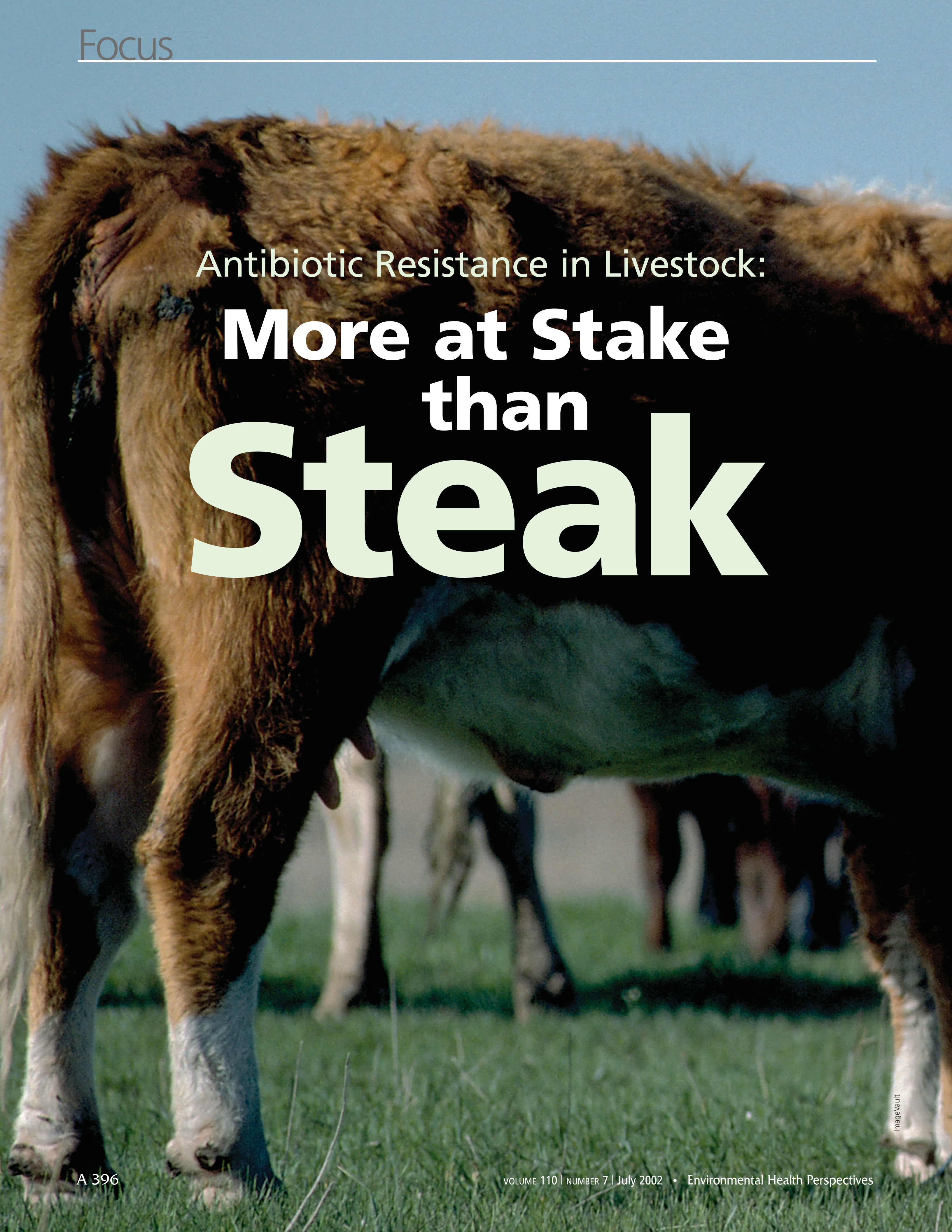
Antibiotic Resistance in Livestock:

More at Stake than Steak



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Imagine, for a moment, this scenario: you, like millions of other people around the world, are lying in a hospital bed suffering from a bacterial infection. Your doctors have told you that your disease, which once would have been easily treated, no longer responds to available drugs. In addition to feeling shock and disbelief, you'd probably wonder how this could have happened.

You would not be alone. The specter of antibiotic resistance is considered by many to be one of the most pressing scientific questions today. With each passing year, former wonder drugs like penicillin, erythromycin, and tetracycline are less effective against strains of treatment-resistant "superbugs." By decreasing the number of effective drugs in the medical arsenal, antibiotic resistance is making bacterial infections and related conditions more difficult to treat. Scientists also worry that the spread of resistance genes among even unrelated strains of bacteria could turn what are now treatable illnesses into killers.

Where are these resistance traits coming from? Certainly overuse in human medicine is an important source. But agricultural uses, particularly in livestock, also contribute significantly toward the problem of antibiotic resistance, scientists say.

As much as 70% of the antibiotics produced in the United States today (including those approved but never or not currently marketed) are for use in food animals, according to the Union of Concerned Scientists, a Cambridge, Massachusetts–based organization of experts that advocates for precautionary principles in environmental debates. In addition to treating disease, substantial amounts of these drugs are given to healthy animals to prevent illness and to promote growth. Exactly why antibiotics enhance weight gain is unclear. Many experts believe they allow animals to conserve energy that would otherwise be devoted to fighting pathogens. But this explanation isn't universally accepted, and the question is still debated.

An Industry under Pressure

The pressure on agriculture to alter its use of antibiotics has never been greater. Earlier this year, in response to pressure from environmental groups, the McDonald's, Wendy's, and Popeyes fast-food chains announced that they would no longer buy chicken treated with an antibiotic called enrofloxacin because it's related to ciprofloxacin, a fluoroquinolone drug used to treat *Campylobacter*—and anthrax—in humans. The U.S. Food and Drug Administration (FDA) is now withdrawing approval for enrofloxacin (marketed as Baytril) from its producer, Bayer, due to fluoroquinolone resistance in strains of *Campylobacter* that infect humans. (The company refused to voluntarily remove the drug from the poultry market.) Three companies—Tyson Foods, Perdue Farms, and Foster Farms—which combined produce a third of the chickens raised in the United States today, announced last February that they will no longer give antibiotics to healthy birds. And two bills in the Congress, one authored by Representative Sherrod Brown (D–Ohio) and the other by Senator Edward Kennedy (D–Massachusetts), have proposed phasing out uses of antibiotic formulations used in both human and veterinary medicine in healthy farm animals altogether.

No day at the spa. Some experts blame the increase in nontherapeutic uses of antibiotics in animals, at least in part, for the increasing resistance of microbes to antibiotics.

The Alliance for the Prudent Use of Antibiotics (APUA), an advocacy group based in Boston, Massachusetts, published a report in the 1 June 2002 supplement to *Clinical Infectious Diseases* culminating an expert review of approximately 500 published studies. The report calls for major changes in antibiotic use. Echoing the group's conclusions, Sherwood Gorbach, a professor of community medicine at Tufts University Medical School in Boston and a member of the APUA's scientific advisory board, says, "Nontherapeutic use of antibiotics in healthy animals for growth promotion and feed efficiency should be discontinued. Furthermore, certain antibiotics that are critically important in human medicine, such as fluoroquinolones and third-generation cephalosporins, should be restricted to use only in critically ill animals and refractory cases under a veterinarian's prescription."

A shot in the dark? Researchers don't really know how—and how much—the use of antibiotics in animals may contribute to resistance in antibiotics that are also used in humans. Many say livestock breeders should err on the side of caution in antibiotic use until more is known.

Some stakeholders insist these drastic measures are unwarranted because antibiotic use among people—not animals—is the main cause of resistance to human antibiotics. They also question the degree to which resistance genes in animal bacteria are transferred to human bacteria. Data addressing this question are just now being collected, says Abigail Salyers, a professor of microbiology at the University of Illinois at Urbana-Champaign and president of the American Society for Microbiology. What's needed, she explains, are more studies that trace resistance genes back to agricultural sources—something scientists are beginning to explore.

In the meantime, industrial agriculture has plenty of incentive to turn the uncertainty to its advantage. Hanging in the balance are billions in drug sales and the future of industrial meat production, which some argue can't be sustained without antibiotics at current use levels. All across the United States, small farms are giving way to huge consolidated feedlots that facilitate the rapid spread of bacteria and disease. Feedlots housing up to 100,000 cows within a few hundred acres are not uncommon, according to GeneNet, a Hays, Kansas–based livestock marketing organization. In 1945, the typical henhouse contained 500 birds. Today, the average ranges from 80,000 to 175,000. In 1980, there were 650,000 hog farms in the United States. In 2001, there were 81,000, including Circle Four Farms in Milford, Utah, a mega-facility

top to bottom: USDA; PhotoDisc

Healthy Animals, Unhealthy People? Popular Antibiotics on Farms and in Pharmacies

Antibiotic Class	Animal Species	Animal Use			Human Use	Bacterial Resistance
		Disease Treatment	Disease Prevention	Growth Promotion		
Aminoglycosides (gentamicin, neomycin, streptomycin)	cattle, poultry, sheep, swine	✓	✓		✓	✓
Beta-Lactams						
Penicillins (amoxicillin, ampicillin)	cattle, poultry, sheep, swine	✓	✓	✓	✓	✓
Cephalosporins (third generation)	cattle, poultry, sheep, swine	✓	✓		✓	✓
Ionophores	cattle, poultry, sheep		✓	✓		✓
Macrolides (erythromycin, tilmicosin, tylosin)	cattle, poultry, swine	✓	✓	✓	✓	✓
Polypeptides (bacitracin)	poultry, swine	✓	✓	✓	✓	✓
Fluoroquinolones (enrofloxacin)	cattle, poultry	✓	✓		✓	✓
Sulfonamides	cattle, poultry, swine	✓		✓	✓	✓
Tetracyclines	cattle, poultry, sheep, swine	✓	✓	✓	✓	✓

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housing 500,000 hogs in a 35-square-mile area, according to the U.S. Department of Agriculture (USDA).

"If you take away the tools we have to manage and control disease, we'll have to look for other alternatives," says Ron Phillips, a spokesperson for the Animal Health Institute, a Washington, D.C.–based trade group representing drug companies that make antibiotics for the food animal industry. "And to date, no one has found an alternative that can match antibiotics for disease control on the scale at which we produce food today—at least not one which allows consumers to buy meat at such low prices."

While no one disputes industry's right to treat sick animals with antibiotics, the real issue, Salyers says, concerns industry's right to give antibiotics to healthy animals for so-called nontherapeutic uses. And what exactly are nontherapeutic uses? "The answer to that question is the core of this whole problem," she says. "For example, consider antibiotics used for prophylaxis, meaning disease prevention. A farmer might treat an entire flock or herd because he believes there is a threat of disease, even in the absence of sick animals. Is this therapeutic? The industry would say it is. Most activists would say it is not. Same for growth promotion, which some industry experts might consider to be prophylactic. You could say antibiotics promote growth because they limit infections. In this context, growth promotion with antibiotics can be said to be prophylactic. If you wanted to, you could even argue that all uses are therapeutic."

This kind of semantics is where the proposed changes in antibiotics-use policies get hung up. In addition to restricting the use of agricultural antibiotics that are also used in humans, groups like the APUA want to eliminate agricultural nontherapeutic uses, particularly growth promotion. In response, industry is striving to minimize the number of defined nontherapeutic use categories.

The Resistance Phenomenon

Antibiotic resistance has been a recognized medical problem ever since the drugs became widely available in the 1940s. With each passing decade, emergent strains of bacteria that defy not only single but also multiple antibiotics have become increasingly common. Some strains of human pathogens, including *Enterococcus faecalis*, *Mycobacterium tuberculosis*, and *Pseudomonas aeruginosa*, are now resistant to more than 100 drugs. Meanwhile, diseases once thought to be nearly eradicated—tuberculosis, for instance—are making a troubling return due to antibiotic resistance.

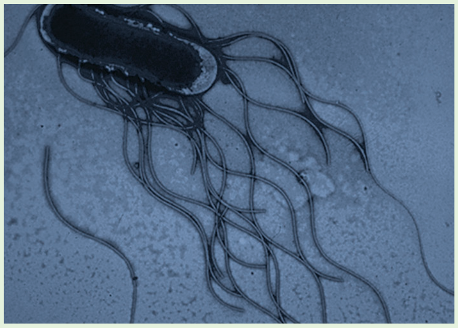
Bacteria acquire resistance genes by any of three routes: inheritance, spontaneous mutations that produce new resistance traits, or acquisition of genes from other bacteria in their vicinity in a process known as "horizontal transfer," or "bacterial sex." Jokes Salyers, "Evidence is mounting that your intestinal tract is a swinging singles' bar for bacteria." She adds, "And it's all-inclusive. We're talking about gene transfer across genus and species lines. That's like a human impregnating a slug."

Evidence for horizontal transfer of resistance genes from bacteria that infect animals to those that infect humans is beginning to emerge. In her own laboratory studies, Salyers has found that the same resistance gene exists in both enterococci of animal origin and *Bacteroides*—the most common bacteria in the human colon. The smoking gun, she says, is in the gene's DNA sequence: the resistance genes have an identical genetic sequence even though the genomes of the organisms themselves are substantially different.

The single greatest factor driving resistance to a given antibiotic is simply use of the drug. The more an antibiotic is used, the more the bacteria become resistant to it. For this reason, experts say, antibiotics should be used sparingly, and at dose levels intended to kill all or as many of the bacteria causing an infection as possible. If too little antibiotic is used (undertreatment), the most susceptible bacteria are killed off, leaving a hardy group of survivors that grow and multiply into resistant strains.

Human abuse of antibiotics in particular is a major public health problem. Many patients demand antibiotics routinely, and just as many doctors dispense antibiotics indiscriminately—often for viral infections against which the drugs are useless. And it's not uncommon for patients to stop taking antibiotics as soon as they feel better, killing only a fraction of the bacteria that are making them sick. Antibiotic use around the world is characterized by widespread chronic undertreatment.

Chronic undertreatment in agriculture, particularly for nontherapeutic uses no matter how they are defined, is also endemic. Regarding the extent of undertreatment in the poultry industry, Richard Lobb, a spokesperson for the National Chicken Council, a Washington, D.C.–based trade



Murder most fowl? Bacteria such as *Salmonella* (inset) and *Campylobacter*, often associated with consumption of undercooked meat, are linked to millions of illnesses and many deaths each year.

PhotoDisc; Inset: USDA

group, says, "Antibiotics for growth promotion are given at very low levels: grams per ton of feed. The compounds are used to manage the gut flora of the bird, which allows it to process feed more efficiently." According to Lobb, the dosage rate for therapeutic use is "considerably higher," although the exact amount depends on the specific drug.

Salyers says her own lab studies show that long-term low-dose use patterns are by far the most effective at selecting for resistant bacteria. "These dosing regimens also give the bacteria time to acquire genetic changes that make them more fit," she adds. "Keep in mind that bacteria predate plants and animals by billions of years, and they are extremely adaptable. If they have extra time to adapt, they will do so with maximal efficiency. That's why the low-dose uses are such a concern."

The Human Health Risk from Antibiotics in Animals

People are typically exposed to resistant foodborne bacteria when they come into contact with farm animals or when they eat meat and meat products. Although many types of foodborne bacteria cause human illness, two are a key concern because they infect so many people. *Salmonella* and *Campylobacter* are each linked to millions of cases of food poisoning annually, according to the Centers for Disease Control and Prevention (CDC). "These switch sides as the number-one and number-two causes of bacterial foodborne disease in the United States," says Lyle Vogel, who heads the Scientific Activities Division at the American Veterinary Medical Association. The effects caused by either organism range from barely noticeable, to uncomfortable, to fatal in rare cases involving infants, the elderly, or people with compromised immune systems.

Resistant strains of these bacteria have been emerging with some frequency. For example, in 1999, scientists at the CDC began tracking a new variety of *Salmonella* called Newport 9+, which is named for its unprecedented resistance to nine antibiotics including ceftriaxone, one of the few drugs that kills most bacteria and the drug of choice for children whose *Salmonella* infections enter the bloodstream (a condition that kills about 1,000 Americans every year).

The National Antimicrobial Resistance Monitoring System (NARMS) surveillance mechanism, which is coordinated by the FDA, the CDC, and the USDA, provides data that allow researchers to correlate trends in animal antibiotic use to resistance in human pathogens. Currently, NARMS collects data on *Salmonella*, *Escherichia coli* O157, *Campylobacter*, and *Shigella* and their susceptibility to 17 antimicrobial drugs. Results can be compared with data from previous years to look for changes in the resistance of the organisms to these drugs. According to data collected by NARMS, 12% of all *Salmonella* isolates obtained from human clinical samples in 2000 were resistant to at least five antibiotics, including ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline. All of these drugs or the classes of drugs they belong to are used in agriculture. In 1996, the year NARMS began gathering data, only 6% of human *Salmonella* isolates showed this resistance pattern. Furthermore, a series of studies published in the 18 October 2001 issue of the *New England Journal of Medicine* showed high levels of resistant foodborne pathogens in supermarket chicken.

While untreatable food poisoning can make someone very sick, an even more serious problem can result if resistant strains of enteric bugs escape the digestive tract and infect other parts of the body. The most likely scenario for this to happen is during surgery. Says Salyers, "If your bowels are accidentally perforated such that intestinal bacteria get into the bloodstream, the chance of developing a hard-to-treat postsurgical infection is greatly increased."

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Draining the supply. In addition to use in animals, the overuse of antibiotics in humans is considered a major factor in the reduction of the number of effective antibiotics.

Stuart Levy, a professor of molecular biology, microbiology, and medicine at Tufts University Medical School and president of the APUA, adds that the flow of resistance genes is hardly limited to foodborne pathogenic bacteria. As members of a microbial ecosystem, any bacterium—even a benign strain—could acquire a resistance gene and pass it on to its neighbors, including the dangerous bugs that cause pneumonia, urinary tract infections, and sexually transmitted diseases. Thus, a resistance gene that starts out in an animal strain of *Salmonella typhimurium* could end up in *Klebsiella pneumoniae* (a cause of human pneumonia); similarly, a resistance gene in an animal strain of *Enterococcus faecium* could end up in *Staphylococcus aureus*, which causes intractable hospital-based infection resistant to nearly 100 drugs. "It would be hard to trace an untreatable urinary tract infection to antibiotic use on a farm," Levy says. "But it's nevertheless possible that farm use could be the source of the resistance."

A Dwindling Arsenal

A troubling parallel to the problem of resistance is the lack of new effective antibiotics—the pipeline for fresh drugs has been running low for years. The goal for public health is therefore to retain the usefulness of as many existing antibiotics as possible. Those used purely in animals—such as ionophores, which improve feed efficiency in sheep and cattle but are too toxic for use in people—are of little concern. The antibiotics experts worry about most are those that are used in both animals and people: mainly tetracycline, fluoroquinolones, third-generation cephalosporins, and macrolides, according to Vogel.

Lately, to industry's dismay, activists have targeted a drug called virginiamycin that has been used in animals, mainly poultry, for 25 years. Virginiamycin is related to a new human drug called Synercid, which is an emerging replacement for one of the most valuable antibiotics in the clinician's arsenal, vancomycin. Practitioners were shocked when vancomycin-resistant strains of *E. faecium* began to emerge in the late 1990s. The source of at least some vancomycin resistance in *E. faecium* was traced back to a related antibiotic called avoparcin—never approved for use in the United States—which was used for growth promotion in the European poultry industry. These uses have since been discontinued. Activists worry that a similar scenario may play out for virginiamycin.

To date, regulatory action to remove an animal antibiotic because of a human resistance threat is limited to the FDA's offensive against fluoroquinolones in the poultry industry, but the FDA is conducting a risk assessment of virginiamycin use. Industry watchers say Baytril withdrawal isn't likely to happen anytime soon—stakeholders say the FDA's campaign against Bayer could take anywhere from 10 to 20 years. In fact, some critics complain that the FDA's hands are inadvertently tied by a multilayered set of hearings and appeals. "The agency doesn't have an effective way to deal with this kind of problem," says Tamar Barlam, director of the Antibiotic Resistance Project at the Center for Science in the Public Interest, a Washington, D.C.–based advocacy group. "The only practical solutions are voluntary industry withdrawals or legislation that bans sale of the drug."

Both the Kennedy and Brown bills propose to ban the use of ciprofloxacin-like antibiotics to treat sick poultry. In addition, both bills would ban the use of eight human antibiotics in feed animals within two years of enactment unless the FDA determines that these uses don't contribute to antibiotic resistance problems.

In recent years, the FDA has revamped its new drug approval process for animal antibiotics, specifically targeting potential human resistance problems as a safety end point. As part of this new approach, says Stephen Sundlof, director of the FDA's Center for Veterinary Medicine, the agency is asking drug companies for better information about resistance implications. "But this is difficult to evaluate," Sundlof says. "We can't really predict when and if resistance will happen and at what rate. If you assume the worst you'll never approve another drug, and if you're too lenient you're not doing your job either. So we're using a risk-based process that takes into account the importance of the drug in human medicine."

The Future for Food Safety and Production

So what happens if antibiotic use in animals is reduced or eliminated? The European experience provides one perspective on the implications of reducing food animal antibiotics. Since 1999, the European Commission has tightly regulated animal antibiotics related to those used in human medicine. The leader in these efforts is Denmark, which reduced its animal use of antibiotics by roughly 60% from 1994 to 2000.

According to a 27 March 2002 article in *The Washington Post*, the use of growth-promoting antibiotics in Denmark has fallen to zero from a 1994 peak of 128 tons. In the article, Henrik C. Wegener, a researcher with the Danish Veterinary Institute in Copenhagen, is quoted as saying the Danish ban has markedly decreased the prevalence of drug-resistant bacteria but has not affected the health of the animals or the price of meat. Wegener does acknowledge that more feed is required to maintain animal weight, but these costs are balanced by the savings in drug costs.

However, Vogel, who represents the veterinary profession on matters related to antibiotics, is skeptical of the Danish claims. Denmark also reports a 30% increase in the use of antimicrobials to treat diseases in 2000, he says. "Until the illnesses are resolved, the health and welfare of the animals are clearly impacted."

Ultimately, the issue of agricultural antibiotic use and resistance boils down to familiar questions in public health: should precautionary measures be taken to minimize a threat that isn't well characterized, or should we wait until more data are available before taking conclusive actions? Just as care providers and patients alike have a role to play in conserving antibiotics, so do farmers and drug companies. But controlling the spread of resistance won't come without a certain degree of economic pain and, potentially, a detrimental effect on animal health and welfare. "If you want cheap meat from cows that are confined to a small number of locations rather than wandering in the suburbs and parks, then you have to face the consequences of that desire," says Salyers. "One of those consequences is massive use of antibiotics."

Reducing antibiotic inputs will require changes in animal husbandry that promote hygiene and minimize the spread of bacteria. Just how the U.S. food animal industry will accommodate these changes is unclear. "Farmers are going to need help," Salyers says. "We can't get them addicted to antibiotics and then just tell them to quit cold turkey. We need to have some respect for their problems. If we're going to move to reduce antibiotics in agriculture, we're going to have to work with agriculture on making that transition."

Charles W. Schmidt

The economic equation. Livestock breeders say that reducing the use of antibiotics in animals will significantly impact the cost of meat, though environmentalists and others say the cost of antibiotic resistance would be far greater.

left to right: ImageVault; PhotoDisc