POLICY: BIOMEDICINE

Medical Consequences of Antibiotic Use in Agriculture

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A related commentary on antibiotic resistance in medicine will appear in next week's issue.

During the past decade, bacteria that cause human disease have developed resistance to many of the antibiotics commonly used for treatment. All of the pathogens usually found in hospitals are affected, as well as mycobacteria, pneumococci, and *Enterobacteriaceae*. Indeed, infections with antibiotic-resistant staphylococci and enterococci that cannot be treated by previously successful regimens have made headline news.

Resistance to antimicrobial drugs can arise either from new mutations in the bacterial genome or through the acquisition of genes coding for resistance. These genetic changes alter the defensive functions of the bacteria by changing the target of the drug, by detoxifying or ejecting the antibiotic, or by routing metabolic pathways around the disrupted point (*1*).

Evolution of resistance to antibiotics is facilitated by the presence of resistance genes on transferable genetic elements and by the use of antibiotics in a way that allows them to act as selective agents (*2*). Hospitals—with their concentrated combination of bacteria adapted to this environment, patients prone to infections, and antibiotic use—offer a prime opportunity for development and transfer of antibiotic resistance (*3*).

Another arena for the development of antibiotic resistance is found in animal husbandry in which antibacterials are used for prophylaxis, chemotherapy, and growth promotion. Animals receiving antibiotics in their feed gain 4 to 5% more body weight than animals that do not receive antibiotics (*4*). More antibiotics are used in this manner than in medical applications: In Denmark in 1994, 24 kg of the glycopeptide vancomycin were used for human therapy, whereas 24,000 kg of the similar glycopeptide avoparcin were used in animal feed. From 1992 to 1996, Australia imported an average of 582 kg of vancomycin per year for medical purposes and 62,642 kg of avoparcin per year for animal husbandry. Vancomycin and avoparcin have the same mode of action; resistance to one can confer resistance to the other.

Antibiotic resistance that arises in animal husbandry affects such zoonotic pathogens as *Salmonella* serovars and *Campylobacter* spp., both of which are associated with diarrheal diseases, and human and animal commensals such as *Escherichia coli* and enterococci. Because the human and animal microbial ecosystems are inextricably intertwined, microbial antibiotic resistance readily crosses boundaries (see the figure). Antibiotics given to animals and closely related compounds used in human therapy have been exerting selective pressure on their target bacteria for decades.

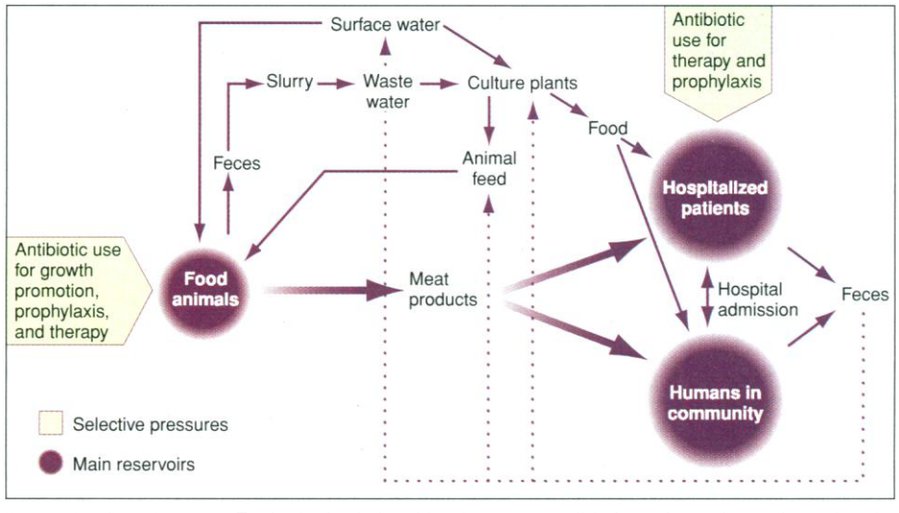
In 1969, the Swann Committee of the United Kingdom concluded that antibiotics used in human chemotherapy or those that promote cross resistance should not be used as growth promoters in animals (*5*). Since then, there has been continuous debate about the extent to which bacterial antibiotic use in food animals promotes resistance in bacteria that infect humans. Improved analytical techniques have provided circumstantial evidence that such resistance is indeed exacerbated by antibiotics in animal feed.

Spread of Resistance

E. coli, a commensal of the human and animal gut flora, easily disseminates drug resistance genes, as demonstrated by the spread of antibiotic resistance associated with antibiotics in animal feed (*6*, *7*). In the former East Germany, nourseothricin was used as a growth promoter from 1983 to 1990, replacing the similar use of oxytetracycline. Resistance to nourseothricin in *Enterobacteriaceae* from humans and animals was negligible in 1983. Two years later, resistance (by means of the transposon-encoded streptothricin acetyltransferase gene) was found in *E. coli* from the gut of pigs and in meat products. By 1990, resistance to nourseothricin had spread to *E. coli* from the gut flora of pig farmers, their families, citizens from municipal communities, and patients suffering from urinary tract infections. The spread among humans occurred without apparent selective pressure. In 1987, the same resistance determinant was detected in other enteric pathogens, including *Shigella*, an organism found only in humans (*7*).

Antibiotic use in animals also has resulted in resistance among nontyphoid *Salmonella* serovars. The resistant bacteria are transmitted to humans in food or through contact with animals. Resistance in *Salmonella* limits the therapeutic options available to veterinarians and physicians in the treatment of certain human cases of salmonellosis. *Salmonella typhimurium* strain DT 104, which is resistant to ampicillin, tetracycline, streptomycin, chloramphenicol, and sulfonamides, has been identified in many places, including the United Kingdom, Europe, and the United States. The recent development of fluoroquinolone resistance is of special concern (*8*). Remaining therapeutic options include only third-generation cephalosporines.

Fluoroquinolone use in poultry husbandry has promoted the evolution of fluoroquinolone-resistant *Campylobacter jejuni* (*9*), which have been detected in meat



Network of resistance. Ecological relationships between antibiotic-resistant bacteria and resistance genes: selective pressures, main reservoirs, and routes of transmission.

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products and in infected human patients. Development of quinolone resistance in both *Salmonellae* and *Campylobacter* spp. is due to mutations in the bacterial enzymes DNA gyrase and topoisomerase IV. *Campylobacter* spp. exist as a variety of strains in their animal hosts, making it impossible to link a specific antibiotic-resistant *Campylobacter* strain with a particular use of fluoroquinolones. Before these compounds were used in poultry farming, resistant *Campylobacter* were unknown in humans with no previous quinolone exposure (9).

Enterococcal infections cause problems for hospitalized patients with impaired immune systems and can be treated with glycopeptide antibiotics. Resistance to glycopeptides, which is most apparent in countries that use large amounts of vancomycin, now contributes to increased morbidity and mortality in these patients, as therapeutic alternatives are limited.

Addition of avoparcin to animal feed has encouraged the presence of genes conferring resistance to related glycopeptides. Enterococci from animals can reach humans through the food chain (*10*). The *vanA* gene cluster, encoding glycopeptide resistance, integrated into conjugative plasmids (*11*), is disseminated among human and animal enterococcal strains.

The potential dissemination of these resistance genes to *Enterococcus faecalis* and other pathogens threatens human health. Transfer of glycopeptide antibiotic resistance to *Staphylococcus aureus*, which is already resistant to other antibiotics (*3*) and for which glycopeptides are the drugs of last resort, would be disastrous.

For infections by glycopeptide-resistant *E. faecium*, streptogramins are a potential treatment. However, streptogramin resistance has been found in bacteria isolated from both patients and animals. The resistance is due to the *satA* gene, which codes for streptogramine A acetyltransferase. In Germany, although streptogramines have not been used in human chemotherapy, resistance has nonetheless appeared, probably driven by the use of the related antibiotic virginiamycin in animal feed for the past 20 years.

These observations suggest that antibiotic use in animal husbandry is a driving force for the development of antibiotic resistance in certain pathogenic bacterial species. However, some claim that assessing the risk incurred by the use of antibiotics in animal husbandry must include documentation of cases in which treatment of a human infection failed because of antibiotic resistance of proven animal origin. Unfortunately, once a resistance gene has become widely disseminated, it is difficult to trace it back to its origin. Prospective studies beginning with the introduction of a new antibiotic or specific labeling of a particular resistance gene might be useful in proving the causative connection.

Global Prevention and Regulation

A workshop sponsored by the World Health Organization (WHO) on the medical impact of the use of antimicrobial drugs in food animals reinforced the recommendations of the Swann committee (*12*, *13*). That the Swann committee's resolution needs repetition after 28 years indicates that we have not seen sufficient adherence to the principles stated. The growth-promoting effect of antibiotics is especially advantageous when primary animal performance is low (*14*). Therefore, procedural modifications can decrease the use of antibiotics without sacrificing production. In Sweden, where the use of antimicrobials for growth was prohibited in 1986, improved hygiene has recouped the productivity losses (*4*).

Enterobacteriaceae:	Normal enteric bacteria including *E. coli*, conditional pathogens causing urinary tract infections, wound infections, septicemia. Related pathogens, including *Salmonella*, *Shigella*, and enterotoxin-forming *E. coli*.
Mycobacteria:	Includes the cause of lung tuberculosis. Other species have significance for patients with HIV.
Pneumococci:	The main cause of acquired pneumonia.
Staphylococci:	Widespread among humans. Conditional pathogen in the hospital setting.
Enterococci:	Commensals of the intestinal flora. Pathogenic in immunocompromised patients.
Camphylobacter coli; *Camphylobacter jejuni*:	Intestinal bacteria of animals, cause of diarrheal infections in humans.

Worldwide differences in the use and licensing of antibiotics are large. Although the regulation of growth promoters in European Union countries incorporates the Swann committee's recommendations and the use of avoparcin was banned in 1997, tylosin and virginiamycin are still in use. Both drugs cause cross resistance to other compounds of the same class of antibiotics used in human therapy. Other growth promoters in the European Union are quinoxalines, ionophores, peptide antibiotics, phospholipols, and oligosaccharides.

In the countries of the developing world, which are responsible for about 25% of world meat production, policies regulating veterinary use of antibiotics are poorly developed or absent. In China, raw mycelia are used as animal growth promoters. In Russia, chloramphenicol is still in veterinary use. In Southeast Asia, use of antimicrobials in shrimp farming is unregulated.

The problems caused by inappropriate use of antibiotics reach beyond the country of origin. Meat products are traded worldwide, and evolving bacterial populations do not respect geographical boundaries. Management of antimicrobial resistance requires worldwide coordination. Pharmaceutical industries and national and international licensing authorities can support improved surveillance for antimicrobial resistance.

Current surveillance mechanisms are unable to link antimicrobial consumption to development of resistance. An analysis of this linkage is essential for arriving at the most effective response strategy. Surveillance should also include analysis of unrelated resistance genes sharing the same plasmid or transposon.

In the future, it seems desirable to refrain from using any antimicrobials for the promotion of animal growth. As exemplified by the use of virginiamycin in animal feed and the subsequent emergence of enterococci resistant to antibiotics, the use of any antimicrobial can lead to unexpected consequences that limit medical choices.

Antibiotics as promoters of animal growth can be phased out gradually. Similar benefits can be generated by improving other aspects of animal care, such as hygiene. In the long run, an industrial investment in alternatives to antimicrobials for animal growth promotion should pay off in more efficient production of food animals as well as protection of the fragile resources that are critical to successful management of human infectious disease.

References and Notes

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