiotic resistance that it has funded since 1998. We added this information to the report. Regarding our conclusion that antibiotic-resistant salmonella and campylobacter bacteria have been transferred from animals to humans, USDA agreed that it is likely that a transfer has occurred. However, USDA suggested that some of the studies we cited to support that conclusion were, by themselves, inadequate to support a causal link. We believe that our conclusion is firmly supported by a body of scientific evidence, but we have clarified our description of some studies in response to USDA's comments. On the issue of human health risks, USDA commented that we cited few sources of scientific evidence to support the view that the human health risks from the transference of antibiotic-resistant bacteria are minimal. We found that only a few studies have concluded that the risk is minimal, while many studies have concluded that there is a significant human health risk from the transference. With respect to our recommendation that USDA and HHS jointly develop and implement a plan for collecting data on antibiotic use in animals, USDA stated that our report highlights the importance of the data that the CAHFSE program could provide on the impact of antibiotic use in various animal species. However, USDA pointed out that additional funding resources would be needed to expand CAHFSE and other data collection and research efforts. We revised the report to better reflect USDA's concern about funding.

HHS agreed with our finding that antibiotic-resistant salmonella and campylobacter bacteria have been transferred from food animals to humans. HHS provided references to additional research studies that support our conclusion. We were aware of all of the studies cited by HHS, but we did not include them in the report because we believe that our conclusion was already amply supported. Regarding our conclusion that researchers disagree about the extent of human health risk caused by the transference of antibiotic resistance, HHS provided information from an unpublished study that found that the course of illness was significantly longer for persons with antibiotic-resistant campylobacter cases than for

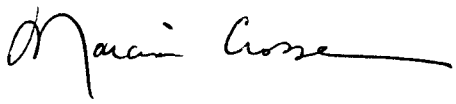
those with antibiotic-susceptible infections. Most of the studies we identified found modest but significant human health consequences, similar to those in the unpublished study described in HHS's comments. Regarding our recommendation that the agencies jointly develop and implement a plan for collecting data on antibiotic use in animals, HHS stated that the most useful and reliable antibiotic use data are those maintained by pharmaceutical companies. HHS said current regulations would have to be revised to put the data that pharmaceutical companies are required to report to FDA in a more relevant format for research on antibiotic resistance. As the two agencies develop and implement their plan to collect the relevant data, if they agree that pharmaceutical companies are an important source, they should take whatever regulatory actions might be necessary if the sources they identify will not provide the data voluntarily. HHS also proposed that discussions between HHS and USDA for improving antibiotic use data collection be conducted through the Interagency Task Force on Antimicrobial Resistance.

We note that while USDA's comments on antibiotic use data emphasized collecting on-farm data through its new CAHFSE program, HHS's comments focused on obtaining data on antibiotic use in animals from pharmaceutical companies. We believe these differing approaches illustrate the need for USDA and HHS to jointly develop and implement a plan to collect data. We agree with HHS that the Interagency Task Force could serve as a forum for discussions between USDA and HHS on this matter.

USDA's written comments and our more detailed responses to them are in appendix VI. HHS's written comments are in appendix VII. In addition, HHS, USDA, the Department of State, and the Office of the U.S. Trade Representative provided technical comments, which we incorporated into the report as appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the date of this letter. At that time, we will send copies of this report to the Secretaries of Agriculture and of Health and Human Services and of State; the U.S. Trade Representative; and other interested officials. We will also provide copies to others upon request. In addition, the report will be available at no charge on GAO's Web site at http://www.gao.gov.

If you have any questions about this report, please call Marcia Crosse at (202) 512-7119 or Anu Mittal at (202) 512-3841. Other contacts and key contributors are listed in appendix VIII.



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Objectives, Scope, and Methodology

This report examines the (1) scientific evidence regarding the transference of antibiotic resistance from animals to humans through the consumption or handling of contaminated meat, and the extent of potential harm to human health, (2) progress federal agencies have made in assessing and addressing the human health risk of antibiotic use in animals, (3) types of data that federal agencies need to support research on the human health risk of antibiotic use in animals and the extent to which these data are collected, (4) use of antibiotics in animals in the United States compared with antibiotic use by its key agricultural trading partners and competitors, and (5) information that is available on the degree to which antibiotic use in animals has affected U.S. trade.

We used the term "animal" to refer to animals raised for human consumption, such as cattle, sheep, swine, chickens, and turkeys; the term "meat" to refer to beef, lamb, pork, chicken, and turkey; and the term "contaminated meat" to refer to meat that contains antibiotic-resistant bacteria. We limited the scope of our work to the transference of antibiotic-resistant bacteria from animals to humans through the consumption or handling of contaminated meat. Specifically, we looked at the evidence for transference of antibiotic-resistant foodborne intestinal pathogens from animals to humans. We did not examine issues related to antibiotics used on plants and seafood, antibiotic residues in animals, or the effects of antibiotics present in the environment because of the application of animal waste to agricultural lands.

To examine the scientific evidence regarding the transference of antibiotic resistance from animals to humans through the consumption or handling of contaminated meat, and the extent of harm to human health, we searched medical, social science, and agricultural databases, which included the Department of Health and Human Services' (HHS) National Library of Medicine, for studies published in professional journals. We identified articles published since the 1970s on antibiotic use and resistance in animals and humans, as well as articles on antibiotic-resistant foodborne illnesses. We interviewed officials from HHS's Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) and the U.S. Department of Agriculture (USDA) to determine how these agencies are assessing the human health risk of antibiotic use in animals. We also reviewed reports related to the human health risk of antibiotic use in animals. Finally, we interviewed officials from relevant professional organizations (e.g., the American Medical Association) and public health advocacy groups (e.g., the Center for Science in the Public

Interest) to identify other data or studies on the issue of human health risk from antibiotic use in animals.

To determine federal agencies' progress in assessing and addressing the human health risk of antibiotic use in animals, we examined documents from FDA, CDC, and USDA. These documents include reports on results from the federal government's antibiotic resistance surveillance program and on the progress of the federal Interagency Task Force on Antimicrobial Resistance, documents presented in an FDA administrative court concerning the agency's proposal to withdraw the approval of the use of a certain antibiotic used in poultry that is also an important antibiotic in human medicine, and FDA's framework to assess the human health risk of antibiotic use in animals.

To examine the types of data that federal agencies need concerning antibiotic use in animals in order to support research on the human health risk and the extent to which these data are collected, we reviewed federal agency documents and reports and interviewed FDA, CDC, and USDA officials. In particular, we discussed the status of FDA's efforts to collect data on U.S. antibiotic use in animals, the status of USDA's programs that collect data on antibiotic use, and CDC's initiatives that would benefit from use data. We reviewed foreign government reports to determine how other countries use antibiotic use data for research; we also reviewed international reports from the World Health Organization (WHO) and the Office International des Epizooties (OIE), which provide guidelines on the types of use data that countries should collect. We also interviewed officials from Denmark, which collects extensive data on antibiotic use in animals, and from Canada, which plans to implement a data collection system. We discussed the availability of data on U.S. antibiotic use in animals with officials from pharmaceutical companies, industry associations, state veterinary offices, firms that collect data on antibiotic use in animals, and public health advocacy groups.

To examine how the use of antibiotics in animals in the United States compares with antibiotic use by its key agricultural trading partners and competitors, we obtained and reviewed information on antibiotic use in animals for the United States and its key partners and competitors in international meat trade.[1] Using international trade data, we identified the European Union (EU) and 11 countries—Australia, Brazil, Canada, China, Denmark,[2] Hong Kong, Japan, Mexico, New Zealand, Russia, and South Korea—as key U.S. trading partners or competitors.[3] We obtained information on countries' antibiotic use in animals through discussions with officials of USDA's Animal and Plant Health Inspection Service and Foreign Agricultural Service (FAS) and literature searches to identify relevant documents. In addition, we discussed antibiotic use in animals with government officials from Canada, a leading U.S. trading partner and competitor, and Denmark, a leading U.S. trading partner and competitor that took significant actions to curtail antibiotic use in animals during the late 1990s. We also e-mailed a questionnaire to FAS agricultural attachés in the EU and the key trading partner or competitor countries, except Canada and Denmark. For Canada and Denmark, we obtained responses to this questionnaire from Canadian and Danish government officials as part of our visits to these countries. We did not send this questionnaire to government officials of the EU and the other nine countries because of Department of State and FAS officials' concerns that antibiotic use in animals may be a sensitive issue for some foreign governments and that some governments may be suspicious about the questionnaire's underlying purposes; for the same reasons, in completing this questionnaire, the FAS agricultural attachés were instructed to not contact foreign government officials. As a result, the amount of information we obtained varies by country, and we were able to obtain only very limited information on antibiotic use in Brazil, China, Hong Kong, Japan, Mexico, Russia, and South Korea. We did not independently verify the information reported in

[1]To the extent information was available, we obtained information on policies to regulate antibiotic use, quantities of antibiotics sold, and systems to monitor antibiotic use in animals and antibiotic resistance associated with this use.

[2]Although Denmark is an EU member, we included it in addition to the EU because it is a major U.S. competitor in pork exports.

[3]To identify these countries, we used USDA's Foreign Agricultural Service data on (1) countries' trade of beef, pork, and poultry with the United States and (2) countries' worldwide exports of these products. We selected those countries whose share of imports or exports of a product was at least 10 percent. In addition, we included China because it is a major importer of poultry although it does not trade extensively with the United States.

responses to this questionnaire or other documents, including laws and regulations, from the foreign countries.

To obtain information on antibiotic use in U.S. animal production, we reviewed FDA regulations;[4] USDA's National Animal Health Monitoring System reports on management practices, including antibiotic use practices in beef cattle and swine production; a University of Arkansas study of antibiotic use in broiler chickens; the Animal Health Institute's annual reports on antibiotic use in animals; and a Union of Concerned Scientists report.[5,6] We did not independently verify the information contained in these reports. In addition, we spoke with officials from state veterinarians' offices and from agricultural industry organizations, including the American Veterinary Medicine Association, the National Pork Producers Council, the American Meat Institute, the National Cattlemen's Beef Association, the U.S. Poultry and Egg Export Council, the National Chicken Council, and pharmaceutical and poultry companies. We also visited livestock and poultry farms in Georgia, Maryland, and Pennsylvania.

We compared the United States' policies regulating antibiotic use in animals with the policies of those key trading partners and competitors for which this information was available. In addition, we summarized available information on countries' activities to address antibiotic resistance associated with antibiotic use in animals, and, for the United States, we developed a list of the antibiotics most commonly used in beef cattle, swine, and broiler chickens.

To examine information that is available on the degree to which antibiotic use in animals has affected international trade, we reviewed reports on trade and food safety issues from USDA's Economic Research Service and FAS, foreign governments, and international organizations. We also examined records of USDA's Food Safety and Inspection Service to identify countries that have requirements concerning antibiotic use for the meat they import. In addition, we reviewed the reports and standards of international trade organizations, such as the World Trade Organization,

[4]21 C.F.R. parts 520, 522, and 558 (2003).

[5]H.D. Chapman, Z.B. Johnson, "Use of Antibiotics and Roxarsone in Broiler Chickens in the USA: Analysis for the Years 1995 to 2000," *Poultry Science*, 81: 356-364, (2002).

[6]M. Mellon, C. Benbrook, and K.L. Benbrook, "Hogging It! Estimates of Antimicrobial Abuse in Livestock," Union of Concerned Scientists, January 2001.

the Codex Alimentarius Commission, and OIE. We discussed antibiotic use and other potential trade issues with officials from the Office of the U.S. Trade Representative, FAS, and meat industry trade associations.

We also identified several studies on estimates of the potential economic impacts of restrictions on antibiotics used in meat production. These are described in detail in appendix II.

We conducted our work from May 2003 through April 2004 in accordance with generally accepted government auditing standards.

Studies of the Economic Impacts of Restricting Antibiotic Uses in Animals

In this appendix we identify and summarize eight recent studies that provide estimates of the potential economic impacts of restrictions on antibiotics used in livestock production. Specifically, these studies estimate the economic effects of a partial and/or total ban of antibiotics used in animals. For several decades, antibiotics have been used for a variety of production management reasons, from therapeutic uses to increased productivity, such as feed efficiency or weight gain. In economic terms, higher productivity results in more final product supplied to the market, at a lower cost to consumers. Despite the use of a variety of economic models, assumptions about model parameters, and data sets, the economic impacts on consumers and producers of the studies that we identified were generally comparable. Overall, the studies conclude that a ban or partial ban on antibiotics in animal production would increase costs to producers, decrease production, and increase retail prices to consumers. For example, the studies indicate that the elimination of antibiotic use in pork production could increase costs to producers ranging from $2.76 to $6.05 per animal,[1] which translates into increased consumer costs for pork ranging from $180 million per year to over $700 million per year. Table 2 summarizes the eight studies.

[1]The WHO study described in this appendix also has estimated a cost of $1.04 per animal; however, the study was done to estimate economic impacts on the Danish swine market. (See World Health Organization, *Impacts of Antimicrobial Growth Promoter Termination in Denmark*, Department of Communicable Diseases, Prevention and Eradication and Collaborating Centre for Antimicrobial Resistance in Foodborne Pathogens, 2003.)

Table 2: Economic Studies That Estimate the Effects of Restrictions on Antibiotic Use

			Economic impacts	
Economic study	**Purpose of the study**	**Year**	**Producers**	**Consumers**
World Health Organization (WHO), *Impacts of Antimicrobial Growth Promoter Termination in Denmark*	To review the economic impacts resulting from the Danish ban of the use of antibiotics for growth promotion purposes in swine and poultry production.	2003	Cost increase of $1.04 per swine or 1 percent of total production costs. No cost changes for poultry.	
Hayes and Jensen, "Lessons from the Danish Ban on Feed-Grade Antibiotics," Center for Agricultural and Rural Development	To determine the economic impacts of a ban on antibiotics in pork production in the United States from the experience with such a ban in Denmark.	2003	Costs increase by $4.50 per head in first year. Total 10-year cost over $700 million.	Retail price increases by 2%.
Miller et al., "Productivity and Economic Effects of Antibiotics Used for Growth Promotion in U.S. Pork Production," *Journal of Agricultural and Applied Economics*	To estimate the net benefit of antibiotics used for growth promotion to swine producers in the United States using the 1990 and 1995 NAHMS swine survey data.[a]	2003	Increased profits of $0.59 per marketed swine or 9% profitability.	
Miller et al., "Producer Incentives for Antibiotic Use in U.S. Pork Production," American Agricultural Economics Association Annual Meetings	To validate the productivity and economic impacts of antibiotic use for swine producers at the farm level using the NAHMS 2000 survey.	2003	Four scenarios:[b] • Ban on AGP: profits decrease by $3,813 • Ban on ADP: profits increase by $2703 • Ban on AGP and ADP: profits decrease by $1128 • Limitation of AGP and ADP: Profits increase by $12,438	
Brorsen, Lehenbauer, Ji, and Conner, "Economic Impacts of Banning Subtherapeutic Use of Antibiotics in Swine Production," *Journal of Agricultural and Applied Economics*	To estimate the economic impacts on producers and consumers of a ban on the use of antibiotics in swine production.	2002	Costs would increase by $2.37 - $3.11 per hog with an average of $2.76 per hog. Total costs would be $153.5 million per year in the short run and $62.4 million per year in the long run.	Costs to consumers increase by $89 million per year in the short run to $180 million per year in the long run.

(Continued From Previous Page)

Economic study	Purpose of the study	Year	Economic impacts: Producers	Economic impacts: Consumers
Mathews, Jr., "Economic Effects of a Ban Against Antimicrobial Drugs Used in U.S. Beef Production," *Journal of Agricultural and Applied Economics*	To examine the economic effects of a ban on antibiotic use in U.S. beef production on two policy alternatives—a partial ban and a full ban.	2002	**Partial ban**: Cattle prices increase by 0.49 percent. Producer income declines by $15 million.[d] **Full ban**: Cattle prices increase by 3.32 percent. Producer income declines by $113.6 million.[d]	**Partial ban**: Costs to consumers increase by $54.7 million.[d] **Full ban**: Costs to consumers increase by about $361 million.[d]
Hayes, Jensen, Backstom, and Fabiosa, "Economic Impact of a Ban on the Use of Over-the-Counter Antibiotics," Center for Agricultural and Rural Development	To estimate the likely economic impacts of a ban on antibiotics in the U.S. pork industry based on the impacts of such a ban in Sweden.	1999	Costs would increase by $5.24 - $6.05 per head. Net profit declines by $0.79/head. Total net present value of forgone profits over 10 years declines by $1.039 billion.	Retail price would increase by 5 cents per pound. Nationally, annual increase of consumer costs of $748 million.
National Research Council "Costs of Eliminating Subtherapeutic Use of Antibiotics" in *The Use of Drugs in Food Animals: Benefits and Risk*	To examine the economic costs to consumers of the elimination of subtherapeutic use of antibiotics for poultry, beef, and pork.	1999		Retail meat price increases (cents per pound):[c] Chicken: (1 – 3) Turkey: (2 – 3) Pork: (3 – 6) Beef: (3 – 6) Total consumer costs for pork: $382 million - $764 million per year. For all meat products, consumer costs increase by $1.2 billion to $2.5 billion per year.

Source: GAO analysis of sources cited.

[a]NAHMS is the National Animal Health Monitoring System.

[b]Within these scenarios, Miller et al. define AGP as antibiotics used for growth promotion and ADP as antibiotics used for disease prevention. The annual estimates of economic impacts for these scenarios are for a producer that has a 1,020-head barn of swine. A swine producer could have many such barns in his/her operation.

[c]The National Research Council estimates of retail price increases are ranges based on whether consumers would substitute other meat. The lower change in price assumes that substitution of other meat mitigates the price impact by 50 percent, while the higher change in retail price assumes no substitution.

[d]These estimates are in 1984 dollars.

While these market effects are important to both producers and consumers of livestock products, they must be balanced against the health care costs of antibiotic resistance due to agricultural uses of antibiotics. Potential health costs imposed by increased antibiotic resistance include more hospitalizations, higher mortality rates, and higher research costs to find new and more powerful drugs.[2] From the point of view of proposals to reduce antibiotic use, these potential costs represent the benefits from reduced antibiotic use. These costs to society, however, are difficult to measure because of limited data on antibiotic use and resistance as well as the problematic nature of measuring the value of a human life. Moreover, while there are some estimates of the costs of antibiotic resistance from both medical and agricultural sources, no estimates exist that directly link the human health costs of antibiotic resistance with antibiotics used in animal production. Nevertheless, studies that have examined the costs of antibiotic resistance from all sources have found a wide range of estimates running into the millions and billions of dollars annually.[3] For example, one recent study (2003) estimated that the health cost to society associated with resistance from only one antibiotic, amoxicillin, was $225 million per year.[4]

We discuss the eight studies we reviewed in reverse chronological order, from 2003 to 1999. Most examine restrictions on antibiotics in the swine industry, but a few look at the beef and poultry industries as well. All of the studies measure the economic impacts of antibiotic restrictions on domestic U.S. markets, except the WHO study of the antibiotic restrictions recently imposed by Denmark. Also, most studies estimate only domestic economic impacts, not impacts on international trade.

[2]Ramanan Laxminarayan, "Fighting Antibiotic Resistance: Can Economic Incentives Play a Role?" *Resources*, Spring 2001, Issue 143.

[3]Phelps (1989) estimated that the annual economic costs of drug resistance range from a best-case scenario of $100 million to a worst-case scenario of $30 billion, with the wide range of estimates accounted for by different assumptions about the economic value of a human life. Also, a study done by the Office of Technology Assessment in 1995 estimated that the cost of antibiotic resistance for six different strains of antibiotic bacteria reached about $1.3 billion in 1992 dollars.

[4]E.H. Elbasha, "Deadweight Loss of Bacterial Resistance Due to Overtreatment," *Health Economics*, 2003, 12(2): 125-138.

WHO (2003) Review of the Economic Impacts of Antibiotics for Growth Promotion in Denmark

In 2002, WHO convened an international expert panel to review, among other issues, the economic impact resulting from the Danish ban of antibiotics for growth promotion, particularly in swine and poultry production.[5] As part of this effort, Denmark's National Committee for Pigs estimated that the cost of removing antibiotic growth promoters in Denmark totaled about $1.04 per pig, or a 1 percent increase in total production costs. In the case of poultry, however, there was no net cost because the savings associated with not purchasing these antibiotics offset the cost associated with the reduction in feed efficiency. Components of these costs included excess mortality, excess feeding days, increased medication, and increased workload.

A subsequent study by Jacobsen and Jensen (2003) used these costs as part of the agriculture sector of a general equilibrium model to estimate the impact on the Danish economy of the termination of antibiotic growth promoters.[6] The model used these cost assumptions in a baseline scenario that projects the likely development of the Danish economy to 2010.

The results of the model indicated a small reduction in pig production of about 1.4 percent per year and an increase in poultry production of about 0.4 percent. The authors explain that the increase in poultry production occurred because of the substitutability of these meats in consumption. In addition, this research included estimates of the consequences of removing antibiotic growth promoters on the export market. The model showed that exports of pork were forecast to be 1.7 percent lower than they would be in the absence of these growth promoters, while poultry exports would increase by about 0.5 percent.

The authors explained that some costs associated with modifications to production systems were difficult to measure and were not included in the analysis, although they may have been substantial for some producers. They also stated that the analysis does not take into account the possible positive effect that the removal of antibiotic growth promoters may have

[5]World Health Organization, *Impacts of Antimicrobial Growth Promoter Termination in Denmark*, Department of Communicable Diseases, Prevention and Eradication and Collaborating Centre for Antimicrobial Resistance in Foodborne Pathogens, 2003.

[6]L.B. Jacobsen and H.G. Jensen, "Sector and Economy Wide Effects of Terminating the Use of Antimicrobial Growth Promoters in Denmark," In: International Invitational Symposium; Beyond Antimicrobial Growth Promoters in Food Animal Production, November 6-7, 2002 (subsequently revised, 2003), Foulum, Denmark.

had on consumer demand, both in the domestic and in the export markets. Moreover, they added that any costs must be set against the likely human health benefits to society.

Hayes and Jensen (2003) Study Based on the Danish Ban of Feed-Grade Antibiotics in the Pork Industry

In 2003, using a 1999 study by Hayes et al. of the potential economic impacts of a U.S. ban based on the ban in Sweden, as described below, and a recent ban on feed-grade antibiotics in Denmark, Hayes and Jensen estimated the economic impacts of a similar ban in the United States.[7] In 1998, the Danish government instituted a voluntary ban on the use of antibiotics in pork production at the finishing stage, and in 2000 it banned antibiotics for growth promotion at both the weaning and the finishing stages. The results of the ban in Denmark, however, may be more applicable than the Swedish experience because, like the United States, Denmark is one of the largest exporters of pork and has somewhat similar production practices.[8] The authors compared the econometric results of a U.S. baseline without a ban with projected results based on assumptions taken from the ban in Denmark. Many of the same technical and economic assumptions that were used in the Swedish study were also used for the impacts based on the Danish ban. For instance, the authors included a sort-loss cost of $0.64 per animal, a similar assumption for loss of feed efficiency, and decreases in piglets per sow.[9] Other key assumptions and features unique to the study include the following:

- the use of only one case or scenario—a "most-likely" scenario—unlike the study based on the Swedish ban;
- increased costs of $1.05 per animal at the finishing stage and $1.25 per animal at the weaning stage;

[7]Dermot J. Hayes and Helen H. Jensen, "Lessons from the Danish Ban on Feed-Grade Antibiotics," Briefing Paper 03-BP 41, Center for Agricultural and Rural Development, Iowa State University, Ames, Iowa, June 2003.

[8]While the United States and Denmark are both leading pork exporters, their market structures are different. In Denmark, unlike in the United States, farmer cooperatives dominate production, processing, and distribution systems.

[9]Sort-loss costs represent discounts or penalties for increased weight variability for marketing swine that are either too light or too heavy. The Swedish experience indicated that removal of antibiotics in feed increased this variability at marketing. However, because they were able to influence the packers to accept more light weight pigs, Swedish producers actually did not have a problem with sort loss.

- a vaccine cost of $0.75 per animal; and
- a capital cost of about $0.55 per animal;

According to the study, a major economic impact in the U.S. pork market of a ban similar to the Danish ban would be a cost increase of about $4.50 per animal in the first year. Across a 10-year period, the total cost to the U.S. pork industry was estimated to be more than $700 million. With a lower level of pork production, retail prices would increase by approximately 2 percent. The authors conclude that a ban at the finishing stage would create very few animal health concerns, while a ban at the weaning stage would create some serious animal health concerns and lead to a significant increase in mortality. They also note that, as happened immediately following the ban at the weaning stage in Denmark, the total use of antibiotics in the United States at this production stage may rise.

Miller et al. (2003) Study Using 1990 and 1995 NAHMS Data on the Economic Effects of Antibiotics Used for Growth Promotion in U.S. Pig Production

Miller et al. (2003) used 1990 and 1995 National Animal Health Monitoring System (NAHMS) swine survey data to estimate the net benefit of antibiotics used for growth promotion to swine producers.[10] The NAHMS database provides statistically valid estimates of key parameters related to the health, management, and productivity of swine operations in the United States.[11] The authors used econometric methods to estimate the relationships between growth-promoting antibiotics and productivity measures, such as average daily weight gain (ADG) and feed conversion ratio (FCR), for grower/finisher pigs. Using these productivity measures, predictions on performance were then generated for an independent, medium-sized, midwestern farrow-to-finish pork producer in 1995. The performance figures were expressed in economic terms, such as profitability, using a swine enterprise budgeting model. The study includes the following key features and assumptions:

[10]Gay Y. Miller, Kenneth A. Algozin, Paul E. McNamara, and Eric J. Bush, "Productivity and Economic Effects of Antibiotics Used for Growth Promotion in U.S. Pork Production," *Journal of Agricultural and Applied Economics*, 35,3(December 2003): 469-482.

[11]The National Animal Health Monitoring System (NAHMS) is a program operated by veterinary and animal science professionals at USDA's Center for Animal Health Monitoring. A primary function of this branch of USDA is to make periodic surveys and assessments of animal health management practices on commercial livestock farms across the United States.

- The productivity measures estimated were ADG, FCR, and mortality rate (MR) during the grower/finisher stage of swine production.
- Explanatory variables included in the model were regional identifiers, size of operation, market structure variables, number of rations, mortality rate, number of days antibiotics were administered, number of antibiotics fed, number of diseases diagnosed in last 12 months, among others.
- The ADG and FCR equations were estimated jointly using the seemingly unrelated regression procedure.
- Because the theory as to an exact specification was unknown, the MR equation was estimated using a backward-stepwise linear regression.

The authors estimated that increases in annual returns above costs from antibiotics for a 1,020-head finishing barn was $1,612, or $0.59 per swine marketed. This represents an improved profitability of approximately 9 percent of net returns in 2000 for Illinois swine finishing operations. The authors also found that there is substitutability between antibiotics as growth promoters and other production inputs (such as number of rations) that could reduce the negative influence of removing antibiotics.

Miller et al. (2003) Study Using 2000 NAHMS Data to Estimate the Productivity and Economic Impacts of Antibiotic Use in U.S. Pig Production

In an updated study, Miller et al. (2003) estimated the combined effects of antibiotics used for growth promotion (AGP) and antibiotics used for disease prevention (ADP) in pork production using the NAHMS 2000 swine survey.[12] Specifically, the authors measured the productivity and the economic impacts of these antibiotics on grower/finisher pigs for individual swine producers. The authors evaluated four scenarios, using varying degrees of bans of both AGP and ADP: (1) a ban on AGP, (2) a ban on ADP, (3) a ban on both AGP and ADP, and (4) a limitation on AGP and ADP to levels that maximize production. These scenarios were chosen because antibiotics that are used for different purposes have different impacts on productivity, improving it on one dimension while possibly diminishing it on another. First, the authors estimated four pork productivity dimensions related to the use of antibiotics using an

[12]Gay Y. Miller, Xuanli Liu, Paul E. McNamara, and Eric J. Bush, "Producer Incentives for Antibiotic Use in U.S. Pork Production," paper prepared for presentation at the American Agricultural Economics Association Annual Meeting, Montreal, Canada, July 2003.

econometric model. Second, using the estimated productivity measures from the econometric model, they estimated economic impacts to pork producers for each antibiotic ban scenario using a spreadsheet farm budget model. The study includes the following key features and assumptions:

- Pork productivity was measured using four measures of productivity, including average daily weight gain, feed conversion ratio, mortality rate, and lightweight rate.

- These productivity measures were estimated using seemingly unrelated regression analysis and are modeled from the perspective of possible structural relationships among the measures.

- The study used the NAHMS 2000 study, which provides the most recent data available to investigate productivity impacts and impacts on farm costs and profitability.

Overall, the authors confirmed their earlier findings that a ban would likely cause substantial short-term losses to producers. However, decreasing the use of certain antibiotics to a more desirable level may be implemented without major losses. For scenario 1, a total ban on AGP would cost producers $3,813 in profits annually.[13] For scenario 2, a ban on ADP would slightly improve profits by a gain of $2703 annually. For scenario 3, a ban on both AGP and ADP would lower producer profits by $1128 annually. For scenario 4, where AGP and ADP are applied at levels where swine productivity is maximized, producers would gain $12,438 annually compared with no antibiotic use. The authors conclude that restrictions on classes of AGP, the amount of time antibiotics are fed, and restrictions on ADP many be implemented by producers without major losses. However, they also note that some time dimensions ignored in their study may be important and that their use of nonexperimental data requires careful interpretation.

[13]Each scenario in the model estimates profit for a 1,020-head barn of swine. A swine producer, however, could have many such barns in his/her operation.

Brorsen et al. (2002) Study on Economic Effects of a Ban on the Use of Antibiotics for Growth Promotion in Swine Production

Brorsen et al. (2002) used a model similar to one developed by Wohlgenant (1993) to estimate the economic impacts on producers and consumers of a ban on antibiotics used for growth promotion in swine production.[14] The authors used a model that allowed for feedback between beef and pork markets and measured changes in producer and consumer surplus resulting from shifts in both supply and demand. Moreover, the authors extended their two-commodity beef and pork model to include poultry. In their model, changes in production costs due to banning the use of antibiotics for growth promotion are measured indirectly by the net benefits from their use. The study includes the following key features and assumptions:

- The ban considered in this model is a complete ban on all antibiotics in feed.
- The effects of using antibiotics for growth promotion were assumed to be from improvements in (1) feed efficiency over drug cost, (2) reduced mortality rate, and (3) reduced sort-loss at marketing.
- The authors assumed a $45.00 per hundredweight market price for hogs.
- All parameters (i.e., demand and supply elasticities) used to solve the model were based on other economic studies, except the parameter that represented the change in production costs. Once these were obtained, retail quantity, retail price, farm quantity, and farm price were determined simultaneously.
- An econometric model was used to obtain the economic benefit from the improvement in feed-to-gain conversions in swine production.
- The mortality benefit in swine was assumed to range from 0 percent, to 0.75 percent (most likely), to 1.5 percent.

[14]B. Wade Brorsen, Terry Lehenbauer, Dasheng Ji, and Joe Conner, "Economic Impacts of Banning Subtherapeutic Use of Antibiotics in Swine Production," *Journal of Agricultural and Applied Economics*, 34,3 (December 2002): 489-500; and M.K. Wohlgenant "Distribution of Gains from Research and Promotion in Multi-Stage Production Systems: The Case of the U.S. Beef and Pork Industries," *American Journal of Agricultural Economics* 75 (1993): 642-651.

- Net benefits of the use of antibiotics for growth promotion were estimated by summing the results of a simulation exercise based on the probability distributions of the three sources of economic benefits at the industry level.

The authors estimated that economic costs to swine producers from a ban on antibiotics used for growth promotion would range from $2.37 per hog to $3.11 per hog, with an average cost of $2.76 per hog. For swine producers, the estimated annual costs would be approximately $153.5 million in the short run to $62.4 million in the long run. Estimated annual costs to pork consumers would increase by about $89 million in the short run to $180 million in the long run.

Mathews, Jr. (2002) Analysis of the Economic Effects of a Ban on Antibiotics in U.S. Beef Production

Mathews, Jr. (2002) examined the economic effects of a ban on antibiotic use in U.S. beef production using two policy alternatives—a partial ban and a full ban.[15] To estimate these effects, the author developed a series of economic models, including a firm-level, cost-minimization model that minimizes the cost of feeding cattle to final output weights for a base case, a full ban, and a partial ban (banning only selected antibiotics) scenario. Imbedded in this model is a growth function that incorporates the interaction between the growth rate of cattle and feed efficiency. The firm-level effects were then aggregated across firms in a partial equilibrium framework to estimate national cattle supply, price, and value of production for the three scenarios. The study includes the following key features and assumptions:

- Variables included in the growth function were lagged average daily weight gain, feed efficiency, seasonal variables, and an interaction variable of average weight gain and feed efficiency. The growth model forms a "dynamic" link to the cost-minimization model by accounting for the impacts of recent feeding experiences.

- In the cost-minimization model, feed costs were minimized, subject to protein levels and other feed constraints. The model finds the minimum cost for feeding a steer to a final weight estimated from the embedded growth function.

[15]Kenneth H. Mathews, Jr., "Economic Effects of a Ban Against Antimicrobial Drugs Used in U.S. Beef Production," *Journal of Agricultural and Applied Economics*, 34, 3 (December 2002): 513-530.

- The resulting model allowed final cattle weights, feeding costs, and the number of cattle fed per year to vary, resulting in livestock supplies that are endogenous to the model.

- In the partial-ban scenario, substitute antibiotics were assumed to be functionally equivalent to and twice as costly as in the base scenario.

- Data for the aggregate analysis included annual average all-cattle prices and commercial beef production for the period 1975 through 1990. A base scenario was estimated using parameter and final steer weight estimates from the growth model for each quarter over an 11-year period, from January 1990 through January 2001.

Results of the partial-ban scenario indicated that aggregate annual income would decrease by nearly $15 million for producers, while annual consumer costs would increase by $54.7 million.[16] For the full ban, a 4.2 percent decline in beef production would yield a 3.32-percent increase in the price of cattle, from $42.60 to $47.12 per hundredweight. Also, the full ban translates into an annual consumer cost increase of $361 million. The author noted that the study did not take into account any effects of a ban or partial ban on trade in beef products.

Hayes et al. (1999) Study Based on the Swedish Ban of Antibiotics in the Pork Industry

A study issued in 1999 by Hayes et al. at Iowa State University estimated the potential economic impacts of a ban on the use of antibiotics in U.S. pork production based on assumptions from a Swedish ban in 1986.[17] To estimate baseline results, the authors used a simultaneous econometric framework of the U.S. pork industry that included several production and marketing segments: live inventory and production, meat supply, meat consumption, meat demand, and retail price transmission. The baseline results, or results with no change in antibiotic use, were compared to a range of estimates of a ban on antibiotics in pork production in the United States based on a set of technical and economic assumptions taken from the Swedish experience. These simulations included three different scenarios: a "most likely," a "best-case," and a "worst-case" scenario if the

[16]All estimates for this study are in 1984 dollars.

[17]Dermot J. Hayes, Helen H. Jensen, Lennart Backstrom, and Jay Fabiosa, "Economic Impact of a Ban on the Use of Over-the-Counter Antibiotics, " Staff Report 99-SR 90, Center for Agricultural and Rural Development, Iowa State University, Ames, Iowa, December 1999.

ban were to be implemented in the United States. The key features and assumptions of the model for the "most likely" case included the following:

- a 10-year projection period from 2000 to 2009 from a 1999 baseline, with deviations from the baseline in the projection period reflecting the technical and economic assumptions taken from the Swedish ban;
- the pork, beef, and poultry markets, although the model assumed no change in the regulation of antibiotics on beef and poultry;
- technical assumptions: feed efficiency for pigs from 50 to 250 pounds declines by 1.5 percent, piglet mortality increases by 1.5 percent, and mortality for finishing pigs increases by 0.04 percent. Also, the "most likely" case extends weaning age by 1 week and piglet per sow per year decrease by 4.82 percent.
- veterinary and therapeutic costs would increase by $0.25 per pig, net of the cost for feed additives;
- additional capital costs would be required because of additional space needed for longer weaning times and restricted feeding, including $115 per head for nursery space and $165 per head for finishing space;
- an estimated penalty of $0.64 per head for sort-loss costs; and
- input markets, such as the cost of antibiotics, are exogenous or not a part of the modeling system.

The authors in their "most likely" scenario estimated that the effects of a ban on the use of antibiotics would increase production costs by $6.05 initially and $5.24 at the end of the 10-year period modeled. Because the supply of pork declines, however, net profit to farmers would decline by only $0.79 per head. Over a 10-year period, the net present value of forgone profits would be about $1.039 billion. For consumers, the retail price of pork increases by $0.05 per pound, which sums to a yearly cost of about $748 million for all consumers.

The authors also cited four important limitations to their study: (1) the estimated impacts represent an "average" farm and may mask wide differences across farms; (2) technical evidence from the Swedish experience must be regarded with caution as an indicator of what might happen in the United States; (3) consumers only respond to changes in the

price of pork; however, the model does not take into account how such a ban would affect the prices of beef and poultry; and (4) there was no attempt to factor in the positive effects of such a ban on consumer willingness to pay for pork produced without the use of feed-grade antibiotics.

National Research Council's (1999) Economic Analysis of the Costs of Eliminating Subtherapeutic Use of Antibiotics in Animals

The National Research Council (NRC) examined the economic costs to consumers of the elimination of all subtherapeutic use of antibiotics in a chapter of a 1999 report entitled *The Use of Drugs in Food Animals: Benefits and Risks*.[18] Instead of measuring the consequences of eliminating antibiotics on farm costs and profits, NRC decided that a more viable alternative would be to measure costs to consumers in terms of the higher prices that would be passed on to consumers. According to NRC, this measurement strategy was followed for several reasons: changes in production costs do not necessarily translate into lower profits; depending on management practices, not all producers rely on these antibiotics to the same extent and would not all be equally affected by a ban; and some producers, for example those who produce for special niche markets, may actually benefit from such a ban.[19] The study includes the following key features and assumptions:

- All cost increases are passed on to consumers in terms of percentage price changes.
- The model measures how much consumers would need to spend in order to maintain a similar level of consumption as before the ban.
- No change in consumption because of a ban on antibiotics would occur.

[18]National Research Council, "Costs of Eliminating Subtherapeutic Use of Antibiotics," Chapter 7, in *The Use of Drugs in Food Animals: Benefits and Risk*, National Academy Press, Washington, D.C., 1999, 179-187. Although the precise definition is the subject of some debate, subtherapeutic use refers to antibiotic use in animal production to improve animal performance, such as enhanced growth rates or improved feed efficiency, whereas therapeutic use refers to antibiotics used to treat specific health problems.

[19]The NRC cites Colemon Natural Beef of Colorado, a company that raises its beef without antibiotic treatments or exogenous growth promoters, as an example of such a company.

- Per capita costs are estimated as the product of three items: (1) percentage increase in annual production costs, (2) retail prices, and (3) per capita annual retail quantity sold.

- Annual costs of a ban were estimated for four domestic retail markets—chicken, turkey, beef, and pork—as well as a total cost for all meat.

NRC estimated that the average annual cost per capita to consumers of a ban on all antibiotic use was $4.84 to $9.72. On a commodity retail price basis, the change in price for poultry was lowest, from $0.013 per pound to $0.026 per pound; for pork and beef, prices ranged from $0.03 per pound to $0.06 per pound. Retail pork price increases ranged from $0.03 per pound to $0.06 per pound. Total national additional costs per year for pork consumption ranged from $382 million to $764 million, depending on assumptions about meat substitutes. As for all meat products combined, total consumer cost increases ranged from $1.2 billion to $2.5 billion per year. Finally, NRC noted that the reduction in profits and industry confidence that would result from such a ban may cause a reduction in research, and that society would lose the research benefits. Also, to determine whether this cost increase would be justified, the amount should be compared with the estimated health benefits.

FDA's Procedures for Evaluating the Importance of an Animal Drug for Human Health

As part of the risk estimation outlined in Guidance for Industry #152, FDA developed a framework for evaluating the importance of an antibiotic to human medicine. FDA has ranked antibiotics as either critically important, highly important, or important. These rankings are based on five criteria, which are ranked from most (criterion 1) to least important (criterion 5):

1. The antibiotic is used to treat enteric pathogens that cause foodborne disease.

2. The antibiotic is the sole therapy or one of the few alternatives to treat serious human diseases or is an essential component among many antibiotics in the treatment of human disease.

3. The antibiotic is used to treat enteric pathogens in nonfoodborne disease.

4. The antibiotic has no cross-resistance within the drug class and an absence of linked resistance with other drug classes.[1]

5. There is difficulty in transmitting resistance elements within or across genera and species of organisms.

Antibiotics that meet both of the first two criteria are considered by FDA to be critically important to human medicine. Drugs that meet either of the first two criteria are considered highly important to human medicine. Drugs that do not meet either of the first two criteria but do meet one or all of the final three criteria are considered important to human medicine. Of the 27 classes of animal drugs relevant to human health, 4 were ranked critically important, 18 highly important, and 5 important. The status of a particular antibiotic may change over time. For example, a drug may be considered to be critically important to human health because it is the sole therapy. Later, if new antibiotics become available to treat the same disease or diseases, the drug may be downgraded in its importance to human health.

[1]Cross-resistance refers to the transmission of antibiotic-resistant determinants between bacterial species or genera and does not refer to transmission of antibiotic-resistant organisms between animals and humans.

Information on Selected Countries' Activities to Address Animal-Related Antibiotic Resistance

This appendix provides information on efforts to address antibiotic resistance associated with antibiotic use in animals for the United States and some of its key trading partners and competitors. For the United States, more detailed information on these activities is in the letter portion of this report. For the United States' key trading partners and competitors, to the extent that information was available, we summarized the countries' activities and described antibiotic resistance surveillance systems and antibiotic use data collection systems.

In addition, table 3 presents information on the total amount of antibiotics sold or prescribed for use in animals for the United States and three trading partners and competitors for which this information was available. Specifically, it shows 2002 antibiotic sales data for the countries that we identified as having government data collection systems on antibiotic use with the available data. Although the United States does not have a government system, we included information collected by the Animal Health Institute for comparison. Total meat production is also shown to represent the size of the animal production industries in these countries.

Table 3: Antibiotic Sales and Meat Production, 2002

	Antibiotic sales (metric tons of active ingredient)	Metric tons of meat production (in millions)	Percent of world total meat production
Denmark[a]	94	2.1	1
New Zealand	106	1.3	1
United Kingdom	433	3.3	1
United States	5,896	39.0	16

Source: Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, Veterinary Institute, the New Zealand Food Safety Authority, the United Kingdom Veterinary Medicines Directorate, the Animal Health Institute, and the Food and Agriculture Organization of the United Nations.

Note: The antibiotic amounts do not include ionophores, an antibacterial that is a unique drug product developed for animal production and not related to traditional antibiotics.

[a]Denmark's information is based on actual use of antibiotics. The other information is based on antibiotics sold for use in animals and includes limited use in other species.United States

Overview of activities. In 1999, federal agencies formed the Interagency Task Force on Antimicrobial Resistance to address antibiotic resistance issues.[1] In October 2003, FDA issued guidelines for assessing the safety of animal drugs (Guidance for Industry #152). FDA is conducting risk assessments of some antibiotics important in human medicine.

Antibiotic-resistance surveillance systems. FDA, CDC, and USDA collect information on antibiotic-resistant bacteria in humans, retail meat, and animals through the National Antimicrobial Resistance Monitoring System (NARMS).

Antibiotic use data collection systems. The Animal Health Institute, a trade association representing veterinary pharmaceutical companies, publishes the only publicly available data on the amount of antibiotics sold annually for use in animals. The Animal Health Institute collects these data from its member companies, which represent about 85 percent of the animal drug sales in the United States. The data show the amount of antibiotics sold by antibiotic class, but certain classes are reported together to abide by company disclosure agreements. See table 3 for information on the amount of antibiotics sold in the United States during 2002. In addition, the United States collects some on-farm data through USDA's National Animal Health Monitoring System (NAHMS) and Collaboration in Animal Health, Food Safety, and Epidemiology (CAHFSE) programs.

Australia

Overview of activities. In 1998, Australia established the Joint Expert Technical Advisory Committee on Antibiotic Resistance to provide independent expert scientific advice on the threat to human health of antibiotic-resistant bacteria caused by use in both animals and humans.[2] Australia has begun to review the approved uses of antibiotics important in human medicine to determine if changes are needed. Australia's review process includes performing a public health and an efficacy assessment. Like the United States' risk assessment approach, Australia's public health assessment considers the hazard, exposure, and potential impact of the

[1]In January 2001, the task force issued *A Public Health Action Plan to Combat Antimicrobial Resistance (Part I Domestic Issues)*.

[2]In September 1999, the committee released *The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans*.

continued use of the antibiotic on public health. The efficacy assessment considers whether the antibiotic is effective in animals for the purpose claimed and whether the label contains adequate instructions. As of April 2003, Australia had completed its assessment of virginiamycin, a member of the streptogramin class, and was considering a recommendation to ban its use for growth promotion. In addition, as of March 2003, Australia was assessing the risk of the macrolide antibiotic class, including tylosin.

Antibiotic resistance surveillance systems. The committee's 1999 report recommended establishing a comprehensive surveillance system to monitor antibiotic-resistant bacteria in animals. As of March 2003, a strategy for developing an antimicrobial resistance surveillance system was being completed.

Antibiotic use data collection systems. Australia uses import data to monitor the annual quantity of antibiotics used in animals because all of the antibiotics used in the nation are imported. The data, which include information on the quantity of antibiotics imported by antibiotic class and end use, are not usually released publicly. A potential problem with this data collection method is that importers are not always able to anticipate how producers will use the antibiotic.

Canada

Overview of activities. Like the United States, Canada plans to do risk assessments of antibiotics important in human medicine and to make changes in approved antibiotic uses as appropriate based on these risk assessments. Canadian officials expect to initially focus on growth promotion uses of several antibiotic classes and antibiotics, including penicillins, tetracyclines, tylosin, and virginiamycin. Canada plans to use risk assessment methods similar to those used in the United States; however, Canada may also consider other factors, such as the benefits associated with antibiotic use. In addition, Canada is considering the adoption of a prescription requirement for all antibiotic uses in animals except growth promotion.

Antibiotic resistance surveillance systems. The Canadian Integrated Program for Antimicrobial Resistance Surveillance, started in 2002 and designed to use resistance surveillance methods consistent with the United States' NARMS, collects information on antibiotic resistance from the farm to the retail levels. Canada issued the first annual report from this surveillance system in March 2004.

Antibiotic use data collection systems. Canada is integrating the collection of data on antibiotic use in humans and animals into its surveillance system and plans to use this information to support risk analysis and policy development. Collection of on-farm data on antibiotic use in animals through pilot projects is ongoing, and collection of data from pharmaceutical companies, importers, and distributors, such as feed mills and veterinarians, is planned.

The European Union

Overview of activities. In 1999, an EU scientific committee on antibiotic resistance recommended that the growth promotion use of antibiotics from classes that are or may be used in human medicine be banned. Later that year, the EU completed action on this recommendation and banned the use of these antibiotics in feed for growth promotion. The scientific committee also recommended that the four remaining antibiotics used for growth promotion be replaced with other alternatives. In 2003, the EU issued a regulation adopting this recommendation, which banned the use of these antibiotics as of January 1, 2006.[3] In addition, Denmark, an EU member, ended the use of all antibiotics for growth promotion in 2000.

Antibiotic resistance surveillance systems. Most EU members have a program to monitor antibiotic resistance, but the EU as a whole does not have a harmonized system that allows comparison of data across nations. A November 2003 directive from the European Parliament and the Council of the European Union set forth general and specific requirements for monitoring antibiotic resistance. Among other things, member countries must ensure that the monitoring system includes a representative number of isolates of *Salmonella* spp., *Campylobacter jejuni*, and *Campylobacter coli* from cattle, swine, and poultry. In particular, Denmark's surveillance system, the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, monitors resistance in these and other bacteria in animals, meat, and humans.

Antibiotic use data collection systems. The EU has proposed that its members collect data on antibiotic use in animals. EU countries' efforts to collect this information are at varying stages of development. For example, while some EU countries are just developing programs to collect antibiotic

[3]The EU will still allow the use of coccidiostat and histomonostat drugs as feed additives for growth promotion. These drugs control parasites and many coccidiostat and histomonostat drugs are not used in humans.

use data, the United Kingdom and Denmark currently collect this information.

The United Kingdom's Veterinary Medicines Directorate collects data from veterinary pharmaceutical companies on the amounts of different antibiotics and other animal drugs sold in the United Kingdom. The directorate then separates these data into chemical groups, administration methods, and target species. For certain antibiotics that are sold for use in more than one species, it is not possible to determine the species in which they were used. However, the directorate is working to more accurately assign sales quantities to each species. See table 3 for information on the amount of antibiotics sold in the United Kingdom during 2002.

Denmark collects extensive data on the use of antibiotics in animals. In particular, through its VetStat program, Danish officials can obtain data on all medicines prescribed by veterinarians for use in animals. This program provides detailed information on antibiotic use, such as the quantity used, class of antibiotic used, species, age of animal, and the purpose of use, as well as the disease the antibiotic was used to treat. In addition, VetStat allows researchers to calculate the average daily doses that animals receive of various antibiotics. See table 3 for information on the amount of antibiotics used in Denmark during 2002.

Hong Kong

Antibiotic resistance surveillance systems. Hong Kong has an antibiotic resistance surveillance system. We did not obtain additional information on this system.

Antibiotic use data collection systems. Hong Kong has an antibiotic use data collection system. We did not obtain additional information on this system.

Japan

Overview of activities. Japan is currently reviewing the use of antibiotics for growth promotion if those antibiotics are from classes used in humans. According to an April 2004 report from the Office of the U.S. Trade Representative, the Japanese government has stated that these reviews will be based on science.

Antibiotic resistance surveillance systems. Japan has an antibiotic resistance surveillance system. We did not obtain additional information on this system.

Antibiotic use data collection systems. Japan has an antibiotic use data collection system. We did not obtain additional information on this system.

Mexico

Antibiotic resistance surveillance systems. In 2000 and 2001, FDA undertook a pilot study with Mexico to monitor the antimicrobial resistance of salmonella and *E. coli* isolates obtained from human samples. In September 2001, the pilot study was expanded into a 3-year cooperative agreement to include both human and animal monitoring. The primary objective of the agreement was to establish an antimicrobial resistance monitoring system for foodborne pathogens in Mexico comparable to the United States' NARMS program.

New Zealand

Overview of activities. New Zealand established an Antibiotic Resistance Steering Group primarily to coordinate a program to gather and analyze information on the use of antibiotics in feed (including antibiotics for growth promotion), assist in developing a policy concerning this use, and assess the potential transfer of resistant bacteria from animals to humans.[4] New Zealand has completed its risk assessments of antibiotics for growth promotion and no longer allows the growth promotion use of any antibiotics that are also related to antibiotics used in human medicine. New Zealand did not carry out a comprehensive risk analysis for any of the antibiotics being used for growth promotion because the available information was not sufficient. Instead, New Zealand used consistent rationale, including the mechanisms and potential for antibiotic resistance and the potential for that resistance to be transferred from animals to humans, in assessing each antibiotic (or class, such as the macrolide class).

Antibiotic resistance surveillance systems. New Zealand is working to implement a comprehensive antibiotic resistance surveillance program. According to a January 2003 antibiotic resistance progress report, New Zealand has programs to monitor specific pathogens in animals, but the programs do not gather information specific to antibiotic resistance. While the government informally monitors the antibiotic resistance of *E. coli* and *Staphylococcus aureus*, the program provides very limited data.

[4]In July 1999, the expert panel released *Antibiotic Resistance and In-Feed Use of Antibiotics in New Zealand.*

Antibiotic use data collection systems. Since 2001, New Zealand has collected antibiotic sales data from a formal survey of pharmaceutical companies. The companies report the data voluntarily. Annual reports provide antibiotics sales statistics by antibiotic class, method of administration, type of use (including growth promotion), and animal species. The data are only indicative of use because antibiotics are used for multiple purposes, and it is impossible to know the exact use of all the antibiotics. New Zealand has considered changes to its data collection system to provide additional information. See table 3 for information on the amount of antibiotics sold in New Zealand during 2002.

South Korea

Antibiotic use data collection systems. The Korea Animal Health Products Association, an industry group, monitors the quantity of antibiotics produced and sold by its members. The data are available on a monthly basis and, at a minimum, provide total antibiotic use quantities by species, specific antibiotic, and antibiotic class.

Antibiotics Frequently Used in Animals

This appendix provides information available on the antibiotics that are frequently used on farms that produce feedlot cattle, swine, and broiler chickens in the United States.

Antibiotic Use in U.S. Feedlot Cattle Production

In 1999, USDA's National Animal Health Monitoring System (NAHMS) collected data on antibiotic use in beef cattle raised in feedlots. Table 4 lists the antibiotics identified as having at least 10 percent of feedlots using them in feed or water, or by injection, and the most frequent purpose of use, when this information is available. NAHMS provided only limited information on how the antibiotics were administered, so this information is not included in the table. The table also presents information on FDA's rankings of the importance of the antibiotic class in human medicine. (See app. III for further information on FDA's ranking system.) For those antibiotics not found in these rankings, we listed them as not important. In particular, over half of the feedlots surveyed used chlortetracycline in feed or water,[1] about one-third used tilmicosin to prevent disease, and over half used tilmicosin, florfenicol, and tetracyclines to treat disease. In addition, about one-third used cephalosporins, fluoroquinolones, and penicillins/amoxicillin to treat disease. However, the feedlots using these antibiotics do not administer them to all cattle. For example, although 42 percent of feedlots use antibiotics to prevent respiratory disease, only 10 percent of feedlot cattle receive antibiotics for this purpose.

[1]NAHMS did not specify the purpose of this use, but included the possible purposes of disease treatment, disease prevention, and growth promotion.

Table 4: Antibiotics Frequently Used in Feedlot Cattle, 1999

Antibiotic class and antibiotic	Most frequent purpose of use	Importance of antibiotic class in human medicine
Cephalosporin (third generation)		Critically important
Ceftiofur[a]	Disease treatment	
Fluoroquinolone		Critically important
Enrofloxacin[a]	Disease treatment	
Macrolide		Critically important
Tilmicosin	Disease treatment, disease prevention	
Tylosin[a]	Disease treatment	
Penicillin/Aminopenicillin		Highly important
Penicillins/amoxicillin	Disease treatment	
Phenicol		Not important
Florfenicol	Disease treatment, disease prevention	
Sulfonamide		Not important
Sulfamethazine[b]	Not specified	
Tetracycline		Highly important
Chlortetracycline	Not specified	
Oxytetracycline	Disease treatment, disease prevention	

Source: GAO analysis of USDA and FDA data.

[a]The National Animal Health Monitoring System cited this antibiotic as an example for the class.

[b]Used in a combination with chlortetracycline.

Antibiotic Use in U.S. Swine Production

In 2000, NAHMS collected data on antibiotic use in swine. Table 5 lists the antibiotics identified as those that at least 10 percent of producers use in feed or water or by injection for either nursery-age or older swine, the most frequent method of administration for these antibiotics, and the most frequent purpose of use. The table also presents information on FDA's ranking of the importance of the antibiotic class in human medicine. For those antibiotics not found in these rankings, we listed them as not important. In particular, about half of the producers surveyed used tylosin and chlortetracycline in feed. In addition, about one-third of the producers surveyed used a penicillin to treat disease and bacitracin to promote growth. However, the producers using these antibiotics do not administer them to all of their swine.

Table 5: Antibiotics Frequently Used in Swine, 2000

Antibiotic class and antibiotic	Most frequent method of administration	Most frequent purpose of use	Importance of antibiotic class in human medicine
Cephalosporin (third generation)			Critically important
Ceftiofur	Injection	Disease treatment	
Lincosamide			Highly important
Lincomycin	Injection	Disease treatment	
Macrolide			Critically important
Tylosin	Feed, injection	Disease treatment, disease prevention, growth promotion	
Penicillin			Highly important
Procaine Penicillin G	Injection	Disease treatment	
Penicillin Benzathine	Injection	Disease treatment	
Penicillin[a]	Feed	Growth promotion	
Pleuromutilin			Not important
Tiamulin	Feed	Growth promotion	
Polypeptide			Not important
Bacitracin	Feed	Growth promotion	
Sulfonamide			Not important
Sulfathiazole[a]	Feed	Growth promotion	
Tetracycline			Highly important
Chlortetracycline	Feed	Disease treatment, disease prevention, growth promotion	
Oxytetracycline	Injection	Disease treatment	
Other			Not important
Carbadox	Feed	Growth promotion	

Source: GAO analysis of USDA and FDA data.

[a]A chlortetracycline/penicillin/sulfathiazole combination is used for growth promotion.

Antibiotic Use in U.S. Broiler Production

USDA has not collected any data on antibiotic use in broiler chickens through NAHMS. However, a University of Arkansas study used data from a corporate database to track patterns of antibiotic use in broiler chickens from 1995 through 2000.[2] This study focused on the use of antibiotics in

[2]H.D. Chapman and Z.B. Johnson, "Use of Antibiotics and Roxarsone in Broiler Chickens in the USA: Analysis for the Years 1995-2000." *Poultry Science*, vol. 81 (2002).

feed to promote growth and to prevent disease. Over the period of the study, the percentage of production units using antibiotics in feed decreased, in part because antibiotics did not prove to be as cost-effective as other feed additives that promote growth.[3] The study did not analyze data on antibiotics used in chickens for disease treatment. According to industry officials, producers seldom treat chickens for diseases.

Table 6 lists the antibiotics identified by the study as being used by at least 10 percent of broiler production units and their purpose of use. Table 6 also presents information on FDA's ranking of the importance of the antibiotic class in human medicine. For those antibiotics not found in these rankings, we listed them as not important.

Table 6: Antibiotics Frequently Used in Feed for Broiler Chickens, 1995-2000

Antibiotic class and antibiotic used	Most frequent purpose of use	Importance of antibiotic class in human medicine
Other		Not important
Bambermycin	Growth promotion/disease prevention	
Polypeptide		Not important
Bacitracin	Growth promotion/ disease prevention	
Streptogramin		Highly important
Virginiamycin	Growth promotion/ disease prevention	

Source: GAO analysis of industry and FDA data.

[3]A production unit in most cases represents a broiler complex comprising a group of farms, in a common geographical area, that is served by a single feed mill.

Comments from the U.S. Department of Agriculture

Note: GAO comments supplementing those in the report text appear at the end of this appendix.

United States Department of Agriculture | Food Safety and Inspection Service | Washington, D.C. 20250

Ms. Anu K. Mittal
Director
Natural Resources and Environment
United States General Accounting Office
441 G Street, NW
Washington, DC 20548

APR - 5 2004

Dear Ms. Mittal:

In your letter dated March 16, 2004, you requested the U.S. Department of Agriculture (USDA) written comments on the Draft report GAO-04-490 "Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals." Thank you for the opportunity to provide comments on the draft report.

We generally agree with the report. The report recognizes the many issues and complexities of efforts to address the risk to humans from antibiotic use in animals. We believe that the Animal National Antimicrobial Resistance Monitoring System (NARMS) and the Collaboration for Animal Health and Foods Safety Epidemiology (CAHFSE) are essential programs. These programs provide data that will protect the public health and assure consumers of the safety of their food. The report highlights the importance of the CAHFSE project and its contribution in supplying antimicrobial use data and information on the impact of antibiotic use in various animal species.

General Comments:

See comment 1.

1. The report should note that CAHFSE is funded with limited base agency resources and that new funding would need to be considered before expanding it to slaughter/processing plants, more swine operations, or other species. To a large extent, the existence of CAHFSE is the result of redirected internal funding from other program areas.

See comment 1.
Now on pp. 7 and 41.

2. Although the report identified several opportunities (on page 10, 2nd paragraph, and page 45, 2nd paragraph) to strengthen data collection and research efforts, the report should explicitly state that new funding would need to be considered before these activities could be supported.

See comment 2.

3. Throughout the document you may want to reconsider when it is appropriate to use the terms "antibiotic resistance in humans" or "antibiotic resistant bacteria in humans." Suppositions or conclusions by authors of studies should be supported with appropriate references. Moreover, many statements in the report about *definitive*

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Now on p. 17.

findings (for example on page 21, 1st paragraph) are redundant, and should make reference to scientific literature.

See comment 3.

4. On page 21, paragraph 1, and elsewhere in the report the collection of antimicrobial use data at the macro (aggregate) level seems to be emphasized. While such data are useful for generating hypotheses about the relationships between antimicrobial use and antimicrobial resistance, they do not provide sufficient information upon which to take specific action or to evaluate appropriate mitigation strategies. As pointed out in the report, antimicrobials can be used in many ways; and without knowing more specifically how they are used, it is impossible to determine which of the uses is responsible for any trends that may be seen in the outcomes being monitored.

See comment 4.

5. The Highlights section opening paragraph states, "Some research has shown that use of antibiotics in food animals poses significant risks for human health, but other researchers contend that the clinical consequences of the transference, if it occurs, are small." The report cites many references supporting the first position, "use of antibiotics in food animals poses significant risks for human health…", but not the second position, "…the clinical consequences of the transference, if it occurs, are small." GAO should consider including more scientific evidence to support the second position.

See comment 5.

6. The report provides a comprehensive overview of several surveillance programs pertaining to antimicrobial resistance throughout the Federal government such as NARMS and CAHFSE. The report would be more complete if it included an overview of research efforts related to antimicrobial resistance. The Cooperative State Research, Education, and Extension Service (CSREES) funded over 30 studies since 2000 related to antibiotic resistance. CSREES awarded an additional $8 million in grants related to antibiotic resistance in 1999 and 2000. Funded studies include research into the prevalence, development, and possible transmission of antibiotic resistance; the epidemiology of antibiotic resistance; risk factors for persistence of antibiotic resistance in the animal and the environment as well as risk factors for transmission; the evaluation of management practices and potential prevention and intervention strategies for antibiotic resistance. In addition, USDA has partnered with FDA to fund education and training programs.

See comment 6.

7. Information significantly impacting conclusions or limitations regarding studies advocating that agricultural use of antimicrobials promotes development of antimicrobial-resistant bacterial populations in humans are not reported, leading the reader to assume that agriculture use is responsible for increases, when scientific evidence may not conclusively support this assumption.

A few specific examples include:

Now on p. 18.

- The report fails to mention that increases in fluoroquinolone resistance in a Minnesota study (page 22) were associated in largest part with foreign travel.
- The report mentions avoparcin use in food animals may lead to increased numbers of vancomycin-resistant enterococci, but fails to mention that

Now on p. 24.

Now on p. 17.

emergence of vancomycin-resistant enterococci in the US occurred despite the fact that avoparcin (page 28) has never been used in food animals in the US.

- The report mentions on page 21 that the finding of genetically-related organisms in food derived from animals and in humans established *definitive* evidence of transfer antimicrobial-resistant pathogens from food animals to humans. Though it is likely that a transfer of antimicrobial-resistant pathogens occurred, epidemiological studies described only provide circumstantial evidence. Many of the studies mentioned in the report are case-control studies which can only reveal associations, not establish cause and effect.

Please find enclosed additional specific USDA comments on the draft report.

Sincerely,

for Ronald F. Hicks
Assistant Administrator
Office of Program Evaluation, Enforcement and Review

Enclosure

GAO's Responses to USDA's Comments

The following are our comments on the USDA letter, dated April 5, 2004.

1. We revised the report to include USDA's concerns that additional funding would be needed to expand CAHFSE.

2. We clarified our discussion of some studies. References are cited in footnotes for studies discussed in the report.

3. We agree that the collection of both aggregate and detailed data on antibiotic use in animals is useful and that researchers need to know specifically how antibiotics are used in order to determine which of the uses is responsible for trends in antibiotic resistance. The report discusses both aggregate and detailed data. As USDA states, the report highlights the CAHFSE program, through which USDA is collecting specific, on-farm data on swine. In addition, the report discusses Denmark's system, which collects detailed data on how antibiotics are used in animals.

4. We found that only a few studies have concluded that the risk is minimal, while many studies have concluded that there is a significant human health risk from the transference.

5. We revised the report to include information on research funded by USDA's Cooperative State Research, Education, and Extension Service.

6. We clarified the report to reflect comments on specific studies. In addition, we clarified the report to indicate which results were from epidemiologic studies alone, and which results were from epidemiologic studies that included molecular subtyping techniques.

Comments from the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES Office of Inspector General

Washington, D.C. 20201

APR 7 2004

Ms. Marcia Crosse
Director, Health Care
Public Health and Military Health Care Issues
United States General `Accounting Office
Washington, D.C. 20548

Dear Ms. Crosse:

Enclosed are the Department's comments on your draft report entitled, "Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals" (GAO-04-490). The comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department provided several technical comments directly to your staff.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely,

Dara Corrigan
Acting Principal Deputy Inspector General

Enclosure

The Office of Inspector General (OIG) is transmitting the Department's response to this draft report in our capacity as the Department's designated focal point and coordinator for General Accounting Office reports. OIG has not conducted an independent assessment of these comments and therefore expresses no opinion on them.

GENERAL COMMENTS BY THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE U.S. GENERAL ACCOUNTING OFFICE'S DRAFT REPORT, "ANTIBIOTIC RESISTANCE: FEDERAL AGENCIES NEED TO BETTER FOCUS EFFORTS TO ADDRESS RISK TO HUMANS FROM ANTIBIOTIC USE IN ANIMALS" (GAO-04-490)

The Department of Health and Human Services (HHS) appreciates the opportunity to review and comment on the General Accounting Office's (GAO) draft report. HHS concurs with the findings of this report and considers it to be very thorough and generally accurate.

The Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) have been and will continue to be actively engaged in: research on the relationship between antibiotic use in agriculture and emerging resistant bacteria, assessing the human health consequences of antibiotic use in food animals, and developing strategies to mitigate antibiotic resistance. We believe these agencies can make important contributions to the scientific knowledge on this issue through agency specific projects as well as through interdepartmental and extramural collaborations.

The draft report presents or refers to significant and growing evidence demonstrating the human health consequences of drug resistant infections related to antibiotic use in agriculture. We discuss below 11 additional studies that GAO did not reference in their draft report. While some of these studies date back to 1971, they remain relevant to this issue. These studies, along with those cited in the GAO report, all demonstrate a relationship between the use of antimicrobials in food-producing animals, antibiotic resistance in humans, and adverse human health consequences as a result. We believe that there is a preponderance of evidence that the use of antimicrobials in food-producing animals has adverse human consequences.

There is little evidence to the contrary. GAO cites one study and one article published in the *Journal of Antimicrobial Chemotherapy*.[1] We believe GAO should note in its report that the article they cite was written by an advisory group to the Animal Health Institute.

Recent studies have demonstrated that antimicrobial resistance among foodborne bacteria, primarily *Salmonella* and *Campylobacter*, may cause prolonged duration of illness, and increased rates of bacteremia, hospitalization, and death. Other studies have determined that the majority of antimicrobial resistant *Salmonella* and *Campylobacter* infections in developed countries are due to antimicrobial use in food animals, findings that GAO does not dispute. Therefore, the studies described here can be used as evidence that adverse human health outcomes are associated with resistant bacteria due to the use of antimicrobials in food animals, although not all of these studies specifically addressed the origin of the resistant bacteria.

Holmberg *et al.* reviewed *Salmonella* outbreaks investigated by the Centers for Diseases Control and Prevention (CDC) between 1971 and 1983 and found a higher case fatality

rate for patients infected with antimicrobial-resistant *Salmonella* (4.2%) than for those with antimicrobial-sensitive infections (0.2%).[2] In a later study (1987) of 28 *Salmonella* outbreaks, greater hospitalization and case-fatality rates were associated with outbreaks caused by antimicrobial-resistant *Salmonella* as compared to susceptible infections.[3] A more recent CDC study of 24 *Salmonella* outbreaks that occurred between 1984 and 2002 also found that outbreaks caused by antimicrobial-resistant *Salmonella* resulted in higher hospitalization rates than outbreaks caused by susceptible *Salmonella.* [4]

Studies of salmonellosis cases not limited to outbreaks have also demonstrated that resistance is associated with higher morbidity and mortality. In a prospective CDC study of 758 salmonellosis cases, patients with resistant infections were significantly more likely be hospitalized than were those with susceptible infections, even after accounting for underlying illness and prior antimicrobial exposure using multivariate techniques. Patients with resistant infections also tended to be ill longer (median, 10 vs. 8 days) and hospitalized longer (median, 5 vs. 4 days) than patients with susceptible infections.[5]

More recent studies, which have utilized epidemiological and/or statistical methodologies to account for potentially confounding factors including serotype and age, have provided further support for the association between resistance in *Salmonella* and increased morbidity and mortality. Varma *et al.* [6] studied *Salmonella* cases diagnosed in the United States between 1996-2000 and found that antimicrobial resistance was associated with increased hospitalization and bloodstream infections. Patients with *Salmonella* isolates resistant to any antimicrobial agent or to commonly used agents (cephalosporins, quinolones, or amino glycosides) were hospitalized more often than patients with pan-susceptible isolates even after controlling for age, race, surveillance site, serotype, and bloodstream infection in a multivariate analysis.[7] Resistance to any antimicrobial or to commonly used agents was also associated with an increase in bloodstream infection compared to pan-susceptible isolates after controlling for age and serotype.[7]

Helms *et al.* [8] conducted a large matched cohort study in Denmark to determine mortality rates associated with different drug resistance patterns in *S.* Typhimurium. Each patient diagnosed between 1995 and 1999 was matched by age, sex, and county to 10 people in the general Danish population. By survival analysis, the 2-year mortality rates for patients were compared with mortality rates in the general population after the data were adjusted for differences in co morbidity. Patients with pan-susceptible strains of *S.* Typhimurium were 2.3 times more likely to die within two years than the general Danish population, whereas patients infected with R-type ACSSuT (resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline) were 4.8 times more likely to die. Resistance to nalidixic acid was associated with even higher mortality (resistance to nalidixic acid often foreshadows reduced susceptibility to the fluoroquinolones); patients infected with nalidixic acid resistant strains were 10.3 times more likely to die than the general population, while those infected with strains resistant to nalidixic acid as well as ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline (ACSSuT) were 13.1 times more likely to die.[8] Another recently completed study in Denmark found that among patients with culture-confirmed *S.* Typhimurium infections between 1995 and 2000, patients with nalidixic acid-resistant infections were

more likely to have bloodstream infections or die in the 90 days following specimen collection than those with susceptible infections.[4]

A study conducted in Canada in 1999 and 2000 investigated the relationship between increased burden of illness in patients with *S.* Typhimurium and both definitive phage type 104 (DT104) and antimicrobial resistance.[9] In this study, after controlling for significant risk factors and confounding variables, including age, hospitalization was 2.3 times more likely to occur among patients whose infections were resistant to at least ampicillin, kanamycin and/or chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline (R-type AK/CSSuT) compared with AK/CSSuT-susceptible patients (p=0.003) and 3.6 times more likely to occur among patients with non-DT104 R-type AKSSuT infections compared with patients with non-DT104 R-type AKSSuT-susceptible infections (p=0.005). [9]

The evidence is not limited to *Salmonella* infections. Several *Campylobacter* case-control studies in the United States and Denmark have demonstrated a relationship between quinolone resistance and prolonged duration of illness. GAO does mention the Smith *et al.* study in Minnesota[10], but there are several others that GAO ignores. In a 1996-1997 study in Denmark, Neimann *et al.* found that among *Campylobacter* cases treated with fluoroquinolones or other antibiotics, the median duration of illness was 14 days in patients infected with ciprofloxacin-resistant strains compared to 9 days in patients with susceptible isolates.[11]

Nelson *et al.* conducted a multistate case-control study of sporadic *Campylobacter* cases in the United States in 1998 and 1999.[12] Among patients who did not take antidiarrheal medications, patients with ciprofloxacin-resistant infections had a longer mean duration of diarrhea than those with ciprofloxacin-susceptible infections (9 vs. 7 days, p=0.04). The difference in mean duration of diarrhea between ciprofloxacin-resistant and ciprofloxacin-susceptible infections was even more pronounced among persons who did not take antidiarrheals or antimicrobials (12 vs. 6 days, p=0.04), suggesting that resistant *Campylobacter* may be more virulent than susceptible strains. In a multivariate model controlling for antimicrobial, antidiarrheal, and antacid use, the mean duration of diarrhea was longer for patients with ciprofloxacin-resistant infections than for patients with susceptible infections (p=0.01) and the effect was independent of foreign travel.[12]

A recently completed study in Denmark evaluated the relationship between resistance in *Campylobacter* and increases in both bacteremia and mortality. Among patients with culture-confirmed campylobacteriosis from 1995 to 2000, those with fluoroquinolone-resistant or erythromycin-resistant *Campylobacter* infections were more likely to have a bloodstream infection or die in the 90 days following specimen collection than those with susceptible infections.[4]

GAO should change the title and update the section in the draft report to read, "FDA's Center for Veterinary Medicine Has Initiated Action to Prohibit the Use of Enrofloxacin in Poultry, but Proceedings Not Yet Complete." Since GAO issued its draft report the Administrative Law Judge issued an initial decision, find that: 1) "poultry is in fact a

major source of fluoroquinolone-resistant *Campylobacte*"; 2) "the use of Baytril in poultry acts as a selection pressure for fluoroquinolone-resistant *Campylobacter* and results in the emergence and dissemination of fluoroquinolone-resistant *Campylobacter*"; 3) "fluoroquinolone-resistant *Campylobacter* are transferred from poultry to humans and contribute to *Campylobacter* infections in humans"; 4) "fluoroquinolone-resistant *Campylobacter* results in an increased severity of campylobacteriosis in humans." http://www.fda.gov/ohrms/dockets/dailys/04/mar04/031604/00n-1571-idf0001-vol389.pdf

Recommendations

1. **FDA expedite its risk assessments of drugs used in food animals that are critically important for human health to determine if regulatory action is necessary**

GAO recommends that FDA expedite its review of the currently approved antimicrobials for food-producing animals using GFI 152 and focusing on the antimicrobials that are critically important for human health. FDA agrees that this review is important and has devoted considerable resources to this process. It is important to point out, however, that if CVM develops sufficient evidence to initiate a withdrawal proceeding under the Federal Food, Drug and Cosmetic Act, this withdrawal proceeding can be quite lengthy. As GAO noted, CVM proposed to withdraw approval of the new animal drug for Baytril use in poultry in October 2000, yet Baytril remains on the market.

2. **Better data is needed on antimicrobial drug use in food animals**

GAO is correct that drug use data are essential to evaluate the development of antimicrobial resistance and to target mitigation strategies intended to prolong the effectiveness of antimicrobials used in food-producing animals. Data generated from monitoring antimicrobial usage can be used in conjunction with surveillance of antimicrobial resistance to inform and educate all stakeholders, to develop national and international policies for the containment of antimicrobial resistance, and to evaluate the impact of the implementation of the prudent use of antimicrobials and other interventions designed to mitigate or contain antimicrobial resistance.

GAO recommends that HHS and USDA develop and implement a plan to collect data on antibiotic use in food animals. However, the most useful and reliable data are those maintained by the drug sponsors. Currently, the drug companies are required under 21 CFR 514.80(b)(4)(i) to report quantities of product marketed to FDA on the anniversary date of approval of their new animal drug application (NADA or ANADA). Sponsors typically provide a quantity for each of the dosage forms marketed but the information is not differentiated by animal species, label indication(s), route of administration or geographic region. The data collection requirements would need to be modified to make the data more relevant for the purposes described above. This would require notice and comment rulemaking to revise the current regulation.

We propose that the forum for discussions between HHS and USDA for improving and creating surveillance for drug use in agriculture should be the Interagency Task Force on Antimicrobial Resistance. The appropriate agencies of HHS are members. USDA is represented as a department, but personnel from specific relevant agencies within USDA can participate in discussions and planning through this group as they did during the drafting of *A Public Health Action Plan to Combat Antimicrobial Resistance.*

END NOTES

[1] Phillips I, Casewell M, Cox T, *et al. Does the use of antibiotics in food animals pose a risk to human health?* A critical review of published data. J Antimicrob Chemother 2004;53:28-52.

[2] Holmberg SD, Wells JG, Cohen ML. *Animal-to-man transmission of antimicrobial-resistant Salmonella: investigations of U.S. outbreaks*, 1971-1983. Science 1984;225:833-5.

[3] Holmberg SD, Solomon SL, Blake PA. *Health and economic impacts of antimicrobial resistance*. Rev Infect Dis 1987; 9:1065-78.

[4] World Health Organization. Joint FAO/OIE/WHO *Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment*. Geneva, 1-5 December, 2003. Available online at: http://www.who.int/foodsafety/micro/meetings/nov2003/en/

[5] Lee LA, Puhr ND, Maloney K, et al. *Increase in antimicrobial-resistant Salmonella infections in the United States, 1989-1990*. J Infect Dis 1994;170:128-34.

[6] Varma J, Mølbak K, Rossiter S, et al. *Antimicrobial resistance in Salmonella is associated with increased hospitalization; NARMS 1996-2000*. International Conference on Emerging Infectious Diseases. March 2002. Atlanta, GA.

[7] Varma J, Mølbak K, Rossiter S, et al. *Antimicrobial resistance in non-typhoidal Salmonella is associated with increased hospitalization and bloodstream infection--United States, 1996-2000. 51st Annual EIS Conference.* April 22-26, 2002. Atlanta, GA.

[8] Helms M, Vastrup P, Gerner-Smidt P, Mølbak K. *Excess mortality associated with antimicrobial drug-resistant Salmonella Typhimurium*. Emerg Infect Dis 2002;8:490-5.

[9] Martin L, Fyfe M, Doré K, et al. *Increased burden of illness associated with antimicrobial-resistant Salmonella enterica serotype Typhimurium infections*. J Infect Dis 2004;189:377-84

[10] Smith KE, Besser JM, Hedberg CW, et al. *Quinolone-resistant Campylobacter jejuni infections in Minnesota, 1992-1998.* N Engl J Med 1999;340:1525-32.

[11] Neimann J, Mølbak K, Engberg J, et al. *Longer duration of illness among Campylobacter patients treated with fluoroquinolones. 11th International Workshop on Campylobacter, Helicobacter, and Related Organisms, 1-5 September, 2001*. Freiburg, Germany.

[12] Nelson JM, Smith KE, Vugia DJ, et al. *Prolonged diarrhea due to ciprofloxacin-resistant Campylobacter infections*. J Infect Dis 2004; in press.

GAO Contacts and Staff Acknowledgments

GAO Contacts

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