EDITORIAL

Antimicrobial Use in Animal Feed

an Ecological and Public Health Problem

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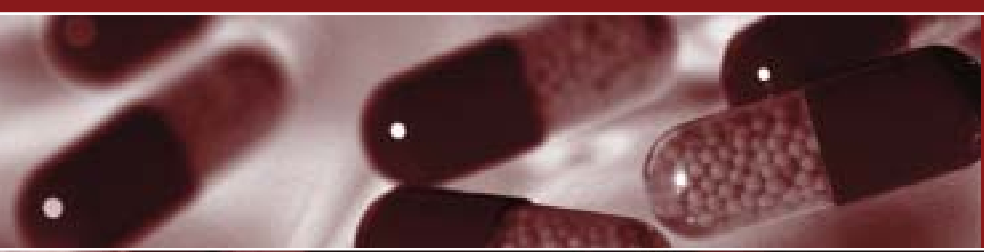

Antibiotics arguably constitute one of the most important medical discoveries of the last century. Unfortunately, many antibiotics now are rapidly losing effectiveness as bacteria increasingly acquire resistance to multiple medicines.

Antibiotic use is the key driver of resistance. Even with appropriate antibiotic use, some resistance will inevitably develop. Misuse and overuse of antibiotics, however, hasten and spread resistance.

Concerns about antibiotic overuse in human medicine are widespread and well founded. In 1998, an Institute of Medicine report determined that between 25 percent and 40 percent of antibiotic use in U.S. hospitals is unnecessary, as is 20 percent to 50 percent of physician use in community settings.[1] Increasing resources have been devoted to changing prescribing practices as well as patient expectations.

In contrast, routine feeding of antibiotics to animals raised for food has only belatedly attracted the medical community's attention—despite last year's editorial in *Science* stating the "strong scientific consensus" that routine administration of antibiotics to food animals is "a bad idea."[2]

Agricultural Uses

Antimicrobials have a variety of uses in agriculture. (Antibiotic refers to an agent produced by microorganisms that inhibits or kills other microorganisms, while antimicrobial is a broader and perhaps more accurate term that also includes agents of semisynthetic or synthetic origin). They are appropriately given to livestock and poultry as therapy for infection. Antimicrobials are also given prophylactically to entire groups of nondiseased animals, typically during periods of high risk for future infection such as after weaning or transport.

For decades, antimicrobials have also been given to food animals routinely in feed or water—over longer periods of time and in the absence of disease—to improve growth rates and feed efficiency. Exactly why routine use of antimicrobials in feed, at relatively low concentrations (ranging from 2.5 ppm to 125 ppm), promotes faster growth on less feed has never been fully explained. Conventional wisdom is that the practice may allow animals to devote less energy to combating endemic or "subclinical" infection or somehow affects digestion-inhibiting bacteria in the gut.

Some antimicrobials given to animals at growth promoter levels may, in addition, help prevent certain diseases promoted by the industrialization and intensification now typical of U.S. livestock and poultry production. Common animal production practices such as crowding, high stocking rates, and extra-early weaning, driven largely by economics, add significantly to animal stress and raise concerns about overall animal health and welfare. Putting antimicrobials in feed or water can help stave off infection in these stressed animals, making it possible for the practices to continue. Antimicrobials added to feed can, as a result, almost always be justified as "disease prevention," at least when administered for limited periods of time.

In the United States, certain antimicrobials are FDA approved for both growth promotion and disease prophylaxis. A clear-cut difference cannot always be discerned between the two types of use. Antimicrobials in both instances are typically purchased and used without a veterinary prescription. In both cases antimicrobials are added to feed or water at lower-than-therapeutic levels, leading some scientists to refer to them as "subtherapeutic" or "nontherapeutic" uses. I use the latter here, although it should be noted that there is no agreed-upon definition of such terms.

Public Health Concerns

Because antimicrobial resistance is driven by antimicrobial use, the sheer volume of pharmaceuticals used in agriculture raises significant public health concerns. The longest-standing concerns, however, revolve around the prevalence of nontherapeutic use.

No formal mechanism at the federal or state level exists for tracking U.S. antimicrobial use in agriculture or elsewhere. Various estimates agree that agricultural use is extensive. The Institute of Medicine (IOM) estimates that about 20 million pounds of antimicrobials are given to farm animals each year and that about 80 percent of these are used for nontherapeutic reasons. The Union of Concerned Scientists (UCS), a public interest group, estimates about 29.5 million pounds annually, with 93 percent of use being nontherapeutic.[1,3] For comparison, the UCS asserts that 3 million pounds are given to humans. In contrast, the livestock and animal pharmaceutical industries, which consider the use of antimicrobials in animal feed for disease prevention to be therapeutic in nature, put the use of antimicrobial growth promoters at just 13.5 percent of total animal use.

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According to the UCS, 70 percent of all the antimicrobials used in the United States for all purposes—or about 24.6 million pounds annually—are fed to poultry, swine, and beef cattle for nontherapeutic purposes, in the absence of disease. Over half are "medically important" antimicrobials, identical or so closely related to human medicines that resistance to the animal drug can confer resistance to the similar human drug. Penicillins, tetracyclines, macrolides, streptogramins, and sulfonamides are prominent examples (see Table).

The Emerging Consensus

There is emerging scientific consensus that antimicrobial use in food animals contributes to antimicrobial resistance that is transmitted to humans, typically—although not exclusively—through the food supply. In 2002 the Alliance for the Prudent Use of Antibiotics convened a two-year scientific advisory panel consisting of physicians, veterinarians, microbiologists, plant pathologists, and animal scientists to review about 500 published studies on antimicrobial use in animal husbandry and to develop consensus recommendations.

The panel's report, which was published as a supplement to the journal *Clinical Infectious Diseases*,[4] identified several lines of evidence linking such use to resistant infections in humans, including:

- epidemiological studies tracing resistant human infections directly to specific livestock and poultry operations;
- temporal studies finding that specific drug resistance in animal-associated bacteria emerged prior to the appearance of the same resistance in human pathogens;
- compelling, albeit circumstantial, evidence that links consumption of food products from animals routinely raised using antimicrobials to human disease and to trends in resistance among food-borne bacteria such as *Salmonella, Campylobacter,* and *E. coli* species, which are rarely transmitted from person to person;
- studies showing that farmers and other handlers of animals receiving antimicrobials are rapidly colonized with intestinal bacteria resistant to the same agents; and

Table 1

Select Antimicrobials Approved for Use in Feed or Drinking Water for Food Animals for >14 Days*

Purpose	Poultry	Swine	Cattle
Growth and Feed Efficiency	Bambermycin *Bacitracin* *Chlortetracycline* Oleandomycin *Oxytetracycline* *Penicillin* Roxarsone *Tylosin* *Virginiamycin*	Arsanilic acid *Bacitracin* Bambermycin *Chlortetracycline* Efrotomycin *Erythromycin* Oleandomycin *Oxytetracycline* *Penicillin* *Sulfamethazine* *Sulfathiazole* Tiamulin *Tylosin* *Virginiamycin*	*Bacitracin* *Chlortetracycline* Laidlomycin Lasalocid Monensin *Oxytetracyline* *Sulfamethazine* *Virginiamycin*
Prevention	*Bacitracin* Ormetoprim *Penicillin* Sulfadimethoxine *Virginiamycin*	Chlortetracycline *Sulfamethazine* *Tylosin*	
Disease Control	*Bacitracin* *Lincomycin*	Arsanilic acid *Bacitracin* Carbadox *Lincomycin* *Sulfamethazine* Tiamulin *Tilmicosin* *Tylosin* *Virginiamycin*	*Chlortetracycline*

* Excluding coccidiostats
** Italicized agents belong to "medically important" classes

Source: Adapted from McEwan SA, Fedorka-Cray PJ. Antimicrobial use and resistance in animals. Clin Infect Dis. 2002:34 (Suppl 3) S93-106; and personal communication, Rebecca Goldburg and Yang Yi Lee-Melk, Environmental Defense, New York, NY, July 1, 2002.

• studies showing that antimicrobial-resistant commensal bacteria from food animals can colonize the human gut, where they potentially can transfer their resistance to ordinary pathogens or to other commensals unrelated to food animals that may become pathogenic later in time in patients with compromised defenses.

In addition, the report's authors stressed that antimicrobial resistance is an ecological problem. Resistance is gene based. Bacteria will acquire resistance genes in the presence of antimicrobials or other agents exerting a selective pressure—creating the conditions, in other words, where resistant bacteria can out-compete and propagate faster than nonresistant bacteria. This is an ecological problem because both the genes coding for resistance as well as the agents that select for them are widely dispersed in the environment in which bacteria live.

For example, an estimated 25 percent to 75 percent of antimicrobials in animal feed will pass unchanged into animal waste.[5] Manure from animals given antimicrobials is often spread onto fields or sold as fertilizer and has also been implicated in contamination of the broader environment, such as surface waters or groundwater, with resistant bacteria. In a recent study by the U.S. Geological Survey, antimicrobial residues were found in 48 percent of 139 streams surveyed nationwide; both wastewater treatment plants and animal agriculture operations were considered possible contributors—45 percent of survey sites were downstream from the latter.[6]

Like the drug residues, the genes coding for resistance are mobile. Because they can confer an evolutionary advantage, such genes spread readily in the bacterial ecosystem. Bacteria can inherit resistance genes, transmit them directly to one another via diverse mechanisms, or acquire free DNA from their environment.

Evolved mechanisms for bacterial transfer of resistance genes include plasmids, transposons, and integrons. Plasmids are extrachromosomal elements that are self replicating and can transfer from bacterial cell to cell. Transposons are segments of DNA that can be recombined into other genomes through the action of enzymes called transposases. Multiple antimicrobial resistance genes in plasmids or transposons often are further clustered into elements called integrons; in integrons, each resistance gene sits within a mobile gene "cassette" that can be easily cut out, then reincorporated into another integron on another genome.[7]

Plasmids and transposons carrying multidrug resistance are now common in bacteria that are found in plants, animals, humans, and the environment. Since the mid-1970s, they have been found with increasing frequency in both clinical and agricultural settings.[8] In the human gut, microbiological studies have demonstrated extensive transfer of antimicrobial resistance genes between enteric bacteria (*Bacteroides* species) and gram-positive bacteria.

Because resistance genes often are physically linked, co-selection of resistance also is an important issue, albeit one largely overlooked in discussions about agricultural use of antimicrobials. Co-selection describes the phenomenon in which use of one antimicrobial selects for resistance not only to itself but to other agents as well. This might help explain persistence of resistance even after use of a particular antimicrobial has been reduced or discontinued.

Efforts to address resistance, therefore, should not be limited to human, animal, or other individual uses of antimicrobials. All uses may contribute to environmental reservoirs of resistance genes. To limit antimicrobial resistance and preserve the effectiveness of existing medicines, it therefore is prudent to eliminate overuse or unnecessary use wherever it occurs.

Based on the findings and facts described above, the advisory panel convened by the Alliance for the Prudent Use of Antibiotics urged several specific policy reforms. Among them were recommendations that all antimicrobial use in food animals be by veterinary prescription only; that it be limited to therapeutic use for diseased animals or to prophylactic use only in the case of documented disease in a herd or flock; and that all use of antimicrobials for growth promotion or feed efficiency be discontinued (with the exception of ionophores and coccidiostats, two antimicrobials not thought to affect resistance in human pathogens).

Federal Intervention

While scientific consensus is emerging that antimicrobial use in food animals contributes to resistance, there is much less agreement on the magnitude of that contribution or what to do about it. New federal legislation is one option that has gained significant support in the medical and public health communities.

Parallel bills (S. 2508 and H.R. 3804), titled "The Preservation of Antibiotics for Human Treatment Act of 2002," have been introduced in the U.S. Senate and House. They carry endorsement by the American Medical Association, the American Osteopathic Association, the American Public Health Association, the American College of Preventive Medicine, the Ambulatory Pediatrics Association, and numerous other health organizations.

The bills would withdraw federal approval for nontherapeutic agricultural use of eight named antimicrobials or classes of antimicrobials: penicillins, tetracyclines, macrolides (including but not limited to erythromycin and tylosin), lincomycin, bacitracin, virginiamycin, aminoglycosides, and sulfonamides.

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If the legislation passes, farmers would retain many options. These include nontherapeutic use of nonmedically important medicines and improved methods of animal hygiene, husbandry, and feed management. The latter already are practiced on some U.S. farms as well as in the European Union, where medically important antimicrobial growth promoters already have been phased out. The Senate bill also authorizes funds to farmers to help defray any costs of eliminating the aforementioned drugs from nontherapeutic use.

In addition, the bills would ban the use of fluoroquinolones for treating respiratory disease in poultry. The Food and Drug Administration first proposed such a ban in October 2000, based on data showing increased fluoroquinolone resistance among isolates of *Campylobacter,* the leading cause of bacterial foodborne illness in the United States. Industry estimates indicate that 38,000 pounds of fluoroquinolones were used in U.S. poultry in 1999. Only one manufacturer currently markets such a product, and it is contesting the FDA proposal.

The FDA theoretically has authority under the Federal Food, Drug and Cosmetics Act to withdraw already-approved animal antimicrobials from market. The procedures required of the FDA are so cumbersome in practice, however, that such withdrawals likely would take years for each type of antibiotic. The FDA's successful actions to remove the approval for use of diethylstilbestrol (DES) and nitrofurans in food animals, for example, required six and 20 years, respectively.

The proposed legislation has ample precedent elsewhere. The European Commission (EC) recently proposed phasing out all remaining uses of antibiotics as growth-promoting feed additives by 2006 (with some coccidiostat exceptions); in 1998, the commission banned the use of medically important growth promoters—bacitracin, spiramycin, tylosin (a macrolide), and virginiamycin (related to Synercid). Certain EC members had previously banned all antimicrobial growth promoters—Sweden banned them in 1986, and Denmark completed its ban by 1999. Danish government veterinarians note that total agricultural use of antimicrobials subsequently dropped more than 60 percent from 1994 to 2001 and that the prevalence of certain resistance in food animals, such as vancomycin-resistant enterococci, also has dropped dramatically. The Danish veterinarians assert that the ban has not affected the health of the animals or the consumer price of meat.

Conclusion

The growing problem of antimicrobial resistance, combined with development of only one new class of antibiotics in the last 25 years, makes it essential that urgent steps be taken to preserve the effectiveness of existing medicines for treating illness in both humans and animals.

Fundamentals of microbiology as well as a strong and growing body of scientific evidence make it clear those steps should include the elimination of unnecessary uses of antimicrobials in food animals. Nontherapeutic animal uses of agents important to human medicine deserve especially prompt action. Proposed federal legislation arguably offers the best opportunity for timely, enforceable changes in antimicrobial use in agriculture. As a major center for medical research and treatment, as well as one of the nation's largest swine, chicken and turkey producers, Minnesota should be a leader in supporting this legislation. MM

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