EXHIBIT Y

TO DECLARATION OF
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GAO

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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GAO Accountability • Integrity • Reliability

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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Accountability * Integrity * Reliability

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

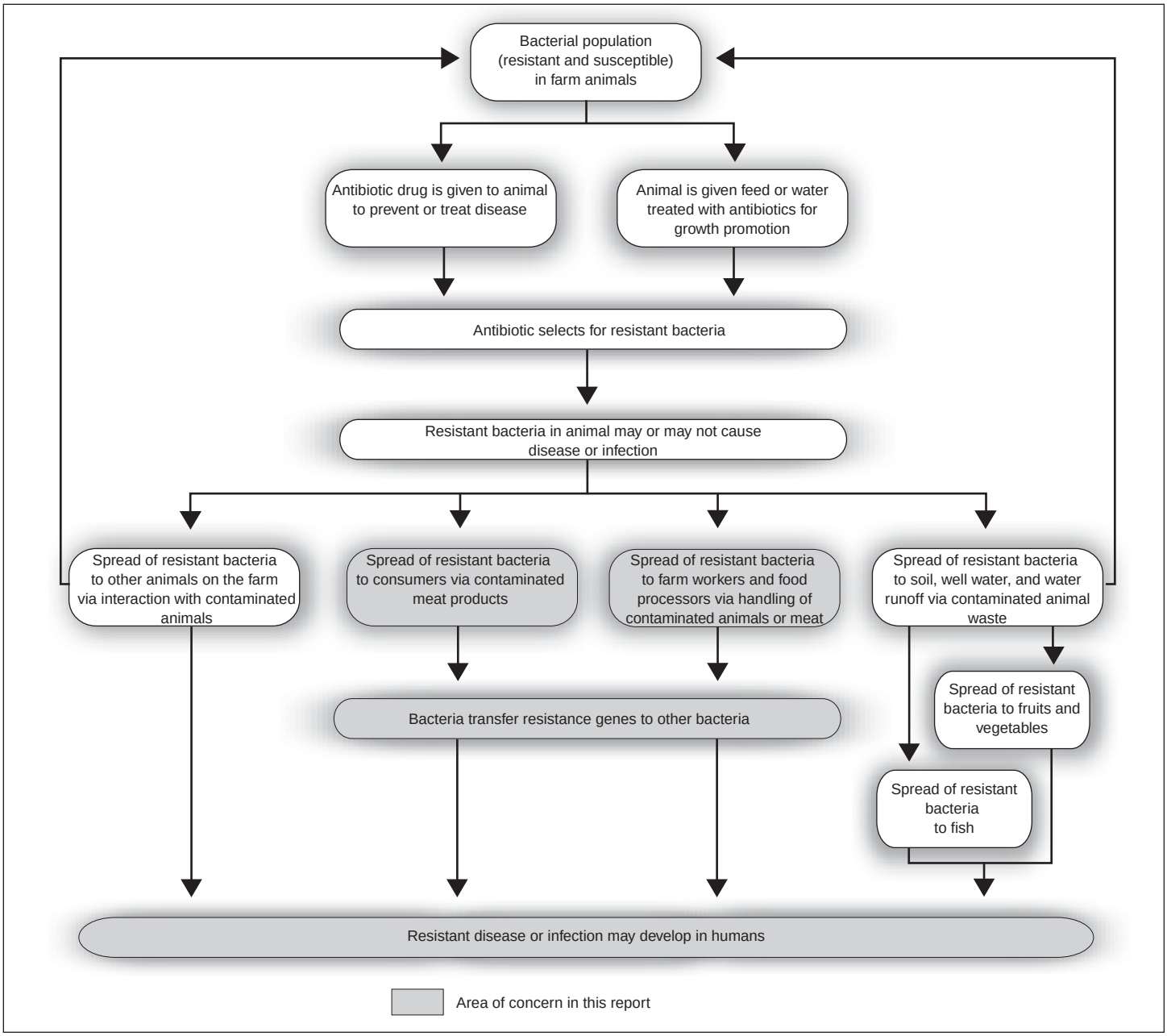
Source: GAO.

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)

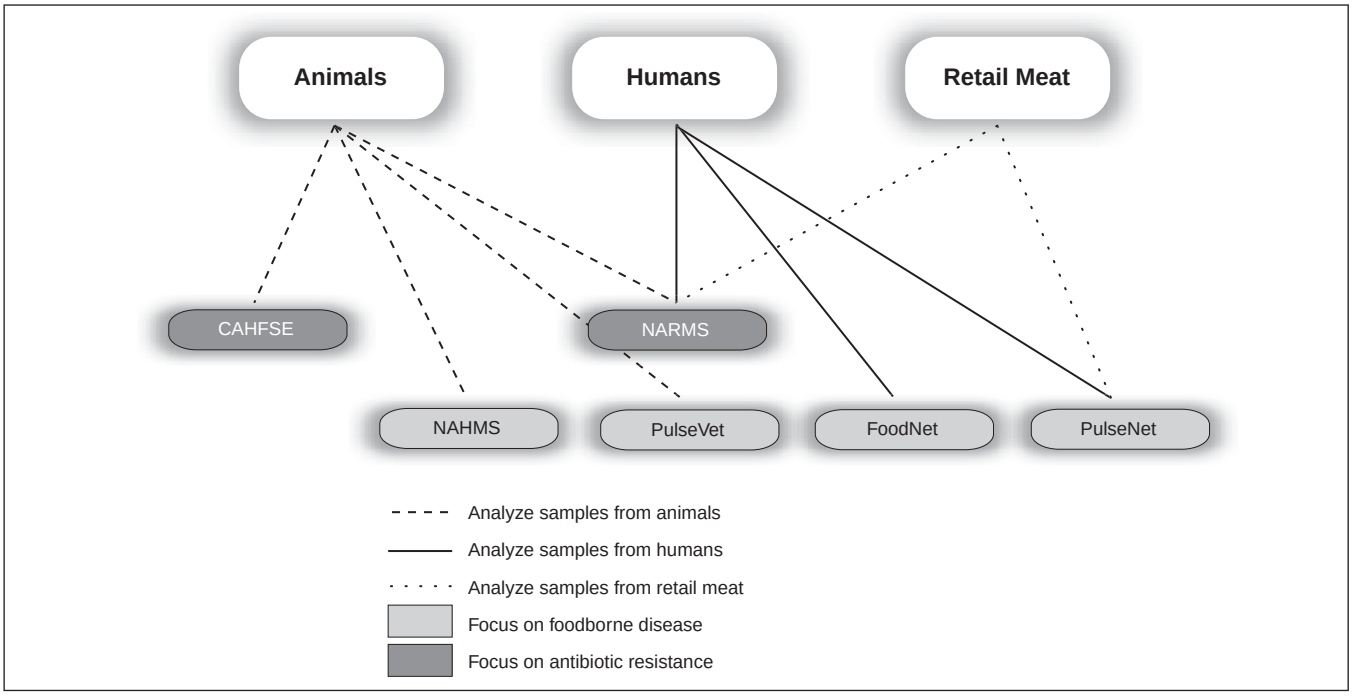
Activity	Purpose	Lead agency	Bacteria	Source of bacteria isolates
National Animal Health Monitoring System (NAHMS)	To collect, analyze, and disseminate data on animal health, management, and productivity.	USDA	• *Salmonella*	Animals on farm

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

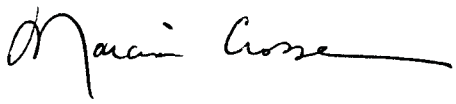
those with antibiotic-susceptible infections. Most of the studies we identified found modest but significant human health consequences, similar to those in the unpublished study described in HHS's comments. Regarding our recommendation that the agencies jointly develop and implement a plan for collecting 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.



Marcia Crosse
Director, Health Care—Public
Health and Military Health Care Issues

Anu K. Mittal
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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.