Antibiotics in Animal Husbandry | 7

What effect does the use of antibiotics in food production have on the occurrence of antibiotic-resistant bacteria? Everyone concerned with that question agrees about a few things: About half of the antibiotics (by weight) used in the United States are used in the production of food animals, much smaller amounts are used to control bacterial diseases in plants and in fish farming, and some proportion of the bacteria that are present in and on food may survive cooking or other preparation in the food eaten by humans. Beyond such small areas of agreement, there is widespread disagreement, or so it would seem. In fact, the real questions about the transfer of antibiotic-resistant bacteria from foods to humans are how often does it happen and what are its consequences, rather than does it happen at all.

The chairman of a National Research Council (NRC) advisory panel that looked at the question neatly posed a scenario for the risks from use of antibiotics in farm animals:

> ...a beef producer feeds tetracycline in low doses to his calves to encourage rapid weight gain; nonpathogenic *Escherichia coli* in the guts of the calves acquire antibiotic resistance. Somewhere along the chain from feedlot to dinner table, the *E. coli* may come into close

association with some salmonella, and the salmonella may acquire resistance to antibiotics by plasmid transfer. The meat eater becomes infected, develops *Salmonella* septicemia and dies while his physicians are treating him with an inadequate antibiotic (Stallones, 1982).

The scenario is clearly stated, but how often does it occur? That question could be answered by identifying people who harbor antibiotic-resistant bacteria and linking those bacteria to meat that was derived from antibiotic-treated animals. That has proved impossible to do; there are many possible sources for bacteria, each one would have to be eliminated, and it is difficult to trace the origins of "meat" as it arrives at a butcher shop or supermarket. "[S]ome studies can be conceived but cannot be delivered" (Stallones, 1982).

In the absence of definitive information, disagreements about the significance of antibiotic use in agriculture on the emergence of antibiotic-resistant human pathogens have fostered several reviews and analyses of the data about animal to human transfer of antibiotic-resistant bacteria. Congress requested an Office of Technology Assessment (OTA) study, *Drugs in Livestock Feed,* that reviewed risks and benefits of antibiotic (and other drug) use in agriculture including

the risks of increasing the prevalence of antibiotic-resistant bacteria in humans (OTA 1979). OTA did not reach a hard and fast conclusion about the magnitude of the risk. Instead, it put that risk in context by comparing it to the risk of antibiotic resistance developing as a result of antibiotic use in medicine, and concluded that the risk exists, but that it is less than the risk from uses of antibiotics in humans:

> The risk from resistant plasmids of animal origin is not quantifiable....The majority of resistance in human bacterial populations is probably caused by widespread use of antibacterials in humans (some of which are unnecessary), but the enormous pool of R-plasmids that now exist in animals, together with the ability of an R-plasmid to be promiscuously transferred among bacterial species, must be regarded as a threat to the therapeutic value of antibacterials in the treatment of both human and animal diseases. (U.S. Congress, Office of Technology Assessment 1979, p. 7)

A year later, an NRC committee (1980) reached a similar conclusion, and painted a bleak picture about the possibility of learning more:

> After reviewing the evidence, the committee concluded that the postulations concerning the hazards to human health that might result from the addition of subtherapeutic antimicrobials to foods have been neither proven nor disproven. The lack of data linking human illness with subtherapeutic levels of antimicrobials must not be equated with proof that the proposed hazards do not exist. The research necessary to establish and measure a definite risk has not been conducted, and, indeed may not be possible.

In contrast to the report's conclusion that suggests the possibility of a link between uses of antibiotics in animals and human health, the chairman of the NRC committee, in a later publication, downplayed any risk: "If the decision were mine, the hog farmers could use all the antibiotic drugs they wish to make the pigs grow. The risk to humans looks to me to be vanishingly small" (Stallones, 1982). Not everyone shared that opinion, and studies and reviews have continued to the present time.

Almost a decade later, the Institute of Medicine (IOM) issued a report that dealt with the risks from subtherapeutic use of two common antibiotics—penicillin and two kinds of tetracyclines (oxytetracycline and chlortetracycline)—in animal feeds (IOM, 1989). Its authors further narrowed the focus of the report to the risks of antibiotic-resistant Salmonella from animal sources causing human deaths. The authors calculated that,

> "The likeliest estimate of excess deaths attributable to subtherapeutic uses of penicillin and/or the tetracyclines...is in the range of 6 per year."

The committee also considered the difficulties that might arise in treating antibiotic-resistant Salmonella infections in humans and calculated that,

> "The likeliest estimate of deaths...arising because of 'increased difficulty of disease treatment' is 20 per year."

At the same time, the committee acknowledged that it

> "was unable to find a substantial body of *direct* evidence that established the existence of a definite human health hazard in the use of subtherapeutic concentrations of penicillin and the tetracyclines in animal feeds."

The controversy over the health effects of antibiotic use in animal husbandy has spawned several expert committee reviews that have clarified the issue somewhat (see table 7-1 for a listing of review bodies other than the three mentioned above). There is no doubt that risk exists. There is also no doubt that direct evidence, in the form of studies that show a direct connection between agricultural use of antibiotics and human illness or death, is sparse and difficult to obtain. Moreover, if the IOM committee's estimate of the number of deaths caused by antibiotic-resistant Salmonella of agricultural origin is in the right range, determining what proportion of the 40,000 cases of reported Salmonella infection each year is related to agricultural use of antibiotics is probably impossible.

TABLE 7–1: Reviews—Antibiotics in Animal Feeds	
1968	Netherthorpe Committee.
1969	British Government Joint Committee ("Swann Report").[a]
1970–1977	FDA makes several reviews of antibiotic use in animal feeds.
1977	FDA directs its Center for Veterinary Medicine to prepare notice of withdrawal of penicillin and tetracyclines from subtherapeutic uses.
	FDA publishes proposals to restrict subtherapeutic uses. Proposals criticized because of reported inadequate evidence for adverse effects from such uses.
1978	Congressional request to the National Academy of Sciences (NAS) for a study by the National Research Council (NRC) of the effects of subtherapeutic uses.
	FDA Draft Environmental Impact Statement on the Banning of Penicillin and Tetracycline from Animals Feeds.[b]
1979	OTA Report on Drugs in Livestock Feed.[c]
1980	NRC[d] reports that data neither prove nor disprove human health effects from subtherapeutic uses.
1981	House Appropriations Committee provides funds to FDA to study antibiotic in feed issue.
1984	FDA-sponsored study completed. No regulatory action taken.
	The Natural Resources Defense Council (NRDC) petitions the Secretary for Health and Human Services (HHS) for suspension of subtherapeutic uses because such uses pose an "imminent hazard."
	House Committee on Science and Technology holds hearings on the NRDC petition and results of FDA-sponsored study.
	FDA Commissioner holds hearings on same subjects.
1985	Secretary of HHS denies NRDC petition.
1987	FDA makes request to the NAS for a quantitative assessment of the risks from subtherapeutic uses. NAS assigns study to the Institute of Medicine (IOM)
1989	IOM[e] concludes that there is no definitive evidence of adverse effects although such effects may exist.
	Council for Agricultural Science and Technology (CAST) report.[f]
1994	FDA review of fluoroquinolone use.

[a] A subcommittee of the Netherthorpe Committee. Its recommendation results in the United Kingdom forbidding the agricultural use of antibiotics used in human medicine.
[b] Feinman, S.E. and J.C. Matheson, 1978.
[c] OTA, 1979.
[d] National Research Council, 1980.
[e] Institute of Medicine, 1989.
[f] Hays and Black, 1989.

SOURCE: Adapted from U.S. Food and Drug Administration. 1993. *Information for Consumers: Antibiotics in Animals Feeds.* Photocopied typescript and other sources.

Levy (1992, pp. 136–157) summarizes studies that show that bacteria are transferred from farm animals to farm workers, as well as a few studies that show transfer of bacteria to the human community beyond the farm. These studies, however, leave unanswered questions about the quantitative importance of such transfer in the spread of antibiotic-resistant bacteria and, especially, how important such transfer is in comparison to medical use (and overuse) of antibiotics.

OTA does not, in this single chapter of a general report about antibiotic-resistant bacteria, attempt to resolve an issue which has persisted for more than two decades. This report does, however, contain a description of antibiotic uses in animal husbandry and some other aspects of agriculture, an update of some research findings since the release of the 1989 IOM study, and a discussion of a current regulatory proceeding

about approving of fluoroquinolone antibiotics for use in food animals.

ANTIBIOTIC USE IN FOOD PRODUCTION

Everyone, whether a city dweller or farmer, knows about antibiotic uses in medicine. Doctors prescribe antibiotics to treat diseases, in advance of certain surgical procedures to prevent infection, and, sometimes, as prophylaxis during dental procedures to prevent infections in people with heart valve abnormalities. In all these cases the administration of the antibiotic is overseen by a physician.

Paralleling physicians' practice in humans, veterinarians use antibiotics to treat infectious diseases in food (and companion) animals.[1] But from there on, things are different on the farm. There are differences in medical and veterinarian diagnostic laboratories, and veterinarian diagnostic laboratories reportedly do not meet the same standards for accuracy and reliability as do medical laboratories (Walker, 1994). Currently, however, practices are changing in veterinary laboratories, and the National Commission for Clinical Laboratory Standards has recently published the first guideline document for detecting antibiotic sensitivity in animal pathogens. Lack of laboratory quality assurance is not, however, the major difference between uses of antibiotics in animals and humans.

The major difference is that about 90 percent of all the antibiotics used in food animals is used in subtherapeutic doses and not for the treatment of sick animals. For instance, in 1985, veterinarians used about 1 million kilograms (about 2.2 million pounds or 1,100 tons) of antibiotics to treat diseases in cattle, swine, and poultry. During the same year, farmers fed about 5 million kilograms of antibiotics to cattle, swine, and poultry for "disease prevention," and another 2 million kilograms for "growth promotion" (table 7-2). The estimated total of all antibiotics used in cattle, swine, and poultry in that year was 8 million kilograms, or 18 million pounds.

"Disease prevention" describes prophylactic actions taken to stave off the spread of a disease. If a poultry producer notices that a few chickens are ill and he suspects that the illness is caused by bacteria, he could add antibiotics to the feed or water in an effort to stop the spread of the disease. These decisions can be made by the poultry producer acting alone without any involvement of a veterinarian.

"Growth promotion" is a little-understood effect from feeding low levels of antibiotics, generally at a rate of 200 grams or less of antibiotic in each ton of feed. How such levels of antibiotics affect growth is not clear; they may ward off undetectable but consequential, minor infections, or they may have other effects.

Both disease prevention and growth promotion are long-term uses, and the U.S. Food and Drug Administration (FDA) uses 14 days as the threshold for long-term use. When a company requests approval for longer-than-14-day use, FDA requires the company to demonstrate that such use will not increase the shedding of Salmonella (through feces) that might infect humans and that it will not increase the number of antibiotic-resistant bacteria that contaminate carcasses. FDA (1995) has stated that submissions of requests for approval of long-term uses of antibiotics are decreasing, being replaced, in part, by requests for approval of somatotropins and other growth-promoting substances. More specifically, R.H. Teske of FDA (1995) has stated that, "It is not likely that FDA will see applications for long-term use of antibiotics that have therapeutic uses."

There is so much overlap between prophylactic uses and doses and growth-promotion uses and doses that the division between the two applications that is shown in table 7-2 must be regarded as uncertain. Furthermore, the estimates

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[1] "In fact, it has been said that the definition of a physician is a veterinarian with a limited knowledge that restricts his practice to a single species." (Walker, R. 1994. Remarks at U.S. Food and Drug Administration, Part 15 Hearing: Surveillance Systems for Antibacterial Resistance, Rockville Civic Center, Rockville, MD, November 10.)

TABLE 7–2: Estimated Annual Use of Antibiotics in Livestock, 1985 All Antibiotics (thousands of kilograms)				
	Therapeutic Use	Subtherapeutic Use		
		Disease Prevention	Growth Promotion	Total
Cattle	458	1100	340	1898
Swine	250	3578	1391	5219
Poultry	304	580	315	1199
Total	1112	5258	2046	8316

SOURCE: IOM, 1989, p. 75.

of agricultural use shown in table 7-2 are some 30 percent higher than the estimates produced by the Animal Health Institute for the same year (IOM, 1989, p. 74).

The data in table 7-2 are from 1985, and OTA looked for newer data as part of this report. The only source was a commercial firm that requires purchases of data to join a syndicate, and, as a condition of membership in the syndicate, the purchaser is not allowed to publish the data. OTA did not purchase those data, but experts in the Center for Veterinary Medicine of FDA assert that agricultural uses of antibiotics continue to decline (FDA, 1995).

Most of the antibiotics used in subtherapeutic applications were "old" antibiotics, and penicillins and tetracyclines accounted for 84 percent of antibiotics sold for use in animal feeds in 1985. Some other antibiotics are used only in animals and not in human medicine. These uses make the development of resistance to an antibiotic that is currently used in human medicine less likely. They do not, however, guard against the possibility that a drug closely related to one used in animals will be developed for human use. In that case, resistance to the animal drug, if transferred to bacteria that infect humans, might be cross-resistant to the human drug and reduce its efficacy.

There is an example of possible cross resistance in Europe. In the United States vancomycin-resistant Enterococci (VRE) are found largely, if not exclusively, in large hospitals. In Europe, they are also found in the feces of non-hopitalized patients and of healthy persons, as well as in waste waters, farm animals, and some food products. A glycopeptide called "avoparcin," which is chemically related to vancomycin, has been used as a growth promoter in animal feeds in Europe since the mid-1970s. Bates et al. (1994) reported that VRE were present in fecal materials from farm animals on German farms where avoparcin was used and not present on farms that did not use avoparcin, suggesting that use of the growth promoter was selecting for vancomycin-resistance in Enterococci. Moreover, VRE of the species that infect humans were found in poultry sold in retail markets (Bates et al., 1994; Klare et al., 1995).

Acting on reports of VRE in chickens that had been fed avoparcin, Denmark has banned the use of the drug, and it is now petitioning the European Union to ban it also. Sweden banned use of all growth-promoting antibiotics several years ago. To reduce the emergence and spread of VRE, Murray (1995) urges decreasing use of glycopeptides in animal husbandry and restricting vancomycin use to essential applications in medical practice.

ANTIBIOTIC-RESISTANT BACTERIA IN HUMANS

"While the number and types vary from day-to-day, at any moment in time over 40 percent of people have some antibiotic-resistant bacteria in their colon" (Gorbach, 1993). In the vast majority of cases, these antibiotic-resistant bacteria appear to cause no harm, and they usually constitute a minute proportion of the total bacteria in the intestines, probably one antibiotic-resistant

bacterium for every million or billion or more sensitive bacteria.

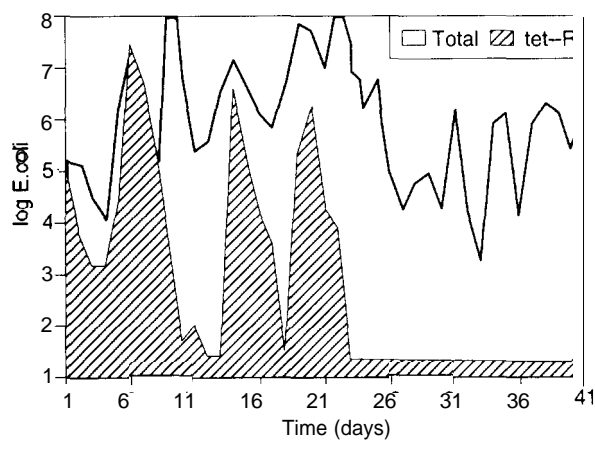## ■ Antibiotic-Resistant Bacteria in Food

The best evidence is that antibiotic-resistant bacteria are ingested with food every day, that they generally fail to establish themselves in competition against the bacteria already resident in the intestine, and that their numbers fluctuate as a result of the opposing effects of ingestion and elimination. That benign situation can be changed by antibiotics, of course. If a person taking an antibiotic ingests Salmonella that are resistant to that antibiotic, the ingested bacteria will have a growth advantage over the other bacteria. In that case, they may multiply to become a major component of the intestinal flora and cause disease.

Figure 7-1 shows the numbers of tetracycline-sensitive and tetracycline-resistant *Escherichia coli* in feces collected from a volunteer over a 41-day period. During the first 21 days, the volunteer ate a regular diet, and the number of sensitive and resistant bacteria fluctuated daily. For instance, the number of tetracycline-resistant *E. coli* dropped from 107 (10 million) bacteria per gram of stool on day 7 to a low of about 2×10^1 (20) per gram on day 13. Although the fluctuations in the number of total *E. coli* (susceptible as well as resistant) were not so great, they still varied from about 10^4 (10,000) per gram on day 4 to over 10^8 (100 million) per gram on day 10. These variations are interpreted to reflect, in part, differences in the numbers of *E. coli* ingested daily.

Beginning on day 21, the volunteer ate only sterilized food. The number of tetracycline-resistant *E. coli* dropped to about 20 or less two days later and remained there. The number of tetracycline-sensitive *E. coli* may also have dropped, but not much below the numbers seen on some days when non-sterile food was consumed (days 1 to 8).

Elder et al. (1 993) examined fecal samples from two groups of non-vegetarians and two groups of vegetarians over a 12-month period.

FIGURE 7-1: Tetracyline-resistant and -sensitive *Escherichia coli* bacteria from a volunteer eating non-sterile food (days 1-21) and sterile food (days 21-40).

SOURCE: Corpet, 1993

There were no differences in the prevalence of antibiotic-resistant bacteria in the two groups, and there was a slightly increased frequency of multiply-resistant bacteria in the vegetarians. These results are consistent with the conclusion that meat is not the only source of antibiotic-resistant bacteria, and the authors suggest that restrictions on antibiotic use in animals would have little effect on antibiotic-resistant bacteria in humans. They do not show, however, that meat is unimportant as a source of antibiotic-resistant bacteria, nor do they pinpoint other sources of antibiotic-resistant bacteria in the diet.

Corpet (1993), who carried out the experiment summarized in figure 7-1, concluded that humans' primary source of antibiotic-resistant bacteria is their food, which is consistent with the knowledge that food is a common source of bacterial infections in humans. For instance, Murray (1995) concluded that more than half of Campylobacter infections in humans arise from ingestion of contaminated poultry, and studies of the same organisms, in particular *Campylobacter jejuni* in Washington State, showed that antibiotic resistance patterns were similar in infected humans and in poultry purchased from retail markets (U.S. House of Representatives, 1984).

It is important in this context that both antibiotic-sensitive and antibiotic-resistant *C. jejuni* caused human disease, underlining the importance of other factors in whether or not ingested bacteria will cause illness.

Virulent, antibiotic-resistant Salmonella caused an outbreak of lethal diseases in cattle in England that infected as many as 500 humans and might have contributed to the deaths of 6 individuals (Anderson, 1968). [The closing down of one farm which was in the business of buying and reselling calves apparently stopped that epidemic (Bywater, 1995).] Furthermore, there is no doubt that farmers and others who are around and care for antibiotic-treated livestock can become carriers of bacteria with the same kinds of antibiotic-resistant bacteria as are found in the animals (Levy, 1978, 1983, 1992 and Levy et al., 1976).

Antibiotic-resistant bacteria in food are ingested by humans along with other bacteria, and antibiotic-resistant bacteria can be passed from animals to humans. Questions remain about how often these transmissions cause disease in human beings or promote the flow of genetic information for antibiotic resistance from bacteria of animal origin to bacteria that can cause human disease.

▍ Antibiotic Residues in Food

FDA, in approving uses of an antibiotic in food animals, specifies a "withdrawal period" following the administration of the antibiotic to allow time for the antibiotic "residue" concentration to fall to a level that is of no concern to the agency. When the withdrawal period is observed, and the residue level falls appropriately, the concentration of antibiotics in meat, according to FDA, should have no effect on the bacterial flora in humans. Any meat that has a higher concentration violates the law.

If, however, residue concentrations were high enough, they could have the same effect on humans as ingesting antibiotics directly. Corpet (1993) summarizes a number of experiments that indicate that the concentrations of antibiotics in meats may rarely be sufficient to have an effect on human bacterial flora. He emphasizes, however, that those effects are less important to human health than the ingestion of antibiotic-resistant bacteria.

A number of papers printed in two special issues of journals about veterinary microbiology reached similar conclusions: *Veterinary and Human Toxicology 35* (supplement 1), 1993, and *Veterinary Microbiology 35* (no. 3,4), 1993. Kidd (1994), in a report prepared for the Fédération Européenne de la Santé Animale, comes to a similar conclusion, but cautions that the lack of evidence for any effect of antibiotics in meat may reflect an absence of investigations of the possibility. While there may remain some lingering suspicions that antibiotic residues in meats can affect the micro-organisms in human beings, the remainder of this chapter will focus on the risks of antibiotic-resistant bacteria from food that was treated with antibiotics.

Antibiotics on Plants and Vegetables
Levy (1992, p. 159–167) estimates that 40,000 to 50,000 pounds of antibiotics are used on fruit trees in the United States each year. While that amount is small in comparison to the 18 million pounds of antibiotics used in animals, some of it is sprayed onto fruit trees and other crops, spreading it into the environment, and some of it could be ingested by humans when they consume fruits and vegetables. Oxytetracycline and streptomycin are used to treat various "rots," "molds," and "spots" on fruits and vegetables, and some of the plant pathogens that cause those diseases have developed resistance to the antibiotics. Levy (1992, pp. 163–165) points to the possibility that the bacteria that infect plants serve as a reservoir for antibiotic-resistant genes that can be transferred to other bacteria that infect humans, but this possibility has not been researched.

Antibiotics in Fish
Commercial fish farming is a fast-growing enterprise, and oxytetracycline, a sulfa drug, and a derivative of trimethoprim are used to control

diseases. FDA requires that the antibiotics be withdrawn from the fish for a specified number of days before the fish are sold to reduce transmission of antibiotics to humans, but bacteria can be carried along with the fish when they go to market.

Catfish, raised in ponds, are the primary commercially farmed fish in the United States. Trout are raised in enclosed raceways, and some salmon are raised in ocean netpens in Puget Sound, Washington, and off the Maine coast.

Farmed fish, when treated with antibiotics, are fed medicated feeds. Thus, antibiotics enter the environment either in fish feces or uneaten food. In catfish farming, antibiotics in feces or food drop to the bottom of the pond and are subject to biological binding or degradation in the sediment. When catfish ponds are drained, the sediment is generally placed on the pond levee, restricting movement of the antibiotics into the general environment.

These U.S. practices differ from those elsewhere. In Norway, antibiotics are sometimes sprayed onto the surface of bodies of water and the antibiotic can then spread throughout the water and possibly cause disturbances in the ecosystem. In that country, quinolones, as well as oxytetracycline, are used to treat diseases in farm-grown fish, and Ervik et al. (1994) showed that detectable residues of antibiotics in the flesh of wild fish and mussels in sprayed water bodies were more common than in fish and mussels taken from waters not known to be treated with antibiotics. The frequency of antibiotic-resistant bacteria in fish and mussels near the fish farms was also higher, but the frequency of such bacteria was not zero, even in fish and mussels from untreated waters. This study demonstrates that antibiotics can move through the aquatic environment and affect the flora of wild fish. Its implications for human health are unknown, and not generally applicable to the United States. In particular, no quinolones are approved for use in aquaculture in the United States, and, according to the Animal Health Institute (1995), no such use is contemplated.

CONTROVERSY ABOUT ANTIBIOTIC USE IN RAISING LIVESTOCK

There is little controversy about the desirability of using antibiotics to treat sick animals. More controversy arises about the subtherapeutic uses in prophylaxis and growth promotion, and the possible diversion of antibiotics licensed only for therapeutic purposes to other uses. Whatever the reason for the use of the antibiotic, treatment of animals can result in contamination of meat by antibiotic-resistant bacteria. Three things can happen as a result. The first is that antibiotic-resistant pathogenic bacteria might be transferred to humans. The second is that antibiotic-resistance genes, although present in non-pathogenic bacteria in the animal, may be transferred to pathogenic organisms in humans. The third is that antibiotic-resistant bacteria that do not normally infect humans will be ingested by people on antibiotic therapy, that the therapy will have altered the human flora, and that the alteration will favor the growth of bacteria that pose a risk to human health.

Any of these effects is a risk to human health. Why would anyone subject himself or herself, his or her family, and his or her customers to a risk? Clearly, if there were no apparent gain from using subtherapeutic doses of antibiotics in animals, no one would do it. The manufacturers of antibiotics gain, of course, because such uses increase their sales. But farmers would not be expected to buy the antibiotics if they did not profit from them.

Discussions about subtherapeutic uses have been dominated by concerns about risks, but the fact that the uses continue and are sanctioned by the federal government is convincing evidence of the received benefits. Whatever the risks may be, any decision about subtherapeutic uses will involve considerations of both risks and benefits, and continued focus on efforts to better pin down estimates of risks to the exclusion of benefits may have little effect on the decisions. In any case, as can be seen from the earlier reviews of this issue, determining actual risk is not simple.

▋ How Well Do Subtherapeutic Doses Work?

A measure of the success of subtherapeutic uses of antibiotics in increasing meat production would be provided by information about the amounts of antibiotics that meat producers buy over time. From the limited information available it appears that success varies from animal to animal and from time to time. As discussed below, a major chicken producer uses the same kinds and amounts of subtherapeutic antibiotics as were used years ago, and large-scale pork producers are reducing their use. In addition, small "niche" markets have been developed for meats from drug-free animals, and some producers do not use antibiotics in order to participate in these markets.

While OTA has not carried out any original research or analysis on this issue, it appears that answers to the question of how well subtherapeutic antibiotics work to promote growth depends on the particulars of the application. Unsatisfying as it may be, the answer appears to be, "It depends."

Chickens—Constant Use and Constant Benefits

Chickens are archetypal food animals (see box 7-1). Because of selection for faster growing chickens and attention to animal husbandry, farmers can now produce a 6-pound chicken in 56 days. Thirty years ago, a chicken of the same age weighed two pounds.

Viral infections, against which antibiotics have no effect, are a far greater threat to chickens than are bacterial infections, and they are controlled by hygiene, vaccination, and isolation of chickens from possible human and animal sources of contamination (Dekich, 1994). A few "old" antibiotics, including tetracyclines, are available for treating bacterial infections, but such actions are uncommon. A large east coast producer treated less than 2 percent of its 7,500 flocks in 1994.

Two antibiotics—virginamycin and bambermicin—are used to promote growth in chickens.

Neither is used in human medicine. The dose for growth promotion has remained constant at 1 to 2 grams per ton of feed for 10 years, and the increased growth rate has remained constant. According to a chicken-producing company, the company would discontinue growth promotion use if it did not contribute to profits.

BOX 7–1: Chickens in the United States

The chicken—not the sparrow, pigeon, or starling—is the most common bird on the planet. The United States produces 7 billion chickens annually, or about 29 chickens for every one of the 240 million Americans.

About 20,000 farm families contract with large chicken producers and packers, and the average farm has two chicken houses. Each house produces all of the chicken consumed by 15,000 Americans annually. Production has doubled since 1978, and increases 4 to 5 percent annually.

Pigs—Decreasing Use with Increasing Concentration of Production

The number of pork producers is decreasing and the number of pigs sold by each producer is increasing (National Pork Producers Council, 1994), and antibiotic use appears to decrease with increasing size of pork production operations (Sundberg, 1994). The reasons for the trend are not well known, but better hygiene is believed to account for part of the decrease in subtherapeutic antibiotic use. More generally, larger operations mean that the producer's income is more dependent on pork production, rather than being drawn from several products, say, corn and pigs, and management probably becomes more focused on the animals.

The National Pork Producers Council has produced a Quality Assurance Program (National Pork Producers Council, 1994) that includes guidelines for the use of all drugs, including antibiotics. Those guidelines are intended to prevent the appearance of levels of drugs that exceed federal limits in finished meat products. According to the pork producers council, the percentage of

violations for all drug residues in pork dropped from 10 percent in the mid-1980s to less than 1 percent in 1994.

Trends in Some Other Sectors of Meat Production

During the early 1980s, sales of tetracyclines and penicillin for use in animal feeds slowly declined from 2.9 million kilograms of tetracyclines in 1980 to 2.4 million in 1985 and from 400,000 kilograms of penicillin in 1980 to 300,000 in 1984 (IOM, 1989, chap. IV). No more recent data are readily available.

Levy (1992, p. 142) states that tetracyclines were added to animal feeds for growth promotion at levels of 5 to 10 parts per million in the 1950s (roughly 5 to 10 grams of antibiotic per ton of feed). Currently, concentrations of 50 to 200 parts per million are commonly used. The higher rates of use have not substantially increased production costs because the cost of antibiotics on a weight basis has decreased over the same period. Because of the slim profit margin in meat production, decreased growth promotion effects, coupled with increased costs, could lead to a reduction in subtherapeutic uses of antibiotics as the costs of the drugs approach or exceed the benefits from faster growth.

▌ Summary of Comments on Subtherapeutic Uses of Antibiotics

Levy (1992, p. 156) suggests that several factors are reducing the agricultural uses of antibiotics: increased concerns about drugs of all kinds in food; greater appreciation of the threat of antibiotic-resistant bacteria and the contribution that agricultural use of antibiotics may make to it; better animal husbandry that reduces the need for antibiotics; and legislative and regulatory initiatives. Indeed, FDA experts report that they see few applications for the subtherapeutic uses of new antibiotics (FDA, 1995). While Levy's impressions may be accurate, and decreases in such uses were reported over a decade ago, the phasing out of subtherapeutic uses would not

necessarily end the controversy about antibiotic use in animals.

CONTROVERSY OVER FLUOROQUINO-LONES IN FOOD PRODUCTION

Just as physicians need new antibiotics to treat human diseases, veterinarians see needs for the use of new antibiotics in their practices. FDA has approved the use of one fluoroquinolone in the treatment of diseases in companion animals, and several manufacturers have requested approvals for the use of fluoroquinolones in the treatment of diseases in food animals. Fluoroquinolone use in animals has been more widespread in Europe, and resistance to the drugs has been reported in bacteria isolated from treated animals.

Because of the importance of fluoroquinolones in medicine, the American Society for Microbiology, the Infectious Diseases Society of America, and officials of the Centers for Disease Control and Prevention have advised FDA to restrict the use of fluoroquinolones in food animals. In particular, the Infectious Diseases Society requested that no formulations of fluoroquinolones in animal feeds be allowed. That request, if honored, would allow veterinarians to treat individual animals, but prevent treatment of herds or flocks. It is opposed by some veterinarians who maintain that using the antibiotic in feed is necessary to treat animals.

FDA has received no applications for the long-term use of fluoroquinolones in agriculture and does not expect to (FDA Veterinarian, 1994), but it held public hearings in May 1994 on possible therapeutic uses. At that meeting FDA announced that it was considering a new policy that would restrict approval of new antibiotics to prescription uses in disease treatment and prevention. The consensus of the advisory panel convened for that study was that the benefits of restricted short-term therapeutic use of fluoroquinolones in food animals outweighed the potential human health risk due to resistant organisms, but that strict controls on usage and improved surveillance were warranted (FDA 1995a).

As therapeutic agents, fluoroquinolones could be used to prevent disease in herds or flocks that are known to contain infected animals. Such preventive use requires formulations of antibiotics that can be incorporated into water or feed, leading to concern that those formulations will find widespread use in growth promotion, exerting heavy selection pressure for the emergence of fluoroquinolone-resistant bacteria. There is a historical base for this concern. Chloramphenicol (CAP) was licensed for therapeutic use in livestock but never for subtherapeutic uses. Nevertheless, veterinarian and husbandry experts published articles that gave details about the use of CAP for growth promotion. As sales soared for such unapproved use, FDA intervened and banned the marketing of oral solutions of CAP that were convenient for treating farm animals. Unlike most antibiotics, CAP causes severe anemias and other diseases of the blood in some humans, increasing concern that any residual CAP in meat might directly harm humans.

At the May 1994 meeting, FDA considered opinions from private organizations and professional societies and other federal agencies that ranged from urging that the fluoroquinolones be completely restricted from agricultural use to arguments that they were necessary for the care of animals and that the risk of resistance from agricultural use paled beside the risk from medical uses. Currently (July 1995) FDA is preparing its policy statement for agricultural uses of fluoroquinolones.

In November 1994, FDA held another meeting about the possible use of surveillance systems to keep track of the emergence of antibiotic-resistant bacteria, including the emergence of fluoroquinolone-resistant bacteria in animals if agricultural uses of those drugs are permitted. FDA is also drafting a statement on surveillance that will consider the questions raised by antibiotic resistance.

REFERENCES

Anderson, E.S. 1968. The ecology of transferable drug resistance in the enterobacteria. *Annual Review of Microbiology 22:*131.

Animal Health Institute. 1995. Personal communication; letter comments on earlier draft of this report. 30 May.

Bates, J., J.Z. Jordens, and D.T. Griffiths. 1994. Farm animals as a putative reservoir for vancomycin-resistant enterococcal infection in man. *Journal of Antibiotics and Chemotherapy 34:*507–516.

Bywater, R.J., SmithKline Beecham Animal Health, Surrey, United Kingdom. 1995. Personal communication; telephone conversation with M. Gough, OTA. April 20.

Corpet, D.E. 1993. An evaluation of methods to assess the effect of antimicrobial residues on the human gut flora. *Veterinary Microbiology 35:*199–212.

Dekich, M., Purdue Farms, Salisbury, Maryland. 1994.   Remarks at U.S. Food and Drug Administration "Part 15 Hearing: Surveillance Systems for Antibacterial Resistance." Rockville Civic Center, Rockville, MD. November 9.

Elder, H.A., I. Roy, S. Lehman, et al. 1993. Human studies to measure the effect of antibiotic residues. *Veterinary and Human Toxicology 35* (Supplement 1):31–36.

Ervik, A., B. Thorsen, V. Eriksen, et al. 1994. Impact of administering antibacterial agents on wild fish and blue mussels *Mytilus edulis* in the vicinity of fish farms. *Diseases of Aquatic Organisms 18:*45–51.

Feinman, S.E. and J.C. Matheson. 1978. *Draft Environmental Impact Statement. Subtherapeutic Antibacterial Agents in Animal Feeds.* U.S. Food and Drug Administration: Rockville, MD.

FDA Veterinarian. 1994. Advisory committees discuss   fluoroquinolones.   July/August issue, pp. 2–5.

Gorbach, S.L. 1993. Perturbation of intestinal microflora. *Veterinary and Human Toxicology 35* (Supplement 1):15–23.

Hays, V.W. and C.A. Black. 1989. *Antibiotics for Animals: The Antibiotic Resistance Issue. Comments from CAST: 1989-92.* Council for Agricultural Science and Technology: Ames, IA.

Institute of Medicine. 1989. *Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed.* National Academy Press: Washington, DC.

Kidd, A.R.M. 1994. *The Potential Risk of Effects of Antimicrobial Residues on Human Gastro-intestinal Microflora.* Fédération Européenne de la Santé Animale: Brussels, Belgium.

Klare, I., H. Heier, H. Claus, R. Reissbrodt, and W. Witte. 1995. *van*A mediated high level glycopeptide resistance in *Streptococcus faecium* from animal husbandry. *FEMS Microbiology Letters 125*:165–172.

Levy, S.B. 1978. Emergence of antibiotic-resistant bacteria in the intestinal flora of farm inhabitants. *Journal of Infectious Diseases 137:*688–690.

Levy, S.B. 1983. Antibiotic-resistant bacteria in food of man and animals. In Woodbine, M. (ed.) *Antimicrobials and Agriculture*. Butterworth: London, pp. 43–61.

Levy, S.B. 1992. *The Antibiotic Paradox.* Plenum Press: New York.

Levy, S.B., G.G. Fitzgerald, and A.B. Macone. 1976. Changes in intestinal flora of farm personnel after introductions of tetracyclines-supplemented feed on a farm. *New England Journal of Medicine 295:*583–588.

Murray, B.E. 1995. Editorial response: What can we do about vancomycin-resistant enterococci? *Clinical Infectious Diseases 20:*1134–1136.

National Pork Producers Council. 1994. *Pork Facts.* National Pork Producers Council: Des Moines, IA.

National Research Council. 1980. *The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds.* National Academy Press: Washington, DC.

Stallones, R.A. 1982. Epidemiology and public policy: Pro- and anti-biotic. *American Journal of Epidemiology 115:*485–491.

Sundberg, P., National Pork Producers Council, Des Moines, IA. 1994. Remarks at U.S. Food and Drug Administration "Part 15 Hearing: Surveillance Systems for Antibacterial Resistance." Rockville Civic Center, Rockville, MD. November 9.

Teske, R.H., Center for Veterinary Medicine, U.S. Food and Drug Administration. 1995. Personal communication. Telephone conversation with M. Gough, OTA. April 21.

U.S. Congress, Office of Technology Assessment. 1979. *Drugs in Livestock Feed.* Washington, DC: U.S. Government Printing Office. [OTA-F-91.]

U.S. Food and Drug Administration. 1995. Comments on earlier draft of this OTA report. Memorandum from Lois Adams, U.S. Food and Drug Administration, to M. Gough, OTA. April 10.

U.S. Food and Drug Administration. 1995a. Comments on second draft of this OTA report. Memorandum from Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration to Office of Technology Assessment. June 16.

U.S. House of Representatives, Committee on Science and Technology, Subcommittee on Investigations and Oversight. 1984. Hearing: *Contract with Seattle.* U.S. Government Printing Office: Washington, DC.

Walker, R., Michigan State University. 1994. Remarks at Food and Drug Administration "Part 15 Hearing: Surveillance Systems for Antibacterial Resistance." Rockville Civic Center, Rockville, MD. November 10.