Appropriate Regulation of Antibiotics in Livestock Feed

by

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APPROPRIATE REGULATION OF ANTIBIOTICS IN LIVESTOCK FEED

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Abstract: For decades, antibiotics have been widely used, saving lives and reducing suffering. Such drugs are routinely employed among both human and farm animal populations. However, scientific data now links the use of antibiotics at subtherapeutic levels in livestock feed to the spread of antibiotic resistant bacteria in the human population. After examining the current research, this Article concludes that despite short-term economic benefits associated with the widespread use of antibiotics in agriculture, the risk to human health justifies a change in policy. This Article recommends a number of steps to minimize the spread of antibiotic resistance. The primary changes would be to phase out the use of antibiotics as livestock feed additives, and to refuse to approve new drugs for this purpose. In either instance, this use would be permissible if the drug sponsor provides convincing evidence that the agricultural use of its particular antibiotic presents no appreciable risk to human health.

INTRODUCTION

The headlines are sensational enough that it wouldn't be surprising to see them in the most notorious supermarket tabloids.[1] The sto-

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[1] *See, e.g.*, Zosi Kmietowicz, *Superbugs are Beating at the Gates*, NEW SCIENTIST (July 17, 1999), *available at* http://www.newscientist.com/ns/19990717/newsstory12.html; *Leading Superbugs Develop Dramatic Resistance to the Newest Antibiotics*, U. OF TORONTO NEWS & EVENTS (July 21, 1999), *available at* http://www.newsandevents.utoronto.ca/bin/19990721.asp; Tamar Nordenberg, *Miracle Drugs vs. Superbugs—Preserving the Usefulness of Antibiotics*, FDA CONSUMER MAGAZINE (Nov.-Dec. 1998), *available at* http://www.parenthoodweb.com/articles/phw894.htm; Michael Day, *Superbugs Take Hold*, NEW SCIENTIST (Apr. 25, 1998), *availabe at* http://www.newscientist.com/ns/980425/nsuperbug.html; *Companies Race to Find Drugs to Kill Superbugs*, NANDO TIMES (Aug. 23, 1997), *available at* http://www.techserver.com.newsroom/ntn/health/082397/health34_5696_noframes.html.

ries behind the headlines are scary enough that they might be th plot of a horror movie.[2] Unfortunately, it is often the scientific pres that is reporting on the spread of antibiotic-resistant bacteria,[3] an the threat to human health and life is very real and growing.[4]

The increase in public awareness about the spread of antibiotic resistant bacteria has been occasioned by a significant increase in the number of reported cases of human illness associated with antibiotic resistance.[5] Studies show that infectious disease mortality rates have risen nearly 60%,[6] with the Centers for Disease Control (CDC) estimating that more than half of the infection-related deaths involve resistant bacteria.[7]

Dubbed "super-bugs" in the popular press,[8] multi-drug resistant bacteria are becoming more and more common. Newspapers and magazines carry stories of bacterial infections that do not respond to the antibiotics typically prescribed to control them.[9] As one legal commentator observed, "[m]any of the killer diseases of the past such as tuberculosis, typhoid fever, diphtheria, and pneumonia have re-

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[2] One recent news story cites an "alarming" spread of drug-resistant bacteria that can "kill people with weak immune systems." Day, *supra* note 1. Another draws parallels between the spread of antibiotic-resistant organisms and the "historical scourge known as the bubonic plague [that] killed up to one-third of Europe's population in the 1300s." Nordenberg, *supra* note 1. *See generally* LAURIE GARRETT, THE COMING PLAGUE (1994) (a recent book on the subject drawing similar parallels).

[3] Antibiotic resistance refers to "a property of bacteria that confers the capacity to inactivate or exclude antibiotics, or a mechanism that blocks the inhibitory or killing effects of antibiotics, leading to survival despite exposure." USDA, ANTIMICROBIAL RESISTANCE ISSUES IN ANIMAL AGRICULTURE 1 (Dec. 1999) [hereinafter USDA REPORT]. For a review of some of the scientific articles on the subject, see *infra* Part III of this article.

[4] "The cause of bacterial reemergence as a threat to human health and life is the abuse of the 'miracle drugs.'" John W. Harrison & Timothy A. Svec, *The Beginning of the End of the Antibiotic Era? Part I. The Problem: Abuse of the "Miracle Drugs,"* 29(3) QUINTESSENCE INT'L 151, 151 (1998) [hereinafter Harrison, *Part I*].

[5] NAT'L RESEARCH COUNCIL, BOARD ON AGRICULTURE, THE USE OF DRUGS IN FOOD ANIMALS, BENEFITS AND RISKS 3 (1999).

[6] Robert W. Pinner et al., *Trends in Infectious Disease Mortality in the United States*, 275 JAMA 189, 190 (1996).

[7] Leslie Alan Horvitz, *It's a War to Restore Antibiotics*, INSIGHT ON THE NEWS, Mar. 18, 1996, at 38, *cited in* Michael Misocky, Comment, *The Epidemic of Antibiotic Resistance: A Legal Remedy to Eradicate the "Bugs" in the Treatment of Infectious Diseases*, 30 AKRON L. REV. 733, 737 n.22 (1997).

[8] *See supra* note 1.

[9] Two recent student-written law review articles have also addressed the problem of antibiotic-resistant bacteria. *See generally* Scott B. Markow, Note, *Penetrating the Walls of Drug-Resistant Bacteria: A Statutory Prescription to Combat Antibiotic Misuse*, 87 GEO. L.J. 531 (1998); Misocky, *supra* note 7. Both of these articles, however, focus solely on the over-prescription of antibiotics.

turned to wreak havoc as bacteria are increasingly resistant to antibiotics."[10] While antibiotics were once regarded as an unending miracle of modern medicine,[11] we are fast approaching a time when the miracle may come to an end.[12]

While there are doubtless many factors contributing to the spread of multi-resistant bacteria, one factor appears to be the widespread addition of antibiotics to livestock[13] feed. A wide range of antibiotics are currently added, in subtherapeutic amounts,[14] to animal feeds.[15] A growing volume of research suggests that this practice is having devastating and potentially irreversible effects on the viability of antibiotics as agents to effectively treat diseases in human beings, but the legal community appears to be lagging far behind scientific experts in calling for an end to this practice in the United States.

The first section of this article will provide a brief introduction to the mechanisms of antibiotic resistance in bacteria and the risks to human health posed by this growing phenomenon. The next section will examine current agricultural practices with regard to the use of antibiotics in subtherapeutic amounts, including an analysis of the beneficial results attributed to these practices. It will then consider whether existing research on antibiotic resistance that identifies a link

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[10] Simon Midgely, *Old Killers Resisting Arrest: Diseases Last Common in the 19th Century Have Returned with an Added Danger—the Prospect of an Antibiotic Resistant Super Bug*, TIMES HIGHER EDUCATION SUPPLEMENT, July 19, 1996, at 20, *cited in* Misocky, *supra* note 7, at 738.

[11] Stuart B. Levy, a professor of molecular biology and microbiology at the Tufts University School of Medicine, has described this phenomenon as follows:

> Ever since antibiotics became widely available in the 1940s, they have been hailed as miracle drugs—magic bullets able to eliminate bacteria without doing much harm to the cells of treated individuals. Yet with each passing decade, bacteria that defy not only single but multiple antibiotics—and therefore are extremely difficult to control—have become increasingly common.

Stuart B. Levy, *The Challenge of Antibiotic Resistance*, 278 SCIENTIFIC AMERICAN 46, need pinpoint cite (Mar. 1998), *available at* http://www.sciam.com/1998/0398issue/0398levy.html [hereinafter Levy, *The Challenge*].

[12] At least 3 strains of bacteria capable of causing life-threatening illnesses in human beings have already been demonstrated to be resistant to *every* currently available antibiotic. Levy, *The Challenge*, *supra* note 11, at 46.

[13] Although the term "livestock" may have a more limited meaning in other contexts, this article uses the term to mean any farm animal or poultry raised for food or food production (such as dairy cows or laying hens).

[14] Despite the fact that differing drugs must normally be administered at differing levels in order to have demonstrable therapeutic effects, the Food and Drug Administration rather arbitrarily defined a subtherapeutic concentration of antibiotics as an amount added to feed at a concentration of <200 g/t. NAT'L RESEARCH COUNCIL, *supra* note 5, at 28.

[15] *See infra* Part II of this article.

between the use of livestock feed and risks to human health is sufficiently convincing so as to justify a change in policy. The final section of this Article suggests legal steps which should be taken to ensure the appropriate use of antibiotics in the agricultural community.

I. The Mechanisms of Antibiotic Resistance

Every human being plays host to millions of bacteria, of many different species.[16] Many of the bacteria that live on and in the human body are beneficial to the host; some are even essential.[17] Of course, pathogenic bacteria (those capable of causing disease) also exist.[18] Symptoms of a harmful bacterial infection may be due to the presence of microbial products such as toxins, or the host's immune response to the bacteria.[19] The development and widespread availability of multiple classes of antibiotics in the latter half of the twentieth century meant that we could cure many potentially life-threatening infections.[20]

Unfortunately, the use of antibiotics, at both therapeutic and subtherapeutic levels, has led to the emergence of resistant bacteria that can survive in the presence of one or more classes of antibiotics.[21] The use of antibiotics promotes resistance by killing off the bacteria that are most susceptible to the antibiotics. If the dosage is insufficient to kill off all the bacteria infecting the host, the bacteria that survive to propagate will be those that were most resistant to the effects of the antibiotics.

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[16] Bacteria are single-celled prokaryotic microorganisms. "Prokaryotic" means that the cell contains a primitive nucleus where the DNA-containing region lacks a limiting membrane. McGraw-Hill Dictionary of Scientific and Technical Terms 1588 (5th ed. 1994).

[17] J. Nicklin et al., Instant Notes in Microbiology 156 (1999).

[18] *Id.* at 156–57.

[19] *Id.* at 157.

[20] Penicillin alone saved countless lives in World War II by preventing soldiers from dying as a result of bacterial infection following wounding. Harrison, *Part I*, *supra* note 4, at 151. *See also* Nicklin, *supra* note 17, at 179. Antibiotics operate in a number of different ways. Harrison, *Part I*, *supra* note 4, at 152. Some antibiotics, such as penicillins and cephalosporins, inhibit bacterial cell wall synthesis. Other antibiotics, such as aminoglycoside antibiotics and tetracycline, interfere with protein synthesis. A third mechanism, employed by sulfonamides and quinolones, inhibit synthesis of bacterial nucleic acid. Nicklin, *supra* note 17, at 178.

[21] Levy, *The Challenge*, *supra* note 11, at 49–50. If the bacteria is resistant to more than one class of antibiotics, it is generally referred to as having multi-drug resistance.

Antibiotic resistance can take a number of different routes.[22] For example, penicillin and chloramphenicol resistance generally occurs because the resistant bacteria are able to inactivate the antibiotics.[23] Tetracycline resistance most commonly occurs when the bacteria are able to increase antibiotic efflux, transport of the antibiotic from the interior to the exterior of the cell.[24] Additionally, bacteria may mutate so that the target sites which the antibiotics effect are altered.[25]

Drug resistance is a particular problem in bacteria because resistance is so readily transmitted from bacteria to bacteria, even to different bacteria species.[26] In fact, noted microbiologist Stuart B. Levy has suggested that it makes sense to think of "the entire bacterial world . . . as one huge multicellular organism in which the cells interchange their genes with ease."[27]

There are a number of mechanisms by which drug resistance can spread among bacteria. While most of the essential genetic information for each bacterium is contained within a single circular deoxyribonucleic acid (DNA) strand,[28] bacteria also carry extrachromosomal material in the form of plasmids and transposons.[29] Plasmids can transmit the characteristic of drug resistance[30] between bacteria by conjugation, transformation, or transduction.[31] Conjugation involves contact between two bacterial cells during which genetic material

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[22] Random mutations may lead to resistance via any of a number of pathways, some of which are identified in the text of this article. Antibiotic use exerts a selective pressure so that the "mutant" strains have an evolutionary advantage, resulting in the creation of a dominant strain which exhibits the characteristic of resistance.

[23] NICKLIN, *supra* note 17, at 179.

[24] *Id.*

[25] Sulfonamide, methicillin, and trimethoprim resistance all occur because of such changes in the resistant bacteria. *Id.*

[26] One normally thinks of inherited characteristics passing only to successive generations of that particular organism. This is not the case for bacteria.

[27] Levy, *The Challenge*, *supra* note 11, at 48; *see also* Robert V. Miller, *Bacterial Gene Swapping in Nature*, 278 SCIENTIFIC AMERICAN 66 (1998).

[28] Harrison, *Part I*, *supra* note 4, at 154.

[29] In the strictest sense of the word, transposons are not extrachromosomal since they are integrated into the chromosomal DNA. Plasmids are an extrachromosomal genetic element found among various strains of *Escherichia coli* and other bacteria. MCGRAW-HILL, *supra* note 16, at 1522. Transposons are a kind of translocatable genetic element which comprise large discrete segments of deoxyribonucleic acid capable of moving from one chromosomal site to another in the same organism or in a different organism. *Id.* at 2061.

[30] Plasmid-mediated resistance is of particular concern, not only because most bacterial species carry plasmids, but because resistance mediated by plasmids frequently results in multi-drug resistance. In addition, plasmids are easily transferred among bacterial strains and species. Harrison, *Part I*, *supra* note 4, at 154.

[31] NICKLIN, *supra* note 17, at 179.

passes from one cell to the other.[32] Transformation consists of the transfer and incorporation of foreign DNA into a cell and subsequent recombination of part or all of that DNA into the cell's genome.[33] Transduction is the transfer of genetic material (which may be either chromosomal or plasmid DNA) between bacteria by bacteriophages.[34] The prevalence of plasmids in bacterial cells therefore means that it is likely that acquired characteristics will be shared with other bacteria.

Transposons also facilitate the transfer of genes that enable the bacteria to become drug-resistant. When a bacterium dies, it typically releases its contents into the environment. Many intact bacteria contain specialized transposons, termed integrons, "that are like flypaper in their propensity for capturing new genes."[35] The presence of these transposons further facilitates the transfer of resistance genes between bacteria.

The speed with which bacteria propagate makes the problem of drug resistance particularly acute. Bacteria have a generation time that can be measured in minutes, and a single bacterium can easily produce more than a million progeny in less than a day.[36] For example, one *Escherichia coli (E. coli)* can produce more than a million progeny (about twenty generations) in seven hours.[37] Starting with a single drug-resistant bacterium, it does not take long to create millions of resistant bacteria first in the host and then in other hosts—as the bacteria itself spreads—or in the environment.

The problem caused by the ready and rapid spread of drug-resistance mechanisms among bacteria is further compounded by the fact that bacteria do not exist in isolated populations, but instead mingle among humans, animals and the environment.[38] Resistance which develops in animal populations may soon emerge in human populations. Scientists have already discovered evidence of similar re

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[32] *Id.* at 125–28.

[33] *Id.* at 144–45.

[34] *Id.* at 140–43. Bacteriophage, "normally called phage, are viruses that infect bacteria. They are obligate intracellular parasites that are capable of existence as phage particles outside the bacteria cell but can only reproduce inside the cell." *Id.* at 127.

[35] Levy, *The Challenge, supra* note 11, at 49.

[36] Harrison, *Part I, supra* note 4, at 152.

[37] John W. Harrison & Timothy A. Svec, *The Beginning of the End of the Antibiotic Era? Part II. Proposed Solutions to Antibiotic Abuse,* 29(4) QUINTESSENCE INT'L 223, 223 (1998) [hereinafter Harrison, *Part II*]; *see also* Wolfgang Witte, *Medical Consequences of Antibiotic Use in Agriculture,* 279 SCIENCE 959, 996–97 (1998).

[38] L. Tollefson et al., *Therapeutic Antibiotics in Animal Feeds and Antibiotic Resistance,* 16(2) REV. SCI. TECH. 709, 709–15 (1997).

sistance genes in bacteria of different genera inhabiting entirely different environments.[39] Organisms originally present in an animal population have been found in humans who are in direct association with these animals or in contact with animal products.[40] Once the resistant bacteria is in the human population, it can easily spread further to increasing numbers of human beings. One recent report characterizes the problem as follows:

> There are opportunities in the microbial environment for interconnected ecosystems to allow exchange of DNA, promoting the spread of resistance from one genus to another. The combination of increased bacterial virulence and increased drug resistance creates a potential for increased risk of morbidity and mortality for animals and humans that some have extrapolated to a catastrophic potential.[41]

While it is impossible to trace specific bacterial infections among human populations back to the original source with 100% certainty, a growing body of scientific data points to the subtherapeutic dosing of livestock as a significant contributing factor in the spread of antibiotic-resistant organisms.[42] Part III of this article will examine the current research, but in order to place the evidence in context, it is critical to understand the role that antibiotics have come to play in American agriculture.

II. The Use of Antibiotics in American Agriculture

At the current time, there are three primary uses of antibiotics in animal agriculture: therapeutic, prophylactic (to prevent potential infection), and growth promotion (with both of the latter two catego

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[39] Stuart B. Levy, *Antibiotic Use for Growth Promotion in Animals: Ecologic and Public Health Consequences*, 50(7) J. of Food Protection 616, 616–20 (1987) [hereinafter Levy, *Antiboitoic Use*]. Not incidentally, the spread of resistance in this manner demonstrates the complexity of microbial spread of resistance determinants.

[40] *See generally* A. H. Linton, *Animal to Man Transmission of* Enterobacteriaceae, 97(3) R. Soc. Health J. 115–18 (1977).

[41] Nat'l Research Council, *supra* note 5, at 70.

[42] S.D. Holmberg et al., *Drug-resistant* Salmonella *from Animals Fed Antimicrobials*, 311 New Eng. J. Med. 617, 621 (1984). "Transfer of antimicrobial-resistant bacteria from animals to human beings under natural conditions is thought to be frequent but impossible to determine accurately." *See id.*

ries being at subtherapeutic concentrations).[43] The use of antibiotics to ward off infections and to promote growth in livestock is not new. For more than 40 years many farmers have fed their animals a diet laced with small, subtherapeutic doses of antibiotics.[44]

The discovery that antibiotics could be used for prevention of infection and growth promotion was serendipitous. Veterinarians began administering antibiotics to sick animals in an effort to determine whether the "miracle drugs" that were saving human lives could also help livestock.[45] These experiments led to the discovery that feeding animals small doses of the drugs not only inhibited diseases but also enhanced growth.[46] This discovery led in turn to an agricultural revolution, with farmers—especially those in very large operations[47]—relying increasingly on subtherapeutic doses of antibiotics to keep their livestock healthy and to promote animal growth.[48]

In the past three decades, agricultural use of antibiotics has increased exponentially. One article has estimated that in the past thirty years, farmers have increased their use of penicillin-type antibiotics in

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[43] NAT'L RESEARCH COUNCIL, *supra* note 5, at 19.

[44] STUART B. LEVY, THE ANTIBIOTIC PARADOX: HOW MIRACLE DRUGS ARE DESTROYING THE MIRACLE 138 (1992) [hereinafter LEVY, ANTIBIOTIC PARADOX].

[45] *Id.* at 137–38.

[46] *Id.* at 138.

[47] "[F]armers with large operations were more likely than those with small farms to use antibiotics in feeds . . . ." George G. Khachatourians, Ph.D., *Agricultural Use of Antibiotics and the Evolution and Transfer of Antibiotic-Resistant Bacteria*, 159 CAN. MED. ASS'N. J. 1129 (1988), *at* http://www.cma.ca/cmaj/vol-159/issue-9/1129.htm.

[48] *See generally*, Barbara O'Brien, Comment, *Animal Welfare Reform and the Magic Bullet: The Use and Abuse of Subtherapeutic Doses of Antibiotics in Livestock*, 67 U. COLO. L. REV. 407 (1996) (for a description of the conditions under which many farm animals are now raised). The author attributes the widespread use of antibiotics at subtherapeutic levels to changes in animal husbandry practices designed to maximize output.

> The farmer, having no rules or guidelines but industry standards by which to abide, will often treat animals like machines in order to maximize output and profit. Such an approach, however, requires an arsenal of drugs to ward off the inevitable infections and health problems that animals suffer when reared under stressful conditions. Antibiotics prevent the spread of infectious disease among herds kept in close confinement. . . . The use of subtherapeutic doses of antibiotics makes factory farm practices feasible. In one trade journal, a hog farmer remarked: 'One reason large confinement systems have worked so well is because of antibiotics. Without the antibiotics it would be hard to have these larger systems and crowd the pigs as we do in some cases.'

Id. at 412–13 (citations omitted).

farm animals by 600% and their use of tetracycline by 1500%.[49] Recent statistical research continues to show an increasing reliance on the routine use of antibiotics for pigs and cattle.[50] Larger operations also continue to be more likely to use antibiotics,[51] and many rely on additives for periods of time in excess of ninety days.[52]

Part of the increase in antibiotic use is attributable to the declining effectiveness of the drugs as growth promoters. Over time, the amount of antibiotics needed to promote growth in farm animals has increased significantly. Some sources have suggested that "[r]oughly 10 to 20 times the amount used four decades ago are required to produce the same level of growth in the 1990s."[53] Moreover, even at concentrations approaching therapeutic levels, "the benefits of growth promotion are less now than those reported several decades ago."[54]

The increasing use of antibiotics in agriculture has paralleled an astonishing growth in the use of antibiotics generally. In 1954 two million pounds of antibiotics were produced in this country; today more than fifty million pounds of antibiotics are manufactured every year.[55] Only half of these antibiotics are consumed by human beings. Most of the remaining tens of millions of pounds annually are given to ani-

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[49] Alex Kirby, *Why Farm Antibiotics are a Worry*, (BBC NEWS, Oct. 8, 1999), *available at* http://news6.thdo.bbc.co.uk/hi/eng...biotics/newsid%5f436000/436398.stm.

[50] USDA REPORT, *supra* note 3, at 21 (examining use of antibiotics in pigs between 1990 and 1995). The same report suggests there has also been a recent decrease in reliance on antibiotics in broiler operations in recent years. *Id.* at 27. The report attributes this decline to both the lack of new antibiotics approved for use in the poultry industry and "the implementation of multi-faceted preventative medicine programs(e.g. biosecurity), increased efforts to reduce production costs, enhanced focus on residue avoidance, and rapid production of efficacious vaccines by manufacturers." *Id.* at 26–27.

[51] *Id.* at 24. Cattle operations with more than 1000 head of cattle were almost 3 times as likely to use antibiotics in food and water. *Id.*

[52] USDA REPORT, *supra* note 3, at 24 (42.1% of large operations that use antibiotic additives use them for periods of time in excess of 90 days, as compared with 32.2% of small operations that do so).

[53] Harrison, *Part I*, *supra* note 4, at 157; *accord* Khachatourians, *supra* note 47. In the 1950s the recommended levels of antibiotics for use as growth promoters were in the 5–10 parts per million range. The 10 to 20 fold increase in recommended dosage is apparently not enough for all producers. An examination of 3,328 feeds in the U.S. National Swine Survey indicated that "up to 25% of the feeds contained antibiotics at concentrations higher than the recommended levels." C.E. Dewey et al., *Association Between Off-label Feed Additives and Farm Size, Veterinary Consultant Use, and Animal Age*, 31 PREV. VET. MED. 133 (1997).

[54] *See generally* LEVY, ANTIBIOTIC PARADOX, *supra* note 44.

[55] Levy, *The Challenge*, *supra* note 11, at 51.

mals.[56] While some of these antibiotics are used to treat infection, the bulk is mixed into animal feed at subtherapeutic levels.[57]

Although farmers, veterinarians and drug companies protest the inadequacies of antibiotics available for use in livestock,[58] a relatively wide variety of antibiotics have been approved for use as subtherapeutic additives to animal feeds.[59] Included in the list of antibiotics used as food additives in American agriculture are a number of drugs that are either themselves used as drug therapies for human patients or are closely related to such drugs. Amoxicillin, ampicillin, erythromycin, neomycin, penicillin, and tetracycline are all used to treat human illness as well as being used in animal agriculture.[60]

A 1992 study examining the top ten drug-resistant microbes suggests that a number of drugs fed to animals are now less effective in

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[56] Some sources estimate that 40% of the total U.S. production of antibiotics is given to animals. *Id.* Other sources place the figure at closer to one half. NAT'L RESEARCH COUNCIL, *supra* note 5, at 25. Most of this amount, which clearly accounts for more than 20 million pounds of antibiotics each year, is fed to animals in subtherapeutic amounts to promote growth or to prevent or limit potential infections. *Id.* (estimating that 90% of all antibiotics given to farm animals are used in subtherapeutic amounts). *Accord* Khachatourians, *supra* note 47.

[57] *Id.*

[58] "As therapeutic options become less effective, drug companies and veterinarians have urged the approval of additional human-use antibiotics, such as fluoroquinolones, to treat animal diseases . . . ." Patricia B. Lieberman, Ph.D., & Margo G. Wootan, D.Sc., *Protecting the Crown Jewels of Medicine—A Strategic Plan to Preserve the Effectiveness of Antibiotics*, Center for Science in the Public Interest (1998), *available at* http:/www.espinet.org/reports/abiotic.htm.

[59] A December 1999 report of the United State Department of Agriculture lists the following antibiotics and sulfonamides for growth promotion and feed efficiency, therapeutic purposes or both in dairy and beef cattle: amoxicillin, ampicillin, bacitracin, ceftiofur, chlortetracycline, dihydrostreptomycin, erythromycin, furamazone, gentramycin, lacalocid, monensin, neomycin, oxytetracycline, penicillin, streptomycin, tetracycline, tilmicosin, tylosin, sulfabromomethazine, sulfachloropyridazine, sulfaethoxypyridazine, sulfaethazine, and sulfamethoxine. USDA REPORT, *supra* note 3, at 19. The following antibiotics are approved for use in hogs: amoxicillin, ampicillin, apramycin, bacitracin, chlortetracycline, efrotomycin, lincomycin, neomycin, oleandomycin, oxytetracycline, penicillin, spectinomycin, streptomycin, tetracycline, tiamulin, tylosin, and virginiamycin. *Id.* Various sulfonamides have also been approved for use in hogs. *Id.* Fewer antibiotics have been approved for use in sheep. They include chlortetracycline, erythromycin, neomycin, oxytetracycline, penicillin, and penicillin/streptomycin. *Id.* The following antibiotics have been approved by the Food and Drug Administration (FDA) for use in chickens and turkeys: bambermycin, bacitracin, chlortetracycline, erythromycin, gentramycin, neomycin, novobiocin, oleandomycin, oxytetracycline, penicillin, roxarsone, spectinomycin, streptomycin, tetracycline, tylosin, virginiamycin and fluoroquinolones. *Id.* Various sulfonamides have also been approved for use in poultry. USDA REPORT, *supra* note 3, at 19–20.

[60] Lieberman, *supra* note 58. Another antibiotic approved for use with livestock, tylosin, is closely related to the family of drugs that includes erythromycin. *Id.*

treating a wide variety of human ailments.[61] *Enterobacteriaceae*, which cause bacteremia, pneumonia, and urinary tract and surgical wound infections, may be resistant to aminoglycosides (such as vancomycin), beta-lactam antibiotics (such as penicillin), chloramphenicol and trimethoprim.[62] *Enterococcus*, which is implicated in all of the foregoing diseases except pneumonia, may be resistant to aminoglycosides, beta-lactams, and erythromycin.[63] *Haemophisus influenzae*, which causes epiglottitis, meningitis, otitis media, pneumonia and sinusitis, may be resistant to beta-lactams, chloramphenicol, tetracycline and trimethoprim.[64] *Mycobacterium tuberculosis*, which causes tuberculosis, may be resistant to aminoglycosides, ethambutol, isoniazid, pyrazinamide and rifampin.[65] *Neisseria gonorrhoeae*, which causes gonorrhea, may be resistant to beta-lactams, spectinomycin, and tetracycline.[66] Other microbes listed as causing serious diseases may be resistant to chloroquine, ciprofloxacin, sulfonamides, and/or clindamycin as well as the drugs listed above.[67]

In 1969, a report commissioned by the English Parliament on the use of antibiotics in animal husbandry and veterinary medicine recommended a ban on the subtherapeutic use of antibiotics in food producing animals.[68] This report, chaired by Professor M.M. Swann, widely known as the "Swann Report," concluded that "the administration of antibiotics to farm livestock, particularly at sub-therapeutic levels, poses certain hazards to human and animal health."[69] The final recommendation of the Swann Report was that only antibiotics that "have little or no application as therapeutic agents in man or animals and will not impair the efficacy of a prescribed therapeutic drug or drugs through the development of resistant strains" should be used for growth promotion.[70] The report specifically identified chlortetra-

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[61] *Exploring New Strategies to Fight Drug-Resistant Microbes*, 257 SCIENCE 1036, 1036 (Aug. 1992) [hereinafter *Exploring New Strategies*].

[62] *Id.*

[63] *Id.*

[64] *Id.*

[65] *Id.*

[66] *Exploring New Strategies*, *supra* note 61, at 1036.

[67] *Id.*

[68] *See* HOUSE OF LORDS, SCIENCE AND TECHNOLOGY—SEVENTH REPORT (Mar. 17, 1998), *available at* http://www.parliament.the-stationery-office ... 199798/ldselect/ldsctech/ 081vii/st0701.htm [hereinafter HOUSE OF LORDS]; REPORT OF THE COMPTROLLER GENERAL OF THE UNITED STATES, NEED TO ESTABLISH SAFETY AND EFFECTIVENESS OF ANTIBIOTICS USED IN ANIMAL FEEDS 10 (1977) [hereinafter COMPTROLLER'S REPORT].

[69] HOUSE OF LORDS, *supra* note 68.

[70] *Id.*

cycline, oxytetracycline, penicillin, tylosin (which is related to erythromycin) and the sulphonamides as unsuitable for use as growth promoters.[71]

Although the Swann Report was relatively influential in the United Kingdom, its recommendations have never been adopted in the United States.[72] At one point, in the 1970s, the FDA proposed rules which would have prohibited the use of penicillin and tetracyclines as food additives for disease prevention and growth promotion.[73] Because of political opposition, however, the proposed rule was never promulgated.[74] Instead, the United States continues to study the issue while new drugs are added to the list of antibiotics approved for use in agriculture.

Most recently, in 1995, the FDA approved the use of fluoroquinolones in farm animals.[75] The FDA approved this use "despite vigorous opposition by the CDC and the Infectious Disease Society of America (IDSA)."[76] To address some of their concerns, the FDA restricted the use of this class of antibiotics to short-term use in limited situations, but the permitted uses still include the dosing of entire poultry flocks through their drinking water.[77] The potential problems posed by fluoroquinolone resistance are significant because

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[71] *Id.*

[72] For comparison purposes, England implemented the Swann Report recommendations in March 1971 by issuing the Therapeutic Substances Regulation of 1971 which, among other things, restricted the availability of penicillin, chlortetracycline, oxytetracycline, tylosin, nitrofurans and most sulfonamides. COMPTROLLER'S REPORT, *supra* note 68, at 10.

[73] *See generally* COMPTROLLER'S REPORT, *supra* note 68, and Lieberman, *supra* note 58. The FDA published rules in the April 20, 1973 Federal Register which stated the agency's intention to withdraw approval for the subtherapeutic use of antibiotics in animal feeds within two years "unless data were submitted by drug sponsors to establish conclusively . . . their safety to humans and animals and effectiveness for their intended purposes." COMPTROLLER'S REPORT, *supra* note 68, at 10–11.

[74] The Comptroller's Report noted that despite the original promulgation of rules which would have withdrawn approval for the subtherapeutic use of antibiotics in 1975, the FDA "permitted the continued use of the products" despite the fact that "a number of the antibiotics currently marketed for subtherapeutic use in animals feeds, including penicillin, tetracyclines, and sulfaquinoxaline, have been shown to either create a hazard to human or animal health or have not been shown to be effective for some of their disease prevention uses." *Id.* at 34.

[75] Lieberman, *supra* note 58.

[76] *Id.*

[77] *Id.* Two years after this approval, the Minnesota State Department of Health reported a significant increase in fluoroquinolone resistance in bacteria isolated from poultry and human beings. The CDC also reported that 13% of human *Campylobacter* isolates have become fluoroquinolone resistant. *Id.*

fluoroquinolones are the primary treatment for resistant stains of *Salmonella typhimurium* in human beings.[78] Fluoroquinolones are critically important in treating several other bacteria as well.[79]

III. Evidence Concerning the Effect of Subtherapeutic Dosing and Its Risk to Human Health

Members of the scientific community and the general public share a growing concern about the decrease in effectiveness and/or usefulness of antibiotics. The question remains, however, whether the use of antibiotics at subtherapeutic levels in farm animals has contributed to the spread of antibiotic-resistant bacteria in a manner which poses a significant risk to human health.[80] Many health organizations, including the World Health Organization and the Institute of Medicine, regard antibiotic resistance as "a documented major health threat around the world."[81] Despite protests from the agricultural community and drug companies, there is a general consensus among scientists that subtherapeutic doses of antibiotics used in animal feed favors the selection of antibiotic-resistant bacteria.[82]

Despite the growing concern in the scientific community, very little has been written about this subject in legal literature. One recent law review article complaining about the use and abuse of subtherapeutic doses of antibiotics in livestock feed focused primarily on the ethics of animal husbandry in the United States.[83] Two other student articles which purport to address the "epidemic of antibiotic resistance" target only physician-prescribing practices, completely ignor-

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[78] *Id.* (noting that 32% of *Salmonella typhimurium* cases in the U.S. (approximately 3,000 cases confirmed with cultures) are resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracyclines (all antibiotics that are or were commonly used in animals)). In addition, fluoroquinolones are important in treating humans for urinary tract infections, sexually transmitted diseases, invasive *Campylobacter* infections, respiratory infections, infections in patients with cystic fibrosis, and many other antibiotic-resistant diseases. Lieberman, *supra* note 58.

[79] *Id.*

[80] Nat'l Research Council, *supra* note 5, at 70.

[81] World Health Org., The Medical Impact of Antimicrobial Use in Food Animals, Report of a WHO meeting. Berlin, Germany (WHO Doc. WHO/EMC/ZOO/97.4 (1997).

[82] Nat'l Research Council, *supra* note 5, at 150. This source also notes a number of other factors, including: crowded confinement of numerous animals with similar disease susceptibilities, poor animal hygiene, and other practices which also contribute to the selection of antibiotic-resistant bacteria. *Id.*

[83] *See generally* O'Brien, *supra* note 48. While this article does address the issue of antibiotic resistance, the author mainly addresses the conditions in which animals in the United States are currently raised.

ing the role of antibiotics in agriculture as a contributing factor in the spread of antibiotic resistance in humans.[84]

Even in the scientific community, there is disagreement as to whether there is sufficient documentation linking subtherapeutic dosing of livestock with the spread of antibiotic-resistant bacteria in human populations. A recent multi-disciplinary report concluded that "the basic answer to the question of human health consequences of antibiotic drug use in food animals is still not known for certain."[85] Despite agreement that antibiotic use "increases the risk of emergence of microorganisms that are resistant to specific, and perhaps other, antibiotics," and acknowledgement that "[a] link can be demonstrated between the use of antibiotics in food animals, the development of resistant microorganisms in those animals, and the zoonotic[86] spread of pathogens to humans," this recent multi-disciplinary report ultimately concluded that "the use of drugs in the food-animal production industry is not without some problems and concerns, but . . . does not appear to constitute an immediate public health concern . . . ."[87]

Given this background, it seems essential to consider the currently available scientific data examining whether and how the practice of feeding farm animals subtherapeutic doses of antibiotics contributes to the spread of antibiotic-resistant bacteria in human beings. A wide variety of studies have been performed which shed light on the link between antibiotic use in animal agriculture and drug-resistant bacterial infections in the human population. Most of the data comes not from controlled, laboratory experiments, but from the collection and analysis of data from animal and human case studies. These studies provide substantial evidence that the subtherapeutic use of antibiotics in livestock promotes the subsequent spread of drug-resistant bacteria which poses a risk to human health.

Some of these studies have focused on the question of how the subtherapeutic use of a particular antibiotic as a food additive for live-

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[84] Markow, *supra* note 9; Misocky, *supra* note 7.

[85] NAT'L RESEARCH COUNCIL, *supra* note 5, at 15. This report was put together by the National Research Council's Committee on Drug Use in Food Animals. *Id.* at 2. This committee consisted of a number of academicians and health care professionals, two consumer group representatives, a farmer and a director of a corporate poultry business unit. *Id.* at 235–38.

[86] A "zoonotic" disease is one that is "biologically adapted to and normally found in lower animals but which under some conditions also infects humans." MCGRAW-HILL, *supra* note 16, at 2193 (defining zoonoses).

[87] NAT'L RESEARCH COUNCIL, *supra* note 5, at 7–9.

stock affects drug resistance in bacteria in the animals and those who come into contact with those animals. One of the most convincing reports involved an analysis of the effects of the growth promoter nourseothricin in the former East Germany.[88] Farmers used this antibiotic in pig feed from 1983 to 1990, replacing the similar use of oxytetracycline.[89] *Enterobacteriaceae* isolated from both humans and animals in 1983 showed little resistance to nourseothricin, but by 1985 transposon-encoded resistant *E. coli* were isolated from pigs and meat products.[90] By 1990, the resistant bacteria had also spread to the farmers, their families, and people living in surrounding areas.[91] The same study also noted that the resistant transposon had further spread among several other species of bacteria including *Shigella*, a human pathogen.[92] Other researchers have reported similar results.[93]

This research is particularly significant because the same drugs are often used in both farm animals and humans, making it difficult to accurately trace the spread of resistance determinants in bacteria found in animals to those found in humans. Nourseothricin, however, was used for growth promotion in pigs but was *not* given directly to humans. Nonetheless, within a few years after its introduction into pig feed, plasmid-borne resistance to nourseothricin was observed not only in *E. coli* from pigs fed subtherapeutic doses of nourseothricin, but also in similar bacteria from employees at the pig farms, their family members, and members of the surrounding community.[94] In this instance, the presence of resistant bacteria in the human subjects was not attributable to the direct use or misuse of the antibiotic in the human population since the drug in question was fed only to the pigs.

A variety of case studies have also been performed in connection with salmonella outbreaks.[95] In each of the following instances, the researchers attempted to trace human infections back to their original source. One such study investigated the origin of drug-resistant salmonella infections in fifty-two outbreaks originally examined by the

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[88] Witte, *supra* note 37, at 996-97.

[89] *Id.* at 996.

[90] *Id.*

[91] *Id.*

[92] H. Tschäpe, 15 FEMS MICROBIOLOGY LETTERS 23 (1994), *cited in* Witte, *supra* note 37, at 996.

[93] *See* Ruth Hummel et al., *Spread of Plasmid-mediated Nourseothricin Resistance Due to Antibiotic Use in Animal Husbandry*, 26 J. BASIC MICROBIOLOGY 461–66 (1986).

[94] *Id.*

[95] *E.g.*, Scott D. Holmberg et al., *Animal-to-Man Transmission of Antimicrobial-Resistant* Salmonella: *Investigations of U.S. Outbreaks, 1971–1983*, at 225 SCIENCE 833, 833–35 (1984).

CDC.[96] Of the fifty-two incidents investigated, thirty-eight outbreaks were associated with identifiable sources. Food animals were found to be the source of eleven of the sixteen resistant outbreak strains and six of the thirteen sensitive strains.[97] This research is particularly alarming because the case fatality rate was significantly higher for patients infected with antimicrobial-resistant salmonella (4.2%) than for those with antimicrobial-sensitive infections (0.2%).[98]

Another report examined case histories of eighteen people infected with resistant *Salmonella newport* in 1983.[99] The researchers in this case ascertained that this particular strain of bacteria, characterized by a 38-kilobase plasmid, was resistant to ampicillin, carbenicillin, and tetracycline.[100] The researchers compared the plasmids isolated from human and animal sources over a period of eighteen months.[101] Examination of meat distribution records indicated that the humans had been infected by eating hamburger originating from South Dakota beef cattle which had been fed subtherapeutic doses of chlortetracycline, a growth promoter.[102] The researchers acknowledged difficulties in studying the complex sequence of events that begin with the selection of drug-resistant organisms in animals fed subtherapeutic quantities of antimicrobials and end with clinically significant infections in human beings; still, they concluded that "antimicrobial-resistant organisms of animal origin cause serious human illness, and [their study] emphasizes the need for more prudent use of antimicrobials in both human beings and animals."[103]

Another case study involved a 1983 outbreak of salmonella poisoning that resulted from ingestion of raw milk contaminated with multi-resistant *Salmonella typhimurium*.[104] In the study, a seventy-two year-old woman did not respond to treatment and died from *salmonella enteridis* and sepsis.[105] Experimental results showed that isolates of *Salmonella typhimurium* from this patient, from other ill persons, and

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[96] *Id.* at 833.

[97] *Id.* Antibiotic susceptibility was not determined in the remaining instances. *Id.* at 833–34.

[98] *Id.* at 834.

[99] Holmberg et al., *supra* note 43, at 617.

[100] *Id.*

[101] *Id.*

[102] *Id.* at 619–20.

[103] *Id.* at 617.

[104] Carol O. Tacket et al., *An Outbreak of Multiple-Drug-Resistant* Salmonella Enteritis *from Raw Milk*, 253 JAMA 2058, 2058–60 (1985).

[105] *Id.* at 2058.

from raw milk from a particular dairy were resistant to several antibiotics including streptomycin, sulfonamide, chloramphenicol, kanamycin sulfate, and tetracycline.[106] The multi-drug resistance in these isolates was traced back to the raw milk that the affected individuals had consumed.[107] The authors of the study concluded that "[t]his outbreak demonstrates the ability of drug-resistant salmonella to spread from the animal to the human reservoir and, in a suitable host, produce a fatal infection."[108]

Researchers also investigated a five-fold increase in *Salmonella newport* cases in California in 1985.[109] Results of genetic analysis showed that nearly 90% of the *Salmonella newport* isolates in the survey population had an unusual pattern of drug-resistance, including resistance to chloramphenicol.[110] This resistance was traced to a single plasmid isolated from hamburger products, slaughterhouses which were the source of the infected meat, a limited number of dairies that sent cows for slaughter, and sick dairy cows.[111] Isolation of salmonella with the unusual resistance to chloramphenicol correlated to the use of chloramphenicol at the dairies where cows had tested positive for *Salmonella newport*.[112] The authors concluded that "food animals are a major source of antimicrobial-resistant salmonella infections in humans and that these infections are associated with antimicrobial use on farms."[113]

Researchers also traced an epidemic outbreak of *Salmonella heidelberg* in a hospital nursery to calves on a dairy farm where the mother of the primary infant patient lived.[114] Salmonella isolates from all identified cases were resistant to several antimicrobials, including chloramphenicol and tetracycline,[115] suggesting that the infections developed from a common source.

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[106] *Id.* at 2058–59.

[107] *Id.* at 2058.

[108] *Id.* "This outbreak demonstrates the importance of animals as a source of antimicrobial-resistant Salmonella. . . . [O]ther outbreaks have clearly demonstrated the spread of resistant organisms from an animal reservoir to humans." *Id.* at 2060.

[109] John S. Spika et al., *Chloramphenicol-Resistant* Salmonella Newport *Traced Through Hamburger to Dairy Farms: A Major Persisting Source of Human* Salmonellosis *in California*, 316 NEW ENG. J. MED. 565, 565 (1987).

[110] *Id.* at 565.

[111] *Id.* at 566–68.

[112] *Id.* at 568.

[113] *Id.* at 565.

[114] Robert W. Lyons et al., *An Epidemic of Resistant* Salmonella *in a Nursery–Animal-to-Human Spread*, 243 JAMA 546, 546 (1980).

[115] *Id.* at 546.

Similar investigations have also focused on other kinds of bacteria.[116] In one case, researchers investigated the presence of *Enterococcus faecium* strains resistant to glycopeptides (such as vancomycin) in a hospital setting.[117] The resistant bacteria in this study were identified in chicken carcasses from a hospital's kitchen.[118] Bacteria with the same resistance patterns were also identified in animals from both a pig farm and a poultry farm where avoparcin (another glycopeptide) was used as a food additive.[119] The researchers concluded that it was "probable" that the bacteria from the farm animals had been transmitted to the hospital.[120] "Obviously as shown here animal farms with ergotropic use of avoparcin are an important reservoir for *vanA*-carrying enterococci. Via food contamination, these bacteria can also be disseminated to humans."[121]

Not all research on antibiotic resistance has involved the study of actual case histories. For example, other research has focused on the mechanisms by which resistance might be transferred between animals and humans. Researchers involved in these efforts have attempted to identify evidence which would make the transfer of resistant bacteria between animal species and human beings plausible.

Regardless of a study's focus, salmonella remains a favorite subject of investigators, possibly because of its serious potential impact on human health. One study concluded that plasmids found in outbreaks of *Salmonella typhimurium* were similar in both animals and humans.[122] Researchers tested isolates of *salmonella* from reference laboratories in the United States to determine their susceptibility to antibiotics, and also extracted plasmids from isolates resistant to dif-

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[116] *E.g.*, Janice Bates et al., *Farm Animals as a Putative Reservoir for Vancomycin-Resistant* Enterococcal *Infection in Man*, 34 J. ANTIMICROBIAL CHEMOTHERAPY 507, 507–14 (1994) (demonstrating farm animals are a source of vancomycin-resistant *enterococci*).

[117] I. Klare et al., vanA-*Mediated High-Level Glycopeptide Resistance in* Enterococcus faecium *from Animal Husbandry*, 125 FEMS MICROBIOLOGY LETTERS 165, 165 (1995) (published erratum appears in 127 FEMS MICROBIOLOGY LETTERS 273 (1995)). This is particularly worrisome because the *vanA* gene confers a high level of resistance to vancomycin, often the antibiotic of last resort in human beings. *See* Bates, *supra* note 116, at 507–14. For a further discussion of the importance of vancomycin resistance, see *infra* notes 125–128 and accompanying text.

[118] *Id.* at 165.

[119] Klare, *supra* note 117, at 165. When researchers tested chickens from a farm where avoparcin was not used, no glycopeptide-resistant enterococci were isolated. *Id.*

[120] *Id.* at 165–66.

[121] *Id.* at 170.

[122] T.F. O'Brien et al., *Molecular Epidemiology of Antibiotic Resistance in* Salmonella *from Animals and Human Beings in the United States*, 307 NEW ENG. J. MED. 1, 1 (1982).

ferent combinations of antibiotics.[123] These researchers used restriction endonuclease digestion to demonstrate that plasmid molecules from animal and human isolates were frequently identical or extremely similar.[124] These findings suggest that resistance plasmids may be widely shared between animal and human bacteria.[125]

Another research team recently demonstrated that the molecular characteristics, as determined by pulsed-field gel electrophoresis (PFGE),[126] of a ceftriaxone-resistant strain of *Salmonella enterica* serotype typhimirium isolated from a child were indistinguishable from one isolated from cattle.[127] The isolates were both resistant to *thirteen* antimicrobial drugs.[128] "This study provides additional evidence that antibiotic-resistant strains of salmonella in the United States evolve primarily in livestock."[129]

Another favorite research subject[130] is vancomycin-resistant bacteria, particularly *Enterococcus faecalis* (*E. faecalis*). The spread of vancomycin-resistant bacteria is significant for human health officials and other observers because vancomycin is the antibiotic of last resort for many human infections.[131] For example, *Staphylococcus aureus* (*S.*

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[123] *Id.*

[124] *Id.*

[125] *Id.*

[126] Pulsed-field gel electrophoresis is considered to be the most sophisticated method of showing that isolates from animals and humans are equivalent. *See* J. Bates, *Epidemiology of Vancomycin-Resistant Enterocci in the Community and the Relevance of Farm Animals to Human Infection*, 37 J. HOSPITAL INFECTION 89, 96 (1997).

[127] Paul D. Fey et al., *Ceftriaxone-Resistant Salmonella Infection Acquired by a Child from Cattle*, 342 NEW ENG. J. MED. 1242, 1242 (2000).

[128] *Id.*

[129] *Id.*

[130] Salmonella and *Enterococcus faecalis* are not the only strains of bacteria which have been studied or identified in both animal and human populations. *See, e.g.*, Lawrence J. Abraham et al., *Worldwide Distribution of the Conjugative* Clostridium perfringens *Tetracycline Resistance Plasmid, pCW3*, 14 PLASMID 37 (1985) (identifying identical conjugative R-plasmids from *C. perfringens* strains from human, animal, and environmental sources in five countries and concluding that *C. perfringens* strains in humans and animals throughout the world have overlapping gene pools).

[131] This topic is addressed thoroughly in a recent biomedical essay by C.P. Hunt of the British Department of Clinical Microbiology. *See* C.P. Hunt, *The Emergence of* Enterococci *as a Cause of* Nosocomial *Infection*, 55 BRITISH J. BIOMEDICAL SCI. 149–56 (1998). Hunt contends that "[t]he possibility that vancomycin-resistant strains of *enterococci* are entering the community via the food chain indicates the need for greater control of the use of glycopeptide antibiotics in animal feed." *Id.* at 149. *Enterococci* readily transfer antibiotic resistance between strains and, in addition, *enterococcal* plasmids frequently encode multiple-resistance determinants which simultaneously allows the transfer of multiple antibiotic resistance. *Id.* at 151. Of particular concern is the potential for the spread of vancomycin resistance. Experiments have demonstrated that the *vanA* gene can be found in *corynebacte-*

aureus) (a major cause of hospital-acquired infections) can be fatal, and "[w]orldwide, many strains of *S. aureus* are already resistant to all antibiotics except vancomycin."[132] Health officials have expressed concern that the spread of vancomycin-resistant *E. faecalis* "will soon deliver strong vancomycin resistance to those *S. aureus* strains, making them incurable."[133]

Vancomycin is a glycopeptide used to treat human infections; avoparcin, a glycopeptide which shows cross-resistance to vancomycin, is or was fed to livestock as a growth promoter worldwide, with the notable exceptions of Canada and the U.S.[134] The use of avoparcin as a growth promoter added to animal feeds was particularly extensive in countries in the European Community.[135] Thus, studies of vancomycin-resistant bacteria provide a basis for concern about the spread of cross-resistance of at least some antibiotics used as additives in livestock feeds.[136]

One study of vancomycin-resistant enterococci (VRE) examined samples of vancomycin-resistant *Enterococcus faecium* (*E. faecium*) from clinical sources, including sixty-two isolates from non-human sources, thirty-five isolates from raw sewage, twenty-two from farm animals, and five from uncooked chickens.[137] All strains possessed the *vanA* gene which confers a high level of resistance to vancomycin.[138] Further characterization of forty-two of these isolates resulted in fourteen clearly distinguishable types, two of which were ribotyping patterns

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rium, arcanobacterium, and *lactobacillus* emphasizing the potential for spread of vancomycin resistance. *Id.* Vancomycin-resistant strains of *E. Faecium* have been found both in healthy animals and in animal products. These findings suggest that vancomycin-resistant bacteria may be entering the community via the food chain. *Id.* at 153. The author concludes that it is quite possible that avoparcin, a glycopeptide with cross-resistance to vancomycin which has been used as a growth promoter in animal feeds since the mid 1970s, contributes to the seriousness of the problem. *Id.*

[132] Levy, *The Challenge, supra* note 11, at 46.

[133] *Id.* Laboratory experiments have demonstrated that, under conditions similar to those found in the environment, high levels of vancomycin resistance can be transferred via conjugation from *E. faecalis* to *S. aureus. E.g.*, W.C. Noble et al., *Co-Transfer of Vancomycin and Other Resistance Genes from Enterococcus faecalis NCTC 12201 to Staphylococcus aureus*, 72(2) FEMS MICROBIOLOGY LETTERS 195, 197 (1992).

[134] Bates, *supra* note 126, at 93.

[135] *Id.*

[136] *Id.* at 99. Bates also cites a study which suggests that the emergence of quinolone-resistance infections in humans is linked to the use of enrofloxacin (a fluroquinolone) as a growth promoter in poultry. H.P. Endtz et al., *Fluroquinolone Resistance in* Campylobacter *spp. Isolated from Human Stools and Poultry Products*, 335 LANCET 787 (1990), *cited in* Bates, *supra* note 126, at 93.

[137] Bates, *supra* note 116, at 507.

[138] *Id.*

found in both animal and human sources.[139] These results indicate that animals may likely serve as a source of VRE which may allow the bacteria to enter humans through the food chain.[140]

Another researcher investigated the occurrence and spread of non-nosocomial highlevel glycopeptide-resistant, *vanA*-positive *E. faecium* strains.[141] Highly resistant *E. faecium* were isolated from commercially available frozen poultry.[142] In addition, glycopeptide-resistant *E. faecium* (*vanA* type) were detected in five of thirteen samples of raw meat from pigs originating from thirteen different butchers' shops.[143] In addition to the animal sources, twelve of 100 non-hospitalized humans from nearby rural areas demonstrated detectable quantities of *vanA* type *E. faecium* strains.[144] This research suggests a wide dissemination of vancomycin resistance, primarily in animal populations but also at significant levels in human populations.

Experiments from Germany using PFGE showed that a strain of VRE from a human and an isolate from minced pork were indistinguishable.[145] Short reports from the Netherlands found indistinguishable isolates (again using PFGE) from a turkey and a turkey farmer.[146] These studies provide substantial evidence that resistant bacteria are present in both animal and human populations, and that the mechanisms for resistance are often indistinguishable.

Other studies have focused on the related question of whether the resulting antibiotic resistance is associated with subtherapeutic dosing of farm animals with antibiotics. For example, in 1995, the Danish Veterinary Laboratory completed a detailed comparison of farms using and not using avoparcin, and concluded that VRE is fifty-five times more likely to be detected if the farm animals in question

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[139] *Id.* at 511.

[140] *Id.* at 507.

[141] I. Klare et al., Enterococcus faecium *Strains with* vanA*-Mediated High-Level Glycopeptide Resistance Isolated from Animal Foodstuffs and Fecal Samples of Humans in the Community*, 1 MICROBIAL DRUG RESISTANCE 265, 265 (1995).

[142] *Id.* No glycopeptide-resistant *enterococci* could be detected in samples of chickens where the feed history did not include avoparcin. *Id.*

[143] *Id.*

[144] *Id.*

[145] Bates, *supra* note 126, at 96.

[146] A. Van den Bogaard et al., *Prevalence of Resistance of Fecal Bacteria in Turkeys, Turkey Farmers and Turkey Slaughterers (Abstract)* E27 36TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 86 (1996), *cited in* Bates, *supra* note 126, at 96.

were fed avoparcin.[147] In five out of eight chicken farms using avoparcin, resistant bacteria were isolated.[148] At the same time, of the six conventional farms where avoparcin was not used, none tested positive for the resistant strains.[149]

Another laboratory experiment examined the plasmid contents and antibiotic susceptibilities of streptococci isolated from pigs fed tylosin.[150] This research showed an increased risk for the spread of resistance as a consequence of tylosin feeding.[151] Data showed the addition of tylosin to the feed selected for multiple antibiotic resistance.[152] More importantly, a strong sequence homology was established between resistance genes in isolates from humans and those from farm animals.[153]

Yet another survey looked at the question of whether food products could act as the vector through which antibiotic-resistant bacteria might travel. An investigation of vancomycin-resistant bacteria in a vegetarian and a non-vegetarian nursing home in the Netherlands revealed that of the forty-two persons in the vegetarian nursing home, although twenty-three tested positive for the bacteria *Enterococcus faecium*, none tested positive for the resistant variety.[154] In comparison, of the sixty-two patients in the non-vegetarian nursing home thirty-two patients tested positive for *Enterococcus faecium* and six residents tested positive for strains resistant to vancomycin.[155]

In addition to the more limited data suggested by these kinds of experiments or case studies, some researchers have attempted to demonstrate the entire process by which subtherapeutic dosing of animals promotes the growth of drug-resistant bacteria and the spread of such microorganisms from animal to man. One such study

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[147] F.M. Aarestrup, *Occurrence of Glycopeptide Resistance Among* Enterococcus faecium *Isolates from Conventional and Ecological Poultry Farms*, 1 MICROBIAL DRUG RESISTANCE 255, 255–57 (1995).

[148] *Id.*

[149] *Id.* at 255–56.

[150] P.J. Christie & G.M. Dunny, *Antibiotic Selection Pressure Resulting in Multiple Antibiotic Resistance and Localization of Resistance Determinants to Conjugative Plasmids in* Streptococci, 149 J. INFECTIOUS DISEASES 74, 74 (1984).

[151] *Id.* at 74.

[152] *Id.* at 77. "These analyses strongly suggest that the introduction of a macrolide antibiotic into the feed of livestock creates a pressure for the selection of a multiple drug-resistant bacteria." *Id.*

[153] *Id.* at 74.

[154] Henrik C. Wegener et al., *Use of Antimicrobial Growth Promoters in Food Animals and* Enterococcus faecium *Resistance to Therapeutic Antimicrobial Drugs in Europe*, 5(3) EMERGING INFECTIOUS DISEASES 329, 331 (1999).

[155] *Id.*

was conducted by Stuart B. Levy and associates in the late 1980s.[156] His experiments started with a group of young chickens, all of which were progeny of hens that had not been exposed to any antibiotic for more than a decade.[157] The chickens were divided into two groups; one group was fed subtherapeutic doses of oxytetracycline while the other group's feed was free of antibiotics. Inspection of the fecal material from the two groups revealed dramatic changes and differences over time. Chickens fed subtherapeutic doses of tetracycline began excreting increasing numbers of tetracycline-resistant organisms in under two days, and in short order more than 90% of the excreted coliforms from this group were resistant.[158] The bacteria isolated from the control group remained mainly sensitive to tetracycline.[159] In addition, the tetracycline-fed chickens were excreting multi-drug-resistant organisms within three months while the control group's excrement did not contain multiply-resistant flora.[160]

Perhaps the most worrisome data reported by Levy was that not only the chickens were affected. Humans living on the farm where the chickens were being given subtherapeutic doses of the antibiotics were also affected.[161] Within six months of the introduction of the tetracycline-supplemented feed, individuals on the farm began to excrete tetracycline-resistant and multiply-resistant organisms. Samples from a group of neighbors showed no corresponding changes.[162]

Further experiments to determine the effects of the removal of tetracycline from the chicken feed showed that removal, even with multiple cleaning of the cages, did not significantly reduce the levels of tetracycline-resistant organisms, even though no tetracycline was detected in the samples.[163] The chickens had to be removed to a new environment before non-resistant bacteria began to reappear in the chickens.[164]

Levy and his co-workers also studied the spread of this resistance. They introduced a marked plasmid (bearing a temperature sensitive chloramphenicol acetyltransferase gene) into *Escherichia coli* (*E.*

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[156] Levy, *Antibiotic Use*, *supra* note 39, at 616–17.
[157] *Id.* at 617.
[158] *Id.*
[159] *Id.*
[160] *Id.*
[161] Levy, *Antibiotic Use*, *supra* note 40, at 617.
[162] *Id.*
[163] *Id.*
[164] *Id.*

coli).[165] Chickens were then inoculated with this bacteria and fed tetracycline to establish the marked strains. The chickens were then divided into two groups, (each group housed separately), with one group being fed tetracycline-supplemented feed and the other fed normal feed.[166] The researchers found that the marked plasmid spread quickly among chicken that were fed subtherapeutic levels of tetracycline. Even more remarkable was the discovery of the marked plasmid in *E. coli* isolated from chickens being fed tetracycline-feed in a second cage fifty feet away.[167] These chickens had never been directly exposed to the *E. coli* containing the marked plasmid. The organisms with the marked plasmid were never found in the control group even though they had also been inoculated.[168] The conclusion of the author of these studies was that "long-term subtherapeutic antibiotic use leads to selection and spread of transferable multiple-resistance plasmids among chickens and man."[169]

Respected members of the scientific community have reviewed this data, and when their opinions are not constrained by the political process or economic pressures, their conclusions are not reassuring. The consensus appears to be that infections with resistant strains of bacteria could pose significant health risks. "For both nosocomial and community-acquired infections, the mortality, the likelihood of hospitalization, and the length of hospital stay were usually at least twice as great for patients infected with drug-resistant strains as for those infected with drug-susceptible strains of the same bacteria."[170] In addition, these researchers conclude that "[a]lthough the adverse economic and health effects of drug-resistant bacterial infections can only be roughly quantified, . . . antimicrobial resistance is an important health problem and an economic burden to society."[171]

The import of these observations is debated. Some respected researchers continue to plead the case for a ban on the use of subtherapeutic doses of antibiotics if the antibiotic in question is or has analogues which are of potential value in treating infections in human

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[165] *Id.*

[166] Levy, *Antibiotic Use, supra* note 39, at 617.

[167] *Id.*

[168] *Id.*

[169] *Id.*

[170] Scott D. Holmberg et al., *Health and Economic Impacts of Antimicrobial Resistance*, 9 REV. OF INFECTIOUS DISEASES 1065, 1065 (1987).

[171] *Id.*

beings or if the antibiotic selects for multi-drug resistance.[172] Consider the following, written in the summer of 1999 by Danish experts:

> Accumulating evidence now indicates that the use of glycopeptide avoparcin as a growth promoter has created in food animals a major reservoir of *Enterococcus faecium*, which contains the high level glycopeptide resistance determinant vanA .... Furthermore, glycopeptide-resistant strains, as well as resistance determinants, can be transmitted from animals to humans. Two antimicrobial classes expected to provide the future therapeutic options for treatment of infections with vancomycin-resistant enterococci have analogues among the growth promoters, and a huge animal reservoir of resistant *E. faecium* has already been created, posing a new public health problem.[173]

The conclusion reached by these scientists was that "antimicrobial agents should not be used for growth promotion if they are used in human therapeutics or are known to select for cross-resistance to antimicrobial drugs used in human medicine."[174]

The Center for Science in the Public Interest has emphasized that any ban should include not only antibiotics which are themselves used in human treatment, but also drugs which select for cross-resistance. They included the following warning in a 1998 report:

> For instance, the new antibiotic Synercid is one of the last hopes against deadly antibiotic-resistant bloodstream infections. Although it has not yet been approved for use in humans, Synercid's value already has been compromised because resistance to one antibiotic can cause resistance to others. Thus, researchers at Wayne State University have found Synercid-resistant bacteria in turkeys that had been fed another antibiotic, virginiamycin, to promote growth.[175]

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[172] Stuart B. Levy is one of the cadre of American experts leading this call. *See generally*, Levy, *The Challenge*, *supra* note 11; LEVY, ANTIBIOTIC PARADOX, *supra* note 44.

[173] Wegener, *supra* note 155, at 329.

[174] *Id.* at 333.

[175] Lieberman, *supra* note 58.

On the other hand, there are other experts who acknowledge the concerns of public health authorities, infectious disease specialists and plasmid biologists,[176] but still conclude that "it is not clear whether the banning of these drugs as feed additives while allowing their use for therapeutic applications through prescription would represent any advantage."[177] The debate between these two camps leads squarely to the issue of what should be done in response to the mounting scientific data which suggests a link between the subtherapeutic dosing of farm animals with antibiotics and the spread of antibiotic-resistant bacteria in human populations.

IV. Recommendations for Appropriate Regulation of Antibiotic Usage in Agriculture

Although therapeutic dosing of farm animals (and human beings) can also lead to the proliferation of resistant bacteria, subtherapeutic dosing regimens are particularly problematic, for a number of reasons. Not only is the sheer volume of antibiotics administered as prophylactics and growth promoters troubling, but this type of dosing creates an ideal situation for the selection and propagation of resistant bacteria.[178] In addition, an objective cost-benefit analysis calls into question the decision to use antibiotics in livestock feed.

On the benefit side of the equation, farmers have attributed lower costs of meat, eggs, and milk to subtherapeutic doses of antimicrobials in animal feed.[179] In 1999, the National Research Council's Committee on Drug Use in Food Animals[180] issued a report which included a detailed economic analysis of the benefits of subtherapeutic dosing of livestock. The report concluded that the total cost of banning subtherapeutic use of antibiotics in agriculture would be between $1.2 billion to $2.5 billion per year.[181] While this number seems high, the number can be put in perspective by examining the approximate cost on a per capita basis. The National Research Council calculated that the average annual per capita cost to consumers of a

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[176] *See, e.g.*, Herbert L. DuPont & James H. Steele, *The Human Health Implication of the Use of Antimicrobial Agents in Animal Feeds*, 9(4) Veterinary Q. 309 (1987).

[177] *Id.* at 320.

[178] *See generally* Levy, *The Challenge*, *supra* note 11.

[179] DuPont, *supra* note 177, at 309.

[180] *See* Nat'l Research Council, *supra* note 5; *see also supra* text accompanying note 85.

[181] Nat'l Research Council, *supra* note 5, at 184.

ban on subtherapeutic drug use in animal agriculture would be in the range of $4.84 to $9.72 per year, with the effect being lowest for poultry ($1.09 to $2.20 for chickens, $0.27 to $0.56 for turkeys) and highest for cattle ($2.01 to $4.02).[182] In terms of the price per pound increase, the report estimated that the cost of chicken would increase somewhere in the range of $0.013–0.026 per pound; the cost of turkey would increase between $0.015–0.031 per pound; beef would cost between $0.03–0.06 more per pound; and pork would increase $0.03–0.06 per pound.[183]

In each case, the high end of the price range is based on the assumption that there is no substitute for the subtherapeutic use of antibiotics. However, there are several possible alternatives, including increased reliance on vaccinations (both those currently approved, and those that have yet to be developed/approved) and numerous changes to animal management practices that should reduce the economic impact of banning the subtherapeutic use of antibiotics.[184] Notably, improvements in animal hygiene and changes in animal confinement practices have the potential for significant improvements in productivity which would help minimize the negative consequences of reducing reliance on subtherapeutic doses of antibiotics.[185]

The National Resource Council has identified other potential economic benefits of allowing the subtherapeutic dosing of farm animals.[186] These include: a slight advantage in export competitiveness,[187] avoiding the personal and financial cost of producers who

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[182] *Id.* at 184–85. These numbers are based on per capita costs, calculated by multiplying the projected percentage increase in annual production costs by the retail price and the annual retail quantity sold per capita. *Id.* at 184.

[183] *Id.* at 185–86. The data is consistent with prior literature on the subject, notably 1992 and 1994 studies that estimated a retail price increase for pork of $0.04 per pound. *Id.* at 186.

[184] *See* WORLD HEALTH ORG., *supra* note 81, at 15.

[185] Research from some European countries suggests that a shift to less intensive farming methods and improved animal hygiene can resolve many situations that create the need for antibiotic dosing. *See, e.g.*, Witte, *supra* note 37, at 997; WORLD HEALTH ORG., *supra* note 81, at 15.

[186] This list was composed by the National Research Council. NAT'L RESEARCH COUNCIL, *supra* note 5, at 185–86.

[187] The extent to which American farmers need this edge is debatable, given that, effective July 1, 1999, the European Union banned four antimicrobials (bacitracin zinc, spiramycin, virginiamycin and tylosin phosphate) considered to be important for treating infections in human beings. USDA REPORT, *supra* note 3, at 1. In addition, the European Union, Japan, Australia, and New Zealand have banned subtherapeutic use of penicillin and tetracyclines. Lieberman, *supra* note 58.

might be forced out of business if subtherapeutic use of antibiotics is prohibited,[188] higher profits for pharmaceutical companies,[189] and reduced costs for eggs, dairy and pet-food.[190]

An additional potential benefit of allowing the subtherapeutic dosing of farm animals is the development of new animal drugs by the animal health industry. The 1999 National Research Council report identifies this as potentially "one of the most important consequences of such a ban."[191] According to this source, approximately $355 million was spent for internal research on animals drugs, and approximately $26 million was spent externally (principally in Universities).[192] On the other hand, of these amounts, only 17% was allocated to food additives,[193] so the significance of a ban on the use of antibiotics as additives at subtherapeutic levels is uncertain. Moreover, the potential benefits of such targeted research for human patients are uncertain, both because the outcome of research is always uncertain and because the very nature of this research is that it is directed towards use in the agricultural sector.

On the cost side is the economic impact of increased antibiotic resistance. These numbers are also difficult to quantify. Researchers generally agree that the long-term, subtherapeutic dosing regimens contribute to the development of drug resistance in bacteria.[194] The very nature of subtherapeutic antibiotic use makes the proliferation of antibiotic-resistant bacteria likely. "Unlike therapeutic doses used by veterinarians to treat infectious diseases in livestock, the small subtherapeutic doses used for growth promotion are administered for many months, sometimes years. This is a particularly dangerous com-

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[188] Note, however, that this does not necessarily mean that the small farmer will face an increasing risk of failure. Rather, the larger operations are more likely to use antibiotics to allow the use of more intensive confinement systems. *See* O'Brien, *supra* note 48, at 412–13. To some extent, limiting the use of subtherapeutic doses of antibiotics may help make smaller operations more competitive.

[189] The British experience, however, suggests that decreased profits due to diminished sales of restricted antibiotics can be at least partially offset by increased sales of antibiotics which are still available for feed use. *See* COMPTROLLER'S REPORT, *supra* note 68, at 22. Thus, if the ban on the subtherapeutic use of antibiotics in animals feed does not extend to all antibiotics, there is at least some possibility that this loss will be minimized.

[190] Presumably, these would be of the same general magnitude as the economic benefits associated with chicken, turkey, beef, and pork production. *See supra* text accompanying notes 180–184.

[191] NAT'L RESEARCH COUNCIL, *supra* note 5, at 186.

[192] *Id.*

[193] *Id.*

[194] *See* discussion *supra* Part III of this Article. *Accord* INST. OF MEDICINE, ANTIMICROBIAL RESISTANCE: ISSUES AND OPTIONS (1998).

bination of antibiotic use that promotes antibiotic resistance."[195] As described in the preceding section of this Article, the extended use of subtherapeutic concentration of antibiotics can lead to the selection of multi-drug-resistant bacteria which then enter a common environmental pool. From there, resistance determinants from various sources disseminate widely.[196] The transfer occurs not only from one bacterium to another, but also from one animal host to another, and from one geographic location to others. The same resistance determinants have been traced to many different genera of bacteria associated with animals, foods, and humans where they pose a threat to public health.[197]

The costs associated with this phenomenon are staggering. The U.S. Office of Technology Assessment has estimated that the "minimal hospital costs" of five types of infections (e.g., surgical wound infection and pneumonia) due to antibiotic resistance were $4.5 billion per year.[198] On a per person basis, the cost of antibiotic-resistance can be overwhelming. One source has reported that "[t]he cost of treating a patient with tuberculosis increases from $12,000 for a patient with a drug-susceptible strain to $180,000 for a patient with a multi-drug-resistant strain."[199] Moreover, the economic cost may not be the most significant factor. The increase in drug-resistance also translates to an increase in human suffering, as death rates increase once resistant bacteria begin to infect the human population.[200]

Ironically, these costs have long been known or anticipated by various authorities. In 1969, a report commissioned by the English Parliament on the use of antibiotics in animal husbandry and veterinary medicine recommended a ban on the subtherapeutic use of an-

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[195] Harrison, *Part I*, *supra* note 4, at 157.

[196] *See* discussion *supra* Part I of this Article.

[197] Levy, *Antibiotic Use*, *supra* note 39, at 616, 618.

[198] Khachatourians, *supra* note 47; LEVY, ANTIBIOTIC PARADOX, *supra* note 44. *Accord* Alexander Tomasz, *Multiple-Antibiotic-Resistant Pathogenic Bacteria—A Report on the Rockefeller University Workshop*, 330 NEW ENG. J. MED. 1247, 1248 (1994) ("Antibiotic-resistant pathogens contribute to the skyrocketing costs of inpatient care." Also citing the increase in cost to be "an estimated minimum of $4.5 billion" each year.) Other estimates of the cost of antibiotic resistance vary greatly. The National Foundation for Infectious Diseases estimates an annual cost "as high as four billion dollars annually." USDA REPORT, *supra* note 3, at 3.

[199] Lieberman, *supra* note 58.

[200] One website reports that "[e]ven with treatment, roughly half of all MDR-TB [multi-drug-resistant tuberculosis] patients die. This mortality rate matches that of patients with regular TB who received no medical care at all." *OnHealth: Tuberculosis—Renewed Concern*, *at* http://onhealthnetworkcompany.com/conditions/resource/conditions/item.681.asp.

tibiotics in food producing animals.[201] The call for a ban has been picked up by a growing number of scientists and medical experts in this country, and indeed, throughout the world. The Environmental Defense Fund, the Center for Science in the Public Interest, the Union of Concerned Scientists, the Public Citizen's Health Research Group and the Food Animal Concerns Trust have all asked the FDA to "end the use in livestock and poultry feeds of antibiotics that are used in . . . [or] closely related to those used in human medicine."[202] This position is supported by the World Health Organization, the CDC, the American Public Health Association, the Association of State and Territorial Health Officials, the Natural Resources Defense Council, the American Medical Women's Association, and other organizations.[203] This Article seeks to join this call to action by bringing the debate into focus in the legal literature.

The specific steps which seem justified at this time include limiting the approval of new antibiotics for agricultural use, phasing out the subtherapeutic use of antibiotics in farm animals, regulating the therapeutic use of antibiotics in farm animals, and developing and disseminating information about alternatives to the use of antibiotics in livestock. Each of these suggestions deserves a more detailed consideration.

A. *Antibiotic Approval Process*

No new antibiotics should be approved for agricultural use unless the drug sponsor can provide convincing evidence that the use of the drug in this manner presents no appreciable risk to human health. At a minimum, compliance with this standard would require proof that the antibiotic in question is not itself approved for use in human therapies, is not related to any such antibiotics or antibiotics that are under development for such purposes in such a manner that cross-resistance is possible, and that use of the antibiotic does not select for multi-drug resistance. The burden of proof would be on the drug's sponsor, typically the manufacturer, to establish that these criteria have been met. In addition, it might be desirable to include a specific

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[201] *See* COMPTROLLER'S REPORT, *supra* note 68, at 9.

[202] *Agricultural Use of Antibiotics Poses Major Public Health Threat*, EDF NEWS RELEASE (Mar. 9, 1999), *available at* http://www.myworld.org/pubs/NewsReleases/1999/Mar/d_agriculture.html [hereinafter EDF NEWS RELEASE].

[203] *See Petition to the U.S. Food and Drug Administration to Ban the Use of Certain Antibiotics in Livestock Feed: Executive Summary*, (Sept. 28, 2000), *available at* http://www.cspinet.org/reports/petition_antibiotic.htm.

requirement that the sponsor prove that the drug is effective for its intended purpose as a feed additive, but consideration of any such requirement is beyond the scope of this Article.

This should be the first step in any appropriate response to the problem of drug resistance among bacteria because of evidence suggesting that the problem is somewhat akin to Pandora's box. Once antibiotic resistance has emerged and becomes prevalent, it may not be easy to address the problem by retroactively revoking approval to use the drug at subtherapeutic levels. The National Research Council, for example, opined that "[o]nce an antibiotic has been introduced into animal management practice, either as a subtherapeutic feed application or as a specific therapeutic drug, the emergence of some microbial resistance is highly probable, and cessation of antibiotic use does not significantly alter the pattern of resistance."[204] The primary evidence for this assertion appears to have come from the European Union, where a ban on many antibiotics has not been immediately effective in redressing the problem of drug resistance.

The accuracy of the conclusion that a ban on the subtherapeutic use of antibiotics already approved for this purpose would be ineffective in addressing the problem is, however, open to debate. Other experts have concluded that it is possible to have an appreciable effect on the spread of antibiotic resistance by rescinding approvals for use of antibiotics in animals.

Consider, for example, the evidence from Europe resulting from the relatively recent decision to ban the use of avoparcin as a food additive for livestock.[205] Prior to 1995, Denmark (and many other European Union countries) widely used avoparcin, a glycopeptide closely related to vancomycin, as a growth promoter. This use was accompanied by a significant increase in the incidence of vancomycin-resistance.[206] Denmark, responding to public health concerns, banned the use of avoparcin as a food additive in 1995; Germany did the same in 1996, and the entire European Union banned its use in 1997.[207] This change resulted in "a marked reduction" in vancomycin-

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[204] NAT'L RESEARCH COUNCIL, *supra* note 5, at 159.

[205] For a discussion of glycopeptide resistance, and the problem of vancomycin-resistance caused by the use of avoparcin in agriculture, see *supra* text accompanying notes 130–136.

[206] Wegener, *supra* note 155, at 332.

[207] *Id.*

resistant bacteria in poultry in Denmark,[208] and significant decrease in resistant bacteria in poultry and human beings in Germany.[209]

This is the type of evidence which both suggests the wisdom of requiring convincing evidence before any decision to approve additional classes of antibiotics for use in livestock is made and supports the second part of the response suggested in this article—the systematic cessation of subtherapeutic dosing of animals with antibiotics.

B. *Phase Out Subtheraputic Use of Antibotics in Farm Animals*

Subtherapeutic use of antibiotics in farm animals should be phased out as rapidly as possible, unless the drug sponsor can provide convincing evidence that the use of the antibiotic in question presents no appreciable risk to human health. Ideally, this suggestion would be accomplished by the voluntary cessation of subtherapeutic dosing of livestock with antibiotics, but the use of antibiotics is so ingrained in this country that it will almost certainly be necessary to implement regulations phasing out the subtherapeutic use of antibiotics in agriculture.[210] An exception to this requirement could be made, however, if the drug's sponsor proves that this type of use presents no risk to human health.

If the antibiotic is not itself approved for use in human therapies, is not related to any such antibiotic or antibiotics that are under development for such purposes in such a manner that cross-resistance is possible, and use of the antibiotic does not select for multi-drug resistance, the health risks and associated costs described in this article would seem to be irrelevant to the question of whether subtherapeutic doses should be permitted.[211] However, even where the risks to human health are not appreciable, regulators might want to consider whether antibiotics approved for use in animals should also be reserved for therapeutic treatment of livestock. Again, however, this suggestion is beyond the scope of this Article.

The justification for prohibiting the subtherapeutic dosing of livestock is principally that the risk to human health is too great to permit the practice to continue. A senior researcher for the Environ-

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[208] *Id.* In 1995, 82% of poultry flocks tested positive for vancomycin-resistant bacteria. This percentage dropped to 12% by 1998. *Id.*

[209] *Id.* The incidence of resistance bacteria in poultry decreased from 100% in 1994 to 25% in 1997, and in fecal samples from human beings it decreased from 12% in 1994 to 3% in 1997. *Id.*

[210] *See* discussion *supra* Part II.

[211] *See* discussion *supra* Part IV.

mental Defense Fund, Rebecca Goldburg, phrased the problem this way: "Few Americans would deliberately choose to jeopardize the health of people for the sake of small economic advantages to the meat industry, yet, current FDA policies do just that."[212] The potential cost to consumers of a ban on this use of antibiotics, on a per capita basis, seems reasonable even if one assumes that there is no way to promote animal growth except through the subtherapeutic use of antibiotics.[213]

This approach is made even more reasonable when one looks at the range of available alternatives to the use of antibiotics at subtherapeutic levels:[214]

> 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.[215]

This conclusion seems supported by evidence from Sweden, where improvements in animal care and hygiene have largely offset any declines in growth rates caused by that country's decision to ban the use of antimicrobials as growth promoters.[216]

C. *Limit Short-Term Agricultural Use of Antibiotics*

Agricultural use of antibiotics should be limited to short-term use under the care of a licensed veterinarian unless the drug sponsor can show that the antibiotic in question is not used in human population, is not medically related to such drugs, and does not select for multidrug resistance in bacteria. Another aspect of the appropriate use of antibiotics in connection with the raising of livestock is to ensure that all antibiotics are administered under the supervision of a licensed veterinarian, in accordance with policies which require such use to be

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[212] EDF NEWS RELEASE, *supra* note 203.

[213] For a discussion of this issue, see *supra* notes 182–184 and accompanying text.

[214] *See* Witte, *supra* note 37, at 997.

[215] *Id.*

[216] *Id.*

short-term.[217] The routine use of antibiotics should not be permitted even if it means that animal husbandry practices have to adapt.

The justification for requiring antibiotics to be administered under the supervision of a veterinarian is to insure compliance with appropriate treatment regimens. If a farmer is permitted to dose his animals with antibiotics without any requirement that the decision to use such medicines be determined by a professional to be medically warranted, the problem of inappropriate use cannot be avoided. Thus, the veterinarian should act as a gatekeeper, in much the same way that a physician controls access of antibiotics to his or her human patients.

D. *Develop and Disseminate Information About Alternatives*

Information about alternatives to the use of antibiotics to maintain livestock health and growth rates should be developed and disseminated among the agricultural and veterinary community. This suggestion is a matter of common sense. "Alternatives to antibiotic use for maintaining animal health and productivity—such as new vaccination techniques, improved animal nutrition, and genetic strategies—must be sought. Existing alternatives should be implemented in a practical manner so that the appropriate uses of antibiotics and their effectiveness are maintained."[218] Once developed, every effort should be made to see that information about these alternatives is widely disseminated. This will help reduce the potentially negative consequences of limiting the subtherapeutic use of antibiotics.

CONCLUSIONS

It is clear that there is no easy solution to the problem of antibiotic resistance. The complexity of the problem is such that it will always be possible to question the data and raise doubts about the appropriate response. For example, it can be argued that other practices (such as the misuse of prescription drugs among the human population or the therapeutic use of antibiotics generally) are more important in promoting the spread of antibiotic-resistant bacteria. In addition, the adequacy of the existing scientific data can be attacked on the basis that there are too few studies which look at dosing levels, or

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[217] Admittedly, this suggestion will probably require expenditures to ensure that veterinarians are educated about the risks of antibiotic resistance and the appropriate use of antibiotics. *See* discussion *supra* Part IV.

[218] NAT'L RESEARCH COUNCIL, *supra* note 5, at 9.

which examine the question of how varying treatment regimes are related to the development of antibiotic resistance. It is also true that many antibiotics have not been studied extensively, and so we do not know for sure if their use promotes antibiotic resistance. It can even be argued that the evidence about whether use of antibiotics in animals causes significant increases in human morbidity or mortality is inconclusive. Finally, it can be asserted that banning the subtherapeutic dosing of animals has not been proven as an appropriate or effective response to the problem.

All of these objections have some merit, but none of them come close to providing convincing evidence that the subtherapeutic use of antibiotics in livestock feeds is prudent or wise. They do, however, tend to make one focus on the larger picture. Realistically speaking, it is clear that the use of subtherapeutic levels of antibiotics for farm animals is only part of the picture. Complicating things significantly is the use and abuse of prescription antibiotics by physicians who over-prescribe and patients who fail to complete their prescribed treatment regimens. These patterns of behavior in the human population undoubtedly are a significant factor in the spread of antibiotic resistance. Sources estimate that as many as one third of all prescriptions in this county are unnecessary or inappropriate,[219] and there are no reliable statistics on how many patients fail to take all of a prescribed course of antibiotics or dose themselves or others with the left-over of a prior course of treatment. Thus, a comprehensive solution to the problem of antibiotic resistance necessarily includes steps to address this problem. Public and physician education and increased reliance on diagnostic tests such as culturing of infections to determine which, if any, antibiotics are appropriate[220] would be desirable components of a response to the over-prescription of antibiotics in the human population. Other steps might also be appropriate.[221]

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[219] The Centers for Disease Control and Prevention estimate that of the approximately 150 million antibiotic prescriptions written by physicians on an outpatient basis each year, as many as 50 million may be unnecessary. Levy, *The Challenge*, *supra* note 11, at 51.

[220] In today's economic climate, this would also necessarily require that health maintenance organizations and private insurance companies cover the cost of diagnostic tests to assure appropriate use of antibiotics. This might also require steps to encourage physicians to perform strep tests in their offices, such as exempting rapid strep tests from requirements imposed by the Clinical Laboratory Improvement Amendments of 1988 (Pub. L. No. 100–578, 102 Stat. 2903 (1988), relevant provisions codified at 42 U.S.C.A. § 263a (1998).

[221] For possible regulatory responses to this problem, see Misocky, *supra* note 7, at 737, and Markow, *supra* note 9, at 545–49.

The recent advent of increasingly popular "antibiotic" household and personal cleansers has also been identified by some as another threat to the continued viability of antibiotics.[222] Certainly, to the extent that such products cross-select for resistant bacteria, they also contribute to the problem. Again, public education might suffice, but it might also be desirable or necessary to regulate the use of antimicrobial products that have the potential to select for cross-resistant strains of bacteria.

There are also additional problems with the agricultural use of antibiotics beyond those identified in this Article. First, there is the questionable practice of allowing antibiotics to be used as pesticides. Between 40,000 and 50,000 pounds of antibiotics are sprayed on fruit trees each year.[223] While this amount may seem trivial in comparison with the millions of pounds of antibiotics used as animal food additives, it has also been identified as a potential factor in the spread of resistance among bacteria.[224] Again, it seems prudent to ban this use of antibiotics unless the proponent can provide convincing evidence that there is no risk to human health from this application.

Similarly, the practice of allowing farmers to choose therapeutic dosing levels of antibiotics for their livestock is also questionable.[225] While existing data may fall short of what would be sufficient to justify a ban on the therapeutic use of antibiotics among livestock, there certainly seems to be enough data to support a requirement that such use be supervised by a licensed veterinarian. When antibiotics were first made available to the human population, there was no requirement that the patient obtain a physician's prescription.[226] The practice of self-dosing quickly promoted the spread of resistant bacteria, as people used antibiotics inappropriately.[227] Similar patterns might be expected for farmers. The risk that farmers will medicate livestock when there is no medical justification for antibiotic use should be lim-

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[222] Levy, *The Challenge*, *supra* note 11, at 48.

[223] Lieberman, *supra* note 58.

[224] *Id.; accord* Khachatourians, *supra* note 47; Levy, Antibiotic Paradox, *supra* note 44.

[225] Lieberman, *supra* note 58. "Currently, many antibiotics, such as tylosin, penicillin, tetracycline, and gentamicin, are available over the counter to farmers to administer at their discretion to livestock by injection, orally, and as feed additives." *Id.*

[226] Harrison, *Part I*, *supra* note 4, at 151.

[227] *Id.* at 152.

ited if antibiotics are available only when supervised by licensed professionals.[228]

In addition, it should be made clear through the regulatory process that the only antibiotics available for mass-dosing (i.e., of the entire herd or flock) will be those which are not used by human beings, are not medically related to drugs used by human beings, and do not select for multi-resistance. Otherwise, animal antibiotic use should be limited to the treatment of individual animals. This would effectively prevent the dosing of large numbers of healthy animals, which significantly increases the likelihood that resistant strains of bacteria will spread among animal populations.

It should also be acknowledged that the failure of the government (which provides funding for a great deal of research, especially at the University level) and pharmaceutical companies to anticipate the speed with which bacteria would become resistance to new treatments is a contributing factor in the seriousness of the problem of antibiotic resistance.[229] Various surveys have noted that there are essentially no new antibiotics on the immediate horizon.[230] Because of the time and expense associated with the development of new treatments,[231] this means that the rapid proliferation of resistant bacteria is of considerable concern because there is no quick fix for this problem. Moreover, if new drugs are found and developed, the potential for cross-resistance may mean that they will be of limited usefulness, as well.[232] Even with these limitations, however, pharmaceutical companies should be encouraged to increase their efforts to develop new

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[228] To encourage the appropriate treatment of sick animals, the FDA or USDA should develop and promulgate a symptom-based formulary describing appropriate treatment regimens for common infections. *See* discussion *supra* Part IV.

[229] Levy, *The Challenge*, *supra* note 11, at 52. Apparently, most pharmaceutical companies focused on the development of treatments for chronic ailments rather than on developing new antibiotics. Whatever the cause, however, the current situation (where we have no new general antibiotics in the pipeline) is not healthy.

[230] Harrison, *Part I*, *supra* note 4, at 155.

> [T]he pipeline of new antibacterial drugs is essentially empty, the result of a prolonged lack of research interest and funding. A survey of large US and Japanese pharmaceutical companies . . . found that half of the companies either reduced or phased out their antibacterial programs in the last decade . . . .

Id.

[231] The cost of development of a new antibiotic has been estimated to approach $300 million and twelve years of time. *Id.* at 156.

[232] *Id.*

classes of antibiotics and new approaches to the problem of antibiotic resistance.

Finally, the failure of the agricultural community to develop or accept alternatives to subtherapeutic dosing of animals makes the problem which this Article addresses politically sensitive. Consider the efforts of the FDA in the 1970s to ban certain agricultural uses of antibiotics.[233] Following a task force's recommendations, the FDA promulgated proposed rules which would remove penicillin and tetracyclines from the list of antibiotics approved for use as food additives for disease prevention and growth promotion. The proposed rules would also have restricted the use of antibiotics in animals to short-term therapeutic use prescribed by a veterinarian, unless the drug's sponsor submitted data establishing that the use for agricultural purposes would pose no risk to human health. The proposed rules prompted vigorous opposition from agri-business and farm-state legislators in Congress, and the proposed limits on the agricultural use of antibiotics were not implemented.[234]

The problem posed by the politics of the situation probably also requires a multifaceted response. It would be foolish not to recognize that the political acceptability of the response suggested here depends on a number of factors. The first step is education of the public about the dangers of antibiotic resistance. Realistically, a political solution will only emerge if it is politically acceptable. This requires an educated and concerned population.

In addition, education of the agricultural community about the risks associated with the routine use of subtherapeutic doses of antibiotics would certainly help, as would education about alternatives to this practice, such as increased reliance on vaccinations and changes in animal hygiene and confinement practices. The U.S. Department of Agriculture can play a significant role in the education process and in seeing that sufficient resources are applied to developing alternatives to the routine use of antibiotics in farm animals.

Taken as a whole, the factors discussed briefly here make it obvious that the problem of antibiotic resistance is incredibly complex. The complexity of the situation does not, however, diminish the dimensions of the problems posed by antibiotic resistance. Whether or not subtherapeutic dosing of animals is *the* major cause of the prob-

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[233] For a general discussion of this issue, see Lieberman, *supra* note 58; *see also supra* notes 73–74 and accompanying text.

[234] Lieberman, *supra* note 59.

lem, it is clearly *a* cause. Whether or not banning such use will solve the problem by itself is not the real question. The question is whether the existing evidence suggests that this is an appropriate and reasonable part of the solution.

Our reading of the evidence suggests that it is.