Resistant Bugs and Antibiotic Drugs

STATE AND COUNTY ESTIMATES OF ANTIBIOTICS IN AGRICULTURAL FEED AND ANIMAL WASTE

ENVIRONMENTAL DEFENSE
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About This Report

Authorship

This report was written principally by Environmental Defense Senior Attorney Karen Florini. Senior Scientist Richard Denison, Ph.D., prepared the database of state and county estimates and the associated methodology description. Staff Scientist Terri Stiffler compiled the excretion-rate estimates and related materials, and played a major role in preparing several of the Appendices. Research Associate Timothy Fitzgerald provided the initial analysis of the findings, and Senior Scientist Rebecca Goldburg, Ph.D., provided overall guidance and editing.

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Background

Massive quantities of antibiotics are used in animal agriculture, contributing to the development and spread of antibiotic-resistant bacteria that increasingly threaten human health. An estimated 70% of the antibiotics used in the United States each year are used as feed additives for chickens, hogs, and beef cattle—not to treat disease, but rather to promote growth and to compensate for crowded, stressful, and often unhygienic conditions on industrial-scale farms. Many of the drugs used for these "nontherapeutic" purposes are identical or related to those used in human medicine, but their use as feed additives requires no prescription. Growing evidence links use of these antibiotic feed additives to the development and spread of resistant bacteria in our food supply and environment, making it harder for physicians to treat people suffering from bacterial disease.

Antibiotic resistance is a serious public-health problem; indeed, the U.S. Centers for Disease Control regards it as one of the agency's "top concerns." The National Academy of Sciences has estimated that "antibiotic-resistant bacteria generate a minimum of $4 billion to $5 billion in costs to U.S. society and individuals yearly."

This report presents state- and county-specific estimates in order to promote broader understanding of how and where antibiotics are used as feed additives. The report also includes state and county estimates of amounts of antibiotics excreted in animal waste resulting from feed-additive use.

Studies of disease outbreaks among farm families and the presence of antibiotic-resistant bacteria in farm workers and community residents suggest that residents of high-use counties may be at greater risk of exposure to resistant bacteria, although few analyses relating to local risk have been conducted to date. Exposure to resistant bacteria may occur when farm workers come into contact with animals and their wastes, or when community residents contact soil, water, or air contaminated by animal facilities or waste-disposal sites. For example, animal wastes are typically spread on nearby fields, and often contain both resistant bacteria and undigested antibiotics (which may select for resistant bacteria in soils). These resistant bacteria can contaminate water used for swimming, fishing, boating, or even drinking. Bacteria can also be tracked into homes from soil or water on shoes or by pets, or can be transferred to gardens and lawns by wildlife or insects. In addition, air inside animal facilities can contain a high prevalence of resistant bacteria, which may be emitted into surrounding areas. Moreover, farm workers exposed to animals or their waste on the job can become "colonized" with resistant bacteria from animals, and can subsequently transfer these resistant bacteria to their families and to community. In addition to direct health problems from disease-causing (pathogenic) bacteria, even seemingly innocuous bacteria can threaten health because of the well-documented ability of bacteria to readily transfer resistance genes to other bacteria belonging to wholly unrelated species.

We derived our estimates using data from the U.S. Department of Agriculture's most recent Census of Agriculture, for 2002, in conjunction with per-animal estimates of antibiotic feed-additive use previously developed by the Union of Concerned Scientists (UCS) for broiler chickens (those raised for meat, rather than eggs), hogs and beef cattle. We used the UCS estimates because they are the most detailed figures on antibiotic use now available. Unfortunately, government statistics on this important topic simply do not exist, and statistics released by industry have serious limitations (for example, they combine agricultural and companion-animal (pet) uses). Obviously, any changes in antibiotic-use patterns after release of the UCS estimates in 2001 would affect the estimates in this report as well. Recent anecdotal information suggests that at least some hog and chicken producers may have reduced use of antibiotics as feed additives, but specific information on such reductions is not publicly available.

Two Excel spreadsheet databases accompany this report, providing estimates for all 50 states and all 3,000-plus counties in the United States. These spreadsheets, available at www.environmentaldefense.org/go/antibiotic.estimates, allow users to calculate and rank state- and county-level estimates of antibiotic feed-additive use and excretion in animal wastes. The spreadsheets provide estimates for antibiotic classes and individual compounds as well as for different animal types. These estimates cover *only* the nontherapeutic use of antibiotics as feed additives; they exclude use of antibiotics for treating sick animals or for controlling disease outbreaks.

Key findings

USE OF ALL ANTIBIOTICS AS FEED ADDITIVES

Substantial quantities of antibiotics are used as feed additives nationwide (see Table 1 and Chart 1), but such use is relatively concentrated in certain states and counties (see Table 2, Map A (state use) and Map B (county use)[*]):

- Two states, North Carolina and Iowa, are each estimated to use three million pounds of antibiotics as feed additives annually—the same quantity estimated to be used for human medical treatment *nationwide*.
- Of the 26.5 million pounds of antibiotics estimated to be used in the United States as feed additives each year, almost all (90%) occurs in 23 states, and nearly two-thirds (64%) in just 10 states.
- Seven other states also use more than an estimated one million pounds of antibiotic feed additives a year: Georgia, Arkansas, Texas, Alabama, Minnesota, Mississippi, and Missouri.
- Use of antibiotic feed additives is highly concentrated in a few counties; indeed, the highest-use *county* in the U.S. (Duplin County, NC) is estimated to use more antibiotics as feed additives than 35 *states*.

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[*] The maps in this report are not directly comparable, as each map legend has a separate scale.

USE OF MEDICALLY IMPORTANT ANTIBIOTICS AS FEED ADDITIVES

"Medically important" antibiotics comprise nearly half of the overall quantity of antibiotics used as feed additives. These drugs belong to classes of antibiotics designated by the U.S. Food and Drug Administration (FDA) as either "critically important" or "highly important" in human medicine (i.e., penicillins, tetracyclines, aminoglycosides, streptogramins, macrolides, clindamycin/ lincomycin, and sulfonamides) for the treatment of serious infections. Because different antibiotics are used as feed additives in different types of farm animals, use patterns for medically important antibiotics differ in some ways from use patterns for all antibiotics (see Table 3):

- Of the total quantity of medically important antibiotics estimated to be used as feed additives, by far the largest fraction is used in hogs (69%), compared to 19% in broiler chickens and 12% in beef cattle. By contrast, when all antibiotic feed additives are considered, hogs accounted for 42% of the total, compared with 44% for broiler chickens and 14% for beef cattle.
- Feed-additive use of medically important antibiotics is very concentrated, with Iowa, North Carolina and Minnesota—the top three hog-producing states—accounting for 26 of the top 30 counties.
- Iowa and North Carolina are each estimated to use more than 1.5 million pounds annually of medically important antibiotics as feed additives.

AREA-ADJUSTED ESTIMATES OF ANTIBIOTIC FEED-ADDITIVE USE

Because states and counties vary dramatically in size, area-adjusted state and county estimates may provide a clearer indication of the relatively intensity of antibiotic use in various locales than do unadjusted numbers. The area-adjusted estimates, which are expressed in pounds per 1,000 square miles, differ in some noteworthy ways from the unadjusted estimates (see Table 4 and Map C):

- Delaware is estimated to be by far the most intensive user of all antibiotic feed additives. Almost all of this use occurs in Delaware's Sussex County. In 2002, Delaware was estimated to use almost three times as many antibiotics per thousand square miles (187,000 pounds) as the next closest state, North Carolina (64,000 pounds).
- Some other smaller states, notably Maryland and Indiana, join the ranks of the top 10 states when area is taken into account.
- North Carolina's Duplin County still tops the county rankings, at almost 570,000 pounds/year. North Carolina and Georgia each account for seven of the top 30 counties; Maryland accounts for an additional four.

Likewise, the area-adjusted rankings for medically important antibiotics vary somewhat from the unadjusted rankings (see Table 5 and Map D):

- Using area-adjusted estimates, Iowa and North Carolina remain two of the top three users of medically important antibiotic feed additives. But Delaware, with its small total area, jumps to number two with almost 39,000 pounds per thousand square miles. These three states are estimated to account for 44% of area-adjusted usage nationwide.
- As with the area-adjusted estimates for all feed-additive antibiotics, some smaller states—namely Maryland and Arkansas—show up as top-ranked users of medically important antibiotics.
- On a county basis, Iowa, Minnesota and North Carolina account for the greatest intensity of use of medically important antibiotic use when area is taken into consideration (26 of the top 30 counties). Iowa alone accounts for 16 of the top 30 counties.

ANTIBIOTICS IN ANIMAL WASTE

Animals excrete a significant fraction of the antibiotics they consume in feed. These wastes, and the antibiotics and resistant bacteria in them, are typically transferred to soil or water—both through intentional land spreading (the primary way that animal waste is disposed of in the United States) and sometimes through unintentional releases following storms or mishaps. These antibiotics in the environment can promote development of resistance in bacteria naturally present in the soil and water.

To estimate the quantity of antibiotics in animal waste, we multiplied our per-animal use estimates by an excretion factor specific to each drug and animal type, and then multiplied by the number of each animal type (chickens, hogs, and beef cattle) (see Appendix 1 for a detailed description of our methodology). As with the use estimates discussed above, we present two sets of estimates for quantities of antibiotics in waste from use of antibiotics as feed additives: one for all antibiotics (see Table 6), the other covering only medically important antibiotics (see Table 7). Key findings include the following:

- Nationwide, an estimated 13.5 million pounds of antibiotics are excreted annually in animal wastes as a result of using antibiotic feed additives. This is nearly half of the total amount of antibiotics added to feeds.
- Iowa and North Carolina account for an estimated 25% of this total, or 3.3 million pounds annually.
- Hogs account for an estimated 47% of *all* antibiotics in waste (compared with 39% for broiler chickens and 14% for beef cattle). For *medically important* antibiotics in waste, however, hogs account for 72% (compared with 14% for broiler chickens and 13% for beef cattle).

As with the antibiotic-use estimates, these waste rankings change when presented on an area-adjusted basis (see Table 8 and Map E for all antibiotics, and Table 9 and Map F for medically important antibiotics):

- On an area-adjusted basis, Delaware is the top-ranked state in terms of estimated quantity of all antibiotics in animal waste (85,000 pounds).
- For all antibiotics in waste from feed-additive use of antibiotics, North Carolina, Georgia, Maryland and Iowa account for 20 of the top 30 counties on an area-adjusted basis.
- For medically important antibiotics in waste from feed-additive use of antibiotics, Iowa, Minnesota and North Carolina account for 26 of the top 30 counties on an area-adjusted basis.

Agricultural antibiotics—public and corporate policies

Use of antibiotics as agricultural feed additives is a decades-old practice, but an increasingly controversial one because of the rise of antibiotic resistance among disease-causing bacteria. Although FDA gave scant consideration to resistance issues when first approving these drugs for use as feed additives decades ago, the agency has recently stated that it intends to reevaluate the safety of antibiotic feed additives now on the market using current scientific standards. However, the agency's track record on removing unsafe agricultural drugs from the market casts doubt on whether the agency can take timely action even in cases where restrictions are needed to protect public health, as prior removals have taken six to twenty years to complete. Meanwhile, antibiotic feed additives continue to be sold, even as resistance to the drugs continues to worsen.

Time is running out. Additional delay in addressing this situation is unacceptable, particularly for medically important antibiotics. The American Medical Association, American Academy of Pediatrics and American Public Health Association are among the nearly 400 organizations that have endorsed federal legislation to phase out use of medically important antibiotics as feed additives unless FDA first determines—based on today’s scientific standards—that such use is safe. The legislation also requires that producers of agricultural antibiotics report to FDA the quantities of the drugs they distribute.

Meanwhile, some large-scale purchasers of meat are beginning to undertake initiatives of their own. In 2003, McDonald's Corporation and Bon Appétit, a leading food-service company, adopted policies under which their chicken suppliers must limit use of antibiotic feed additives. In addition, growing numbers of retailers and restaurants are offering meat and poultry raised without antibiotic feed additives to individual consumers (see www.EatWellGuide.org). Both the American Nurses Association and American Public Health Association recently adopted formal resolutions urging meat purchasers, including governmental entities, to adopt purchase preferences for meat and poultry produced without overuse of antibiotics.

If FDA cannot act in a timely way, Congress and meat purchasers must. Antibiotics are simply too precious to lose.

CHAPTER 1

Antibiotic feed additives: an overview

> "Our grandparents lived during an age without antibiotics.
> So could many of our grandchildren."
> – *World Health Organization*[1]

Most of the feed administered to the roughly eight billion chickens, 100 million hogs and 29 million beef cattle produced in the United States each year[2] contains antibiotics.[3] These antibiotic feed additives are used "nontherapeutically"—not to treat illness, but rather on the grounds that they may promote faster growth or prevent disease that could result from the crowded, stressful conditions common at large-scale animal production facilities.[4] Although definitive data are not available, an estimated 70% of the total quantity of antibiotics used in the United States each year are feed additives for chicken, hogs and beef cattle.[5] Half of these feed additive antibiotics belong to classes of antibiotics also used in human medicine.[6]

This massive nontherapeutic use of antibiotics as feed additives contributes to the development and spread of antibiotic resistance,[7] a problem that the U.S. Centers for Disease Control regards as one of the agency's "top concerns."[8] In 1998, the National Academy of Sciences concluded that "antibiotic-resistant bacteria generate a minimum of $4 billion to $5 billion in costs to U.S. society and individuals yearly"[9]—a situation that has only worsened in subsequent years.

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[1] World Health Organization, Overcoming Antimicrobial Resistance, Epilogue. Available at www.who.int/infectious-disease-report/2000/ (accessed Apr. 19, 2005).

[2] See Appendix 1 for animal-production figures. Unless otherwise indicated, we use the term "chicken" to refer to chickens produced for human consumption, which are more technically referred to as "broiler chickens" (as opposed to, e.g., layers or breeders).

[3] Strictly speaking, the term "antibiotic" means a naturally occurring chemical (i.e., one not manufactured by humans) that kills or inhibits the growth of bacteria. Often, however, the term is used more broadly to include synthetic chemicals that also kill or inhibit the growth of bacteria. The term is also generally used to include compounds that affect other microorganisms such as fungi and parasites (technically known as "antimicrobials").

[4] Disease-treatment antibiotics are sometimes also administered via food, but such use is not considered feed-additive use.

[5] Mellon M, Benbrook, C and Benbrook, K.L. (2001). *Hogging It!: Estimates of Antimicrobial Abuse in Livestock.* Washington, DC: Union of Concerned Scientists. Available at www.ucsusa.org/food_and_environment/antibiotic_resistance/page.cfm?pageID=264 (accessed Apr. 19, 2005).

[6] *Ibid.*

[7] Wegener HC, Aarestrup FM, Jensen LB, Hammerum AM, Bager F (1999). Use of antimicrobial growth promoters in food animals and Enterococcus faecium resistance to therapeutic antimicrobial drugs in Europe. *Emerging Infection Diseases* 5: 329-335. Available at www.cdc.gov/ncidod/EID/vol5no3/pdf/wegener.pdf (accessed Apr. 19, 2005).

[8] Centers for Disease Control. Background on Antibiotic Resistance. Atlanta, GA. Available at www.cdc.gov/drugresistance/community (accessed Apr. 19, 2005).

[9] National Academy of Sciences/Institute of Medicine (1998). *Antimicrobial Resistance: Issues and Options.* Washington, DC: National Academies Press. Available at

Patients infected with drug-resistant organisms “are more likely to have longer hospital stays and require treatment with second- or third-choice drugs that may be less effective, more toxic, and/or more expensive.”[10] Though resistant infections may strike anyone, those at greatest risk of serious disease from such infections include the very young, seniors and those with medical conditions that result in weakened immune function, such as cancer and transplant patients and people with HIV/AIDS.[11]

The Infectious Disease Society of America warns that the pipeline of new drugs to combat bacterial diseases is "drying up" even as bacteria are becoming increasingly resistant to existing antibiotics.[12] The new-drug drought reflects in part the fact that it is far more profitable for pharmaceutical companies to develop drugs to treat chronic conditions because a patient must take those drugs for years. By contrast, in most instances a patient need take antibiotics only for a week or so.

This worsening health crisis makes it imperative to prevent further losses in antibiotic effectiveness. While human overuse of antibiotics is certainly part of the problem, a wide array of scientific and medical experts have concluded that the overuse of antibiotics in agriculture promotes the development and spread of antibiotic-resistant bacteria, and must be curtailed in order to protect human health.[13] For example:

- National Academy of Science’s Institute of Medicine: "Clearly, a decrease in the inappropriate use of antimicrobials in human medicine alone is not enough. Substantial efforts must be made to decrease inappropriate overuse in animals and agriculture as well."[14]
- World Health Organization: “There is clear evidence of the human health consequences [from the agricultural use of antibiotics, including] infections that would not have otherwise occurred, increased frequency

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http://books.nap.edu/books/0309060842/html/1.html#pagetop (accessed Apr. 19, 2005).

[10] Centers for Disease Control (not dated) . Campaign to Prevent Antimicrobial Resistance in Healthcare Settings: Why a Campaign? Available at www.cdc.gov/drugresistance/healthcare/problem.htm (accessed Apr. 19, 2005).

[11] Shea K, Florini K, and Barlam T (2001). *When Wonder Drugs Don’t Work: How Antibiotic Resistance Threatens Children, Seniors, and the Medically Vulnerable.* Washington, DC: Environmental Defense. Available at www.environmentaldefense.org/documents/162_abrreport.pdf (accessed Apr. 19, 2005).

[12] Infectious Diseases Society of America (2003). "Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates ... A Public Health Crisis Brews," p. 3. Available at www.idsociety.org/pa/IDSA_Paper4_final_web.pdf (accessed Apr. 19, 2005).

[13] A detailed review of the available scientific literature was published by the Alliance for Prudent Use of Antibiotics in 2002, titled "The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences." *Clinical Infectious Diseases* 34(Supplement 3):71-144. Available at www.journals.uchicago.edu/CID/journal/contents/v34nS3.html (accessed Apr. 19, 2005).

[14] Institute of Medicine, Board on Global Health (2003). *Microbial Threats to Health: Emergence, Detection, and Response,* p. 207. Washington, DC: National Academy of Sciences Press. Available at http://books.nap.edu/books/030908864X/html/207.html (accessed Apr. 19, 2005).

> of treatment failures (in some cases death) and increased severity of infections."[15]

Antibiotics were initially approved for use in feed by FDA decades ago—long before antibiotic resistance had emerged as a serious threat to human health and even before scientists recognized the many ways bacteria are able to share their resistance genes. (For details on how antibiotic resistance occurs, and its health implications, see Appendix 2.) Indeed, bacteria are now known to share resistance genes readily, even among wholly unrelated bacterial species. As a result, resistance is a concern even in innocuous bacteria because resistance genes can be transferred from them to other bacteria that cause disease. As one recent study notes, "If antibiotic resistance were limited to spontaneous mutations in a few thousand bacteria among the hundreds of billions in one treated host [animal], it would not be the epidemic problem it is today." [16]

Resistant bacteria (and resistance genes) that result from the agricultural use of antibiotics can reach humans through three distinct pathways: food, the environment, and occupational exposures. All of these pathways may be involved simultaneously. The example of nourseothricin, introduced for use in pigs in Germany in the 1980s, illustrates how resistant bacteria can spread from food animal production to people.[17] Prior to use of nourseothricin in pig feed, there was no detectable resistance to this class of antibiotics (streptothricins) in bacteria isolated from animals or humans. Within three years after nourseothricin was introduced for agricultural use, resistance appeared in bacteria isolated from pigs, manure, river water, food, farm workers and their families, and even from adults who had no close connection to animal production.

The food pathway for spread of resistant bacteria is the most obvious. As discussed in Appendix 3, intestinal bacteria from animals can contaminate meat during slaughter; consumers are exposed to these bacteria if the meat products are not properly cooked or if the bacteria are spread during food preparation through cross-contamination of surfaces or utensils in the kitchen. However, because meat-processing and distribution systems in the U.S. are predominantly regional or national, local variations in antibiotic use are not likely to result in local variations in food-borne exposures to resistant bacteria.

By contrast, local variations in agricultural use of antibiotics may well significantly impact local environmental pathways. As a result, residents of agricultural communities may have a greater risk of exposure to resistant bacteria, although few analyses relating to local risk have been conducted to date.

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[15] Joint WHO/FAO/OIE Expert Workshop on Non-human Antimicrobial Usage and Antimicrobial Resistance (2003, p. 1. Available at www.who.int/salmsurv/links/en/GSS1JointFAOOIEWHOWorkshopAMRdec%2003.pdf (accessed Apr. 19, 2005).

[16] Nandi S, Maurer JJ, Hofacre C, and Summers AO (2004). Gram-positive bacteria are a major reservoir of Class 1 antibiotic resistance integrons in poultry litter. *Proceedings of the National Academy of Sciences* 101(18): 7118–7122 . Available at www.pnas.org/cgi/doi/10.1073/pnas.0306466101 (accessed Apr. 19, 2005).

[17] Tschape, H (1994). The spread of plasmids as a function of bacterial adaptability. *FEMS Microbiology Ecology*. 15: 23-32.

Environmental contamination can result from releases of resistant bacteria from animal waste, which is typically disposed of on land relatively close to the livestock facilities. Such waste contains significant amounts of bacteria, many of which are resistant.[18] Moreover, animal waste often contains antibiotics as well, because as much as 75% of the antibiotics consumed by the animals are excreted unchanged.[19] Animal wastes are often stored in open-air lagoons or piles and then simply spread on farm fields (see Appendix 4). These holding areas can also result in environmental contamination. For example, hog waste is often held in open-air "lagoons" that are vulnerable to heavy rains and storm damage. In 1999, millions of gallons of waste released into North Carolina waterways during Hurricane Floyd.[20]

Even absent storms, resistant bacteria can be routinely released from hog waste lagoons (and thus contaminate nearby surface and ground water) as a result of the lagoons' structural weaknesses.[21] Studies have found resistant bacteria and resistance genes in surface and ground water near such facilities in several locations.[22] Contaminated water can flow into lakes, rivers, and coastal waters that are used for swimming, boating, and fishing, or even wells used for drinking water. In addition, bacteria can be transferred from agricultural facilities to other locations by birds, rodents, insects and other wildlife.[23]

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[18] Fransen NG, vandenElzen AMG, Urlings BAP, and Bijker PGH (1996). Pathogenic micro-organisms in slaughterhouse sludge—a survey. *International Journal of Food Microbiology* 33 (2-3): 245-256.

[19] Campagnolo ER, Johnson KR, Karpati A, et al. (2002). Antimicrobial residues in animal waste and water resources proximal to large-scale swine and poultry feeding operations. *Science of the Total Environment* 299:89-95; Chee-Sanford JC, Aminov RI, Krapac IJ, Garrigues-Jeanjean N, and Mackie RI (2001). Occurrence and Diversity of Tetracycline Resistance Genes in Lagoons and Groundwater Underlying Two Swine Production Facilities. *Applied Environmental Microbiology* 67(4): 1494–1502. Whitehead TR, Cotta MA, Whittle G, et al. (2003). The Commensal Bacterial Populations Of Swine Feces And Stored Swine Manure: Reservoirs Of Antibiotic Resistance? *Journal of Animal Science*. 81(suppl.1): 461 (abstract). Available at www.ars.usda.gov/research/publications/publications.htm?SEQ_NO_115=145390 (accessed Apr. 19, 2005).

[20] Cauchon D (27 Sept. 1999). "N.C. farmers, scientists begin taking the toll," USA Today, 6A. See also Schmidt C. (2000). Lessons from the Flood: will Floyd Change Livestock Farming? *Environmental Health Perspectives*. 108(2): A74-77. Available at http://ehp.niehs.nih.gov/docs/2000/108-2/108pa74.pdf (accessed Apr. 19, 2005).

[21] Environmental Protection Agency (12 Jan. 2001). Proposed Rule: National Pollutant Discharge Elimination System Permit Regulation and Effluent Limitations Guidelines and Standards for Concentrated Animal Feeding Operations, *Federal Register* 66: 2960-3008.

[22] Chee-Sanford JC, Aminov RI, Krapac IJ, Garrigues-Jeanjean N, and Mackie RI (2001). Occurrence and Diversity of Tetracycline Resistance Genes in Lagoons and Groundwater Underlying Two Swine Production Facilities. *Applied and Environmental Microbiology* 67(4): 1494-1502. Meyer MT, Bumgarner JE, Varns JL, Daughtridge JV, Thurman EM, Hostetler KA (2000). Use of radioimmunoassay as a screen for antibiotics in confined animal feeding operations and confirmation by liquid chromatography/mass spectrometry. *Science of the Total Environment* 248(2-3):181-7. Cole DJ, Robinette DW, Bumgarner JE, Sobsey MD (2003). Antimicrobial resistance among enteric bacteria isolated from human and animal wastes and impacted surface waters: comparison with NARMS findings. *Environmental Sciences and Engineering Research Notes, U. North Carolina at Chapel Hill School of Public Health* 1(2): 14-20.

[23] Kruse H, Kirkemo AM, and Handeland K (2004). Wildlife as Source of Zoonotic Infections. *Emerging Infectious Diseases* 10(12): 2067-2072. Available at

Animal facilities may also directly release antibiotic-resistant bacteria to air. Multidrug-resistant bacteria have been found at high prevalence in air in animal-agriculture facilities[24] and downwind from such facilities at levels that pose a potential health hazard.[25]

Local patterns of antibiotic use also clearly influence workers' exposures to resistant bacteria. It has long been known that workers who come into contact with animals or their waste can become "colonized" with resistant bacteria, meaning that the bacteria are in and on the workers' bodies without necessarily making them sick; those bacteria can also be transferred to family members and others in the community.[26] More recently, a small pilot study of residents in a poultry-producing community found that 100% were colonized with poultry bacteria (this study did not examine resistance),[27] while another study found that poultry farmers and processors were colonized with resistant bacteria closely related to those present in the animals.[28]

Some particularly dangerous multidrug-resistant “superbugs” have been found in children and adults who have close contact with food animal production. For example, salmonella bacteria resistant to more than a dozen antibiotics including ceftriaxone were isolated from a 12-year-old boy who lived on a cattle farm in Nebraska. Molecular "fingerprinting" revealed that an isolate from the boy was indistinguishable from one of the isolates from the cattle on the farm. No additional ceftriaxone-resistant salmonella infections were reported in that state or adjoining states that could have been the cause of the infection.[29]

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www.cdc.gov/ncidod/EID/vol10no12/04-0707.htm (accessed Apr. 19, 2005).

[24] Chapin A, Rule A, Gibson K, Buckley T, and Schwab K (2005). Airborne Multi-drug Resistant Bacteria Isolated from a Concentrated Swine Feeding Operation. *Environmental Health Perspectives* 113(2):137-42. Available at http://ehp.niehs.nih.gov/members/2004/7473/7473.html (accessed Apr. 19, 2005). Zahn JA, Anhalt J, Boyd E (2001). Evidence for transfer of tylosin and tylosin-resistant bacteria in air from swine production facilities using sub-therapeutic concentrations of tylan in feed. *Journal of Animal Science* 79 (Supplement 1):189 (abstract no. 783). Available at www.asas.org/jas/jointabs/iaafsc83.pdf (accessed Apr. 19, 2005).

[25] Gibbs SG, Green CF, Tarwater PM, Scarpino PV (2004). Airborne antibiotic resistant and nonresistant bacteria and fungi recovered from two swine herd confined animal feeding operations. *Journal of Occupational and Environmental Hygiene* 1: 699-706.

[26] Levy SB, Fitzgerald GB, and Macone AB (1976). Changes in Intestinal Flora of Farm Personnel After Introduction of a Tetracycline-supplemented Feed on a Farm. *New England Journal of Medicine* 295: 583-88. Tschape, H. 1994. The spread of plasmids as a function of bacterial adaptability. *FEMS Microbiology Ecology* 15: 23-32.

[27] Furuno JP (2002). Epidemiological Survey of Bacterial Colonization in Poultry Production Workers and a Human Referent Population. *International Conference on Emerging Infectious Diseases 2002 – Program and Abstracts Book,* p. 92-93 (abstract no. 75). Abstract available at www.cdc.gov/iceid/asm-iceid_program.pdf (accessed Apr. 15, 2005).

[28] Van den Bogaard AE, Willems R, London N, Top J, and Stobberingh EE (2002). Antibiotic resistance of faecal enterococci in poultry, poultry farmers and poultry slaughterers. *Journal of Antimicrobial Chemotherapy* 49: 497-505. Available at http://jac.oupjournals.org/cgi/content/abstract/45/5/663 (accessed Apr. 15, 2005).

[29] Fey PD, Safranek TJ, Rupp ME, Dunne EF, Ribot E, Iwen PC, Bradford PA, Angulo FJ, and Hinrichs SH (2000). Ceftriaxone-Resistant *Salmonella* Infection Acquired by a Child from Cattle. *New England Journal of Medicine* 342(17): 1242–49.

Finally, studies have shown that residents of agricultural areas are at greater risk of infections caused by pathogens associated with animal agriculture[30] or that such residents have higher levels of antibodies indicating prior exposure to such pathogens[31] (these studies did not examine resistance issues).

Prior to publication of this report, no figures on local use of agricultural antibiotics were available. No definitive figures exist in the United States for any geographic level, whether state, county, or national. Neither FDA nor any other government agency collects data on the quantities of antibiotics administered to agricultural animals, either as nontherapeutic feed additives or to treat disease.[32] In 2001, the Union of Concerned Scientists (UCS) developed detailed estimates of the quantities of antibiotics used in livestock and poultry production nationally, based on information about average per-animal use.[33] This report presents estimates at a greater level of geographic detail, as discussed in the next section.

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[30] Valcour JE, Michel P, McEwen SA, and Wilson JB (2002). Associations between Indicators of Livestock Farming Intensity and Incidence of Human Shiga Toxin-Producing *Escherichia coli* Infection. *Emerging Infectious Diseases* 8(3): 252-257. Available at www.cdc.gov/ncidod/EID/vol8no3/Web-pdf/01-0159.pdf (accessed Apr. 19, 2005). Louis VR, Gillespie IA, O'Brien SJ, Russek-Cohen E, Pearson AD, and Colwell RR (2005). Temperature-Driven Campylobacter Seasonality in England and Wales. *Applied and Environmental Microbiology* 71(1): 82-92.

[31] Haack JP, Jelacic S, Besser TE, Weinberger E, Kirk DJ, McKee GL, Harrison SM, Musgrave KJ, Miller G, Price TH, and Tarr PI (2003). Escherichia coli 0157 Exposure in Wyoming and Seattle: Serologic Evidence of Rural Risk. *Emerging Infectious Diseases* 9(10): 126-1231. Available at www.cdc.gov/ncidod/EID/vol9no10/pdfs/02-0254.pdf (accessed Apr. 19, 2005).

[32] The Animal Health Institute, a trade association for makers of animal drugs, has released some information on quantities of sales of antibiotics for animals, but these figures have several important limitations. See discussion in Appendix 1.

[33] Mellon M, et al. (2001), *op. cit*.

CHAPTER 2

Key findings

Important caveat: All figures presented in this section are *estimates,* not measurements. **They are not definitive, and no margin of error can be calculated.** Potential sources of error include errors in the underlying estimates of per-animal use of antibiotic feed additives or in the excretion factors, or in the numbers of animals produced annually per county or state. Since the per-animal antibiotic use estimates we use date from 2001, and the animal census data we use are for 2002, our estimates of antibiotic use may not be accurate for 2005. In addition, our estimates assume that patterns of antibiotic use are uniform on a per-animal basis across the country. They do not reflect the fact that some producers may have reduced antibiotic usage since 2001 and others, including organic producers, do not use any antibiotic feed additives at all. Neither the Census of Agriculture nor any other readily available source indicates which producers are located in which counties (much less describe their antibiotic-use practices or number of animals produced). Recent anecdotal information suggests that at least some hog and chicken producers may have reduced use of antibiotics as feed additives, but specific information on such reductions is not publicly available.

To generate state- and county-specific estimates of the quantities of antibiotics used as feed additives, we used data from the U.S. Department of Agriculture's (USDA) Census of Agriculture. This Census is compiled from data collected every five years, most recently in 2002 (the 2002 data set was released in mid-2004). We used USDA's county-by-county 2002 inventory data for broiler chickens (i.e., those raised for human consumption rather than egg production), hogs and beef cattle to derive annual production estimates for each animal type. We then multiplied the individual production estimates by the Union of Concerned Scientists' (UCS) estimates of the amount of specific antibiotics used as feed additives for each animal type.[34] See Appendix 1 for a full description of our methodology.

This report presents findings on four categories of estimates. First are state and county estimates regarding the quantities of antibiotics used as feed additives, in pounds per year. We initially address all antibiotics, then the subset of those that are "medically important" as described below. Second, we present these state and county use estimates on an area-adjusted basis—i.e., dividing each state or county's total estimate by that state or county's square mileage. Adjusting by square mileage provides a better indicator of intensity of use, given

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[34] Mellon M, et al. (2001), *op. cit*. Contrary to some assertions, the UCS estimates did not simply assume that all antibiotics were used at the maximum approved doses and for the maximum allowed duration in all animals. Rather, as the UCS report itself describes in detail, the UCS estimates reflect information from governmental and other authoritative sources indicating dose rate, duration, and frequency of use for each life stage of each type of animal.

that states and counties differ dramatically in size (for ease of comparison, the adjusted values are expressed in pounds per 1,000 square miles). Third, we present our findings regarding quantities of antibiotics excreted into animal waste, again on both a state and county basis, for overall quantities of both all antibiotics and medically important ones. Finally, we present the excretion estimates on an area-adjusted basis.

For each of these main categories, we provide a narrative summary of key findings, followed by a table listing the top-ranked 10 states and top 30 counties within the category. Selected tables are accompanied by maps to help illustrate the estimates.[35]

Categories of estimates, and accompanying tables and maps

Use estimates – overall
    All antibiotics (state, county) – Table 2, Maps A (state) & B (county)
    Medically important antibiotics (state, county) – Table 3
Use estimates – area-adjusted
    All antibiotics (state, county) – Table 4, Map C (county)
    Medically important antibiotics (state, county) – Table 5, Map D (county)
Waste estimates – overall
    All antibiotics (state, county) – Table 6
    Medically important antibiotics (state, county) – Table 7
Waste estimates - area-adjusted
    All antibiotics (state, county) – Table 8 & Map E (county)
    Medically important antibiotics (state, county) – Table 9 & Map F

Although the tables cover only the top 10 states and top 30 counties in each category, the maps reflect the estimates for all 50 states and 3,000-plus counties, respectively. All of the estimates are contained in two comprehensive Excel spreadsheets, available at www.environmentaldefense.org/go/antibiotic.estimates. These interactive spreadsheets also contain additional details by type of animal and by individual antibiotic compound, and allow users to rank both counties and states by antibiotic use. (Complete instructions for use are included on-line with the spreadsheets.)

On the county-level maps, counties shaded with gray and white stripes are those for which Census of Agriculture data for all three animal types (broiler chickens, hogs and beef cattle) were withheld. Additionally, in some counties, data on one or two of the three animal types were withheld. These counties are not designated on the maps, but can be identified by consulting the county-

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[35] **The maps included in this report are not directly comparable, as each map legend has a separate scale.** Specifically, for the estimate series represented in each map, the maximum value was rounded up to the nearest 10,000 units; five data "bins" were then created by dividing the maximum value into fifths, and the individual estimates assigned to the appropriate color-coded bin.

specific estimates in the spreadsheets. Also shaded with gray and white stripes are some counties that are not listed in the Census of Agriculture.

Finally, it is important to note that all of the use and excretion estimates presented in this report reflect *solely* the quantities of antibiotics used as feed additives for nontherapeutic purposes. These estimates do not reflect any use of antibiotics (whether in feed or otherwise) to treat sick animals or to control disease outbreaks.

A. State and county estimates of antibiotic use in agricultural feed

1. ALL ANTIBIOTICS

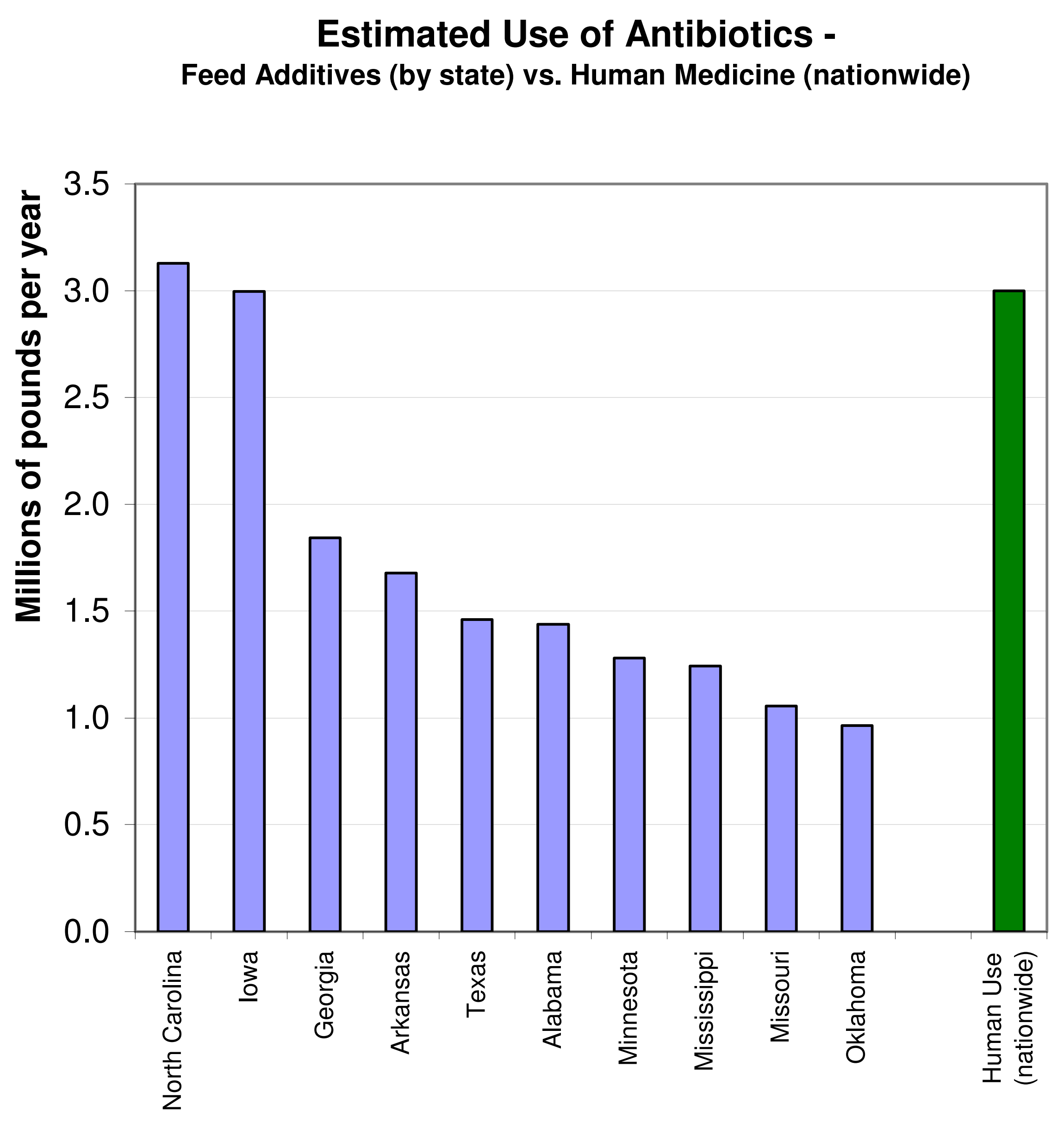
Substantial quantities of antibiotics are used as feed additives nationwide (see Table 1 and Chart 1), but such use is relatively concentrated in certain states and counties (see Table 2, Map A (state use) and Map B (county use):

- Two states, North Carolina and Iowa, are each estimated to use three million pounds of antibiotics as feed additives annually—the same quantity estimated to be used for human medical treatment *nationwide*.
- Of the 26.5 million pounds of antibiotics estimated to be used in the United States as feed additives each year, almost all (90%) occurs in 23 states, and nearly two-thirds (64%) in just 10 states.
- Seven other states also use more than an estimated one million pounds of antibiotic feed additives a year: Georgia, Arkansas, Texas, Alabama, Minnesota, Mississippi, and Missouri.
- Use of antibiotic feed additives is highly concentrated in a few counties; indeed, the highest-use *county* in the U.S. (North Carolina's Duplin County) is estimated to use more antibiotics as feed additives than 35 *states*.

County rankings need to be viewed with caution; results for certain counties are not available or are understated because some or all animal inventory data for those counties were withheld from USDA's Census of Agriculture in order to avoid disclosing data for individual farmers. Antibiotic use in these undisclosed counties is not insignificant:

- An estimated 9% of antibiotic feed additives (2.3 million pounds annually) are used in counties whose animal inventory data were not disclosed in the Census. For example, undisclosed Texas counties alone account for more than 300,000 pounds per year, although it is impossible to determine how this use was distributed among the Texas counties for which data were withheld.
- For broiler chickens, data were withheld for 740 counties; for hogs, 494 counties; and for beef cattle, 584 counties. There are 50 counties for which data on all three animal types were withheld, 328 for which data on two types were withheld, and 1,012 for which one type was withheld.

CHART 1



Estimated Use of Antibiotics -
Feed Additives (by state) vs. Human Medicine (nationwide)
Millions of pounds per year
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
North Carolina
Iowa
Georgia
Arkansas
Texas
Alabama
Minnesota
Mississippi
Missouri
Oklahoma
Human Use (nationwide)

(All units are pounds per year)

***Table 1*. Estimated use of all antibiotic feed additives in chicken, hogs and beef cattle in all 50 states**

State	Rank	All Antibiotics Used
North Carolina	1	3,127,995
Iowa	2	2,997,062
Georgia	3	1,843,468
Arkansas	4	1,678,720
Texas	5	1,460,423
Alabama	6	1,438,243
Minnesota	7	1,280,307
Mississippi	8	1,244,396
Missouri	9	1,055,202
Oklahoma	10	964,656
Illinois	11	806,909
Nebraska	12	763,164
Indiana	13	702,833
Kentucky	14	570,667
Virginia	15	531,272
Kansas	16	454,456
South Dakota	17	445,406
Maryland	18	433,103
Pennsylvania	19	431,488
Louisiana	20	431,098
California	21	390,007
Delaware	22	383,652
Tennessee	23	378,790
South Carolina	24	348,796
Ohio	25	342,141
Florida	26	280,768
Colorado	27	225,959
Montana	28	200,499
Michigan	29	190,686
Wisconsin	30	171,494
Utah	31	163,371
North Dakota	32	135,871
West Virginia	33	126,471
Wyoming	34	103,109
Oregon	35	101,651
Washington	36	72,767
Idaho	37	60,549
New Mexico	38	58,470
New York	39	29,279
Nevada	40	27,410
Arizona	41	19,189
Hawaii	42	15,342
New Jersey	43	3,699
Massachusetts	44	2,890
Maine	45	2,416
Vermont	46	1,809
Connecticut	47	1,635
New Hampshire	48	1,246
Alaska	49	840
Rhode Island	50	607

2. MEDICALLY IMPORTANT ANTIBIOTICS

In addition to preparing estimates of overall use of antibiotics as feed additives, we focused on the antibiotics of greatest concern—those in classes that FDA has identified as being "critically " or “highly important" in human medicine:[36]

•Penicillins[37]
•Aminoglycosides
•Macrolides
•Sulfonamides [39]

•Tetracyclines
•Streptogramins
•Clindamycin/lincomycin[38]

Maintaining the effectiveness of these drugs is of special concern to physicians and patients (Appendix 5 discusses clinical uses of these drugs). Nonetheless, these are not the only antibiotics of interest, because today's "unimportant" drug can turn into tomorrow's "critical" one. For example, until recently streptogramins were regarded as too toxic for use in humans, although they have long been used as agricultural feed additives. However, after some pathogens became increasingly resistant to the other antibiotics used to treat them, FDA in 1999 approved a new human-use streptogramin with somewhat lower toxicity, in order to combat life-threatening infections.

Because different antibiotics are used as feed additives in different types of farm animals, use patterns for medically important antibiotics differ in some ways from use patterns for all antibiotics (see Table 3):

- Of the total quantity of medically important antibiotics estimated to be used as feed additives, by far the largest fraction is used in hogs (69%), compared to 19% in broiler chickens and 12% in beef cattle. By contrast, when all antibiotic feed additives are considered, hogs accounted for 42% of the total, compared with 44% for broiler chickens and 14% for beef cattle.

- Feed-additive use of medically important antibiotics is very concentrated, with Iowa, North Carolina and Minnesota—the top three hog-producing states—accounting for 26 of the top 30 counties.

- Iowa and North Carolina are each estimated to use more than 1.5 million pounds of medically important antibiotics as feed additives.

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[36] Food and Drug Administration (2003). *Guidance for Industry #152: Guidance on Evaluating the Safety of Antimicrobial New Animal Drugs with regard to their Microbiological Effects on Bacteria of Human Health Concern.* Available at www.fda.gov/cvm/guidance/fguide152.pdf (accessed Apr. 19, 2005).

[37] The Guidance includes four categories of penicillins: natural penicillins, penase resistant penicillins, antipseudomonal penicillins and aminopenicillins.

[38] Table A1 in Guidance #152 lists clindamycin, which is essentially identical to lincomycin. Clindamycin is the primary form of the human drug, while lincomycin is primarily used in animals. They differ by a single atom group: lincomycin's hydroxyl (OH) group is a chlorine atom in clindamycin. "Antimicrobial Chemotherapy," www.bmb.leeds.ac.uk/mbiology/ug/ugteach/icu8/antibiotics/protein.html (accessed Apr. 19, 2005).

[39] Guidance #152 designates one member of the sulfonamides class—namely trimethoprim/sulfamethoxazole—as critically important (albeit abbreviated as "trimeth/sulfameth," see Guidance Table A1).

(All units are pounds per year)

***Table 2*. Estimated use of all antibiotic feed additives in chicken, hogs and beef cattle in a) Top 10 states; b) Top 30 counties**

State	Rank	All Antibiotics Used
North Carolina	1	3,127,995
Iowa	2	2,997,062
Georgia	3	1,843,468
Arkansas	4	1,678,720
Texas	5	1,460,423
Alabama	6	1,438,243
Minnesota	7	1,280,307
Mississippi	8	1,244,396
Missouri	9	1,055,202
Oklahoma	10	964,656

County	State	Rank	All Antibiotics Used
Duplin	North Carolina	1	454,646
Sampson	North Carolina	2	395,281
Sussex	Delaware	3	334,954
Texas	Oklahoma	4	200,526
Cullman	Alabama	5	192,245
Bladen	North Carolina	6	174,222
Sioux	Iowa	7	165,671
Benton	Arkansas	8	165,322
Hardin	Iowa	9	164,678
DeKalb	Alabama	10	152,652
Washington	Arkansas	11	151,487
Wilkes	North Carolina	12	149,175
Union	North Carolina	13	146,676
Rockingham	Virginia	14	143,263
Lancaster	Pennsylvania	15	138,400
Wayne	North Carolina	16	136,748
Scott	Mississippi	17	135,790
Nacogdoches	Texas	18	133,038
Smith	Mississippi	19	129,216
Shelby	Texas	20	127,552
Union	Louisiana	21	126,368
Martin	Minnesota	22	119,838
Robeson	North Carolina	23	112,859
Franklin	Georgia	24	112,157
Plymouth	Iowa	25	107,591
Wicomico	Maryland	26	106,588
Le Flore	Oklahoma	27	106,188
Neshoba	Mississippi	28	99,915
Barry	Missouri	29	99,840
Carroll	Iowa	30	99,613

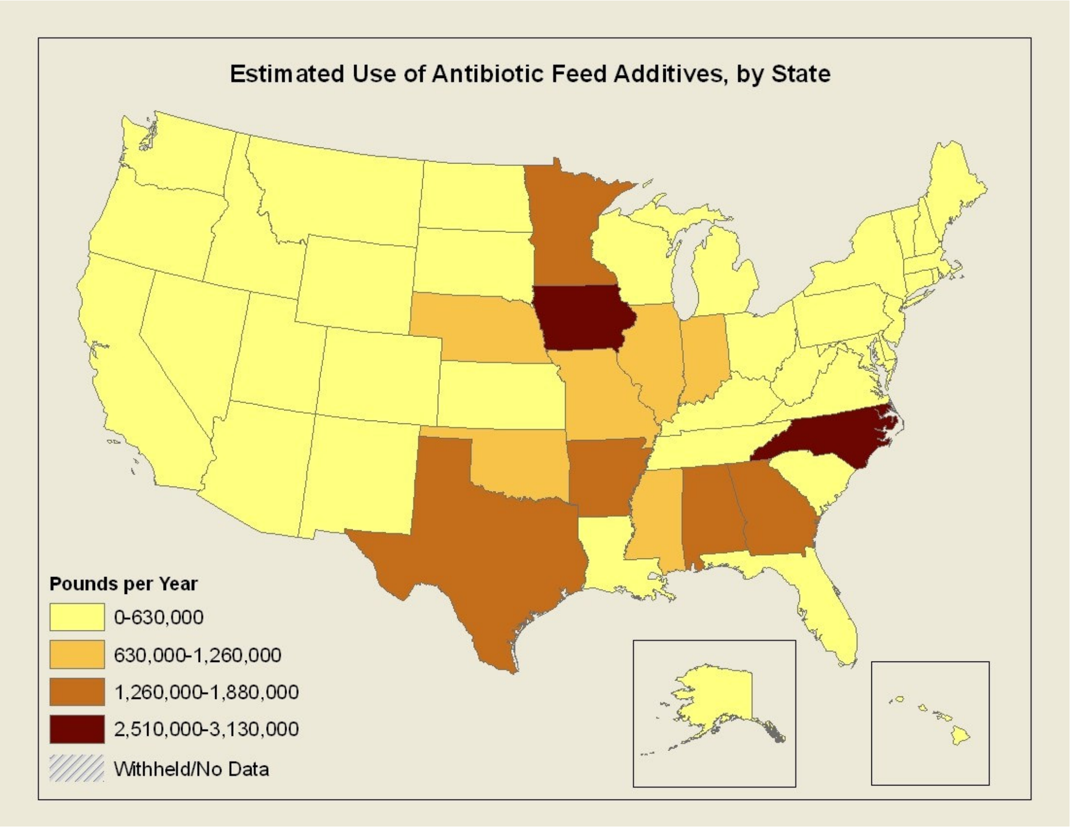
***Table 3*. Estimated use of medically important antibiotic feed additives in chicken, hogs and beef cattle in a) Top 10 states; b) Top 30 counties**

State	Rank	Medically Important Antibiotics Used
Iowa	1	2,248,680
North Carolina	2	1,680,293
Minnesota	3	941,932
Illinois	4	600,926
Missouri	5	563,839
Texas	6	515,427
Indiana	7	511,355
Nebraska	8	502,382
Oklahoma	9	475,026
Georgia	10	427,530

County	State	Rank	Medically Important Antibiotics Used
Duplin	North Carolina	1	319,130
Sampson	North Carolina	2	289,847
Texas	Oklahoma	3	153,197
Hardin	Iowa	4	126,271
Bladen	North Carolina	5	125,903
Sioux	Iowa	6	124,719
Martin	Minnesota	7	91,811
Wayne	North Carolina	8	86,892
Plymouth	Iowa	9	81,809
Carroll	Iowa	10	76,023
Sussex	Delaware	11	69,771
Lancaster	Pennsylvania	12	68,932
Hamilton	Iowa	13	66,446
Robeson	North Carolina	14	64,594
Greene	North Carolina	15	63,798
Lyon	Iowa	16	61,322
Washington	Iowa	17	61,214
Sac	Iowa	18	60,479
Kossuth	Iowa	19	60,472
Blue Earth	Minnesota	20	57,608
Palo Alto	Iowa	21	53,963
Yuma	Colorado	22	50,250
O'Brien	Iowa	23	50,015
Franklin	Iowa	24	47,526
Wright	Iowa	25	45,860
Buena Vista	Iowa	26	44,860
Nobles	Minnesota	27	43,889
Delaware	Iowa	28	42,210
Pender	North Carolina	29	41,571
Lenoir	North Carolina	30	40,675

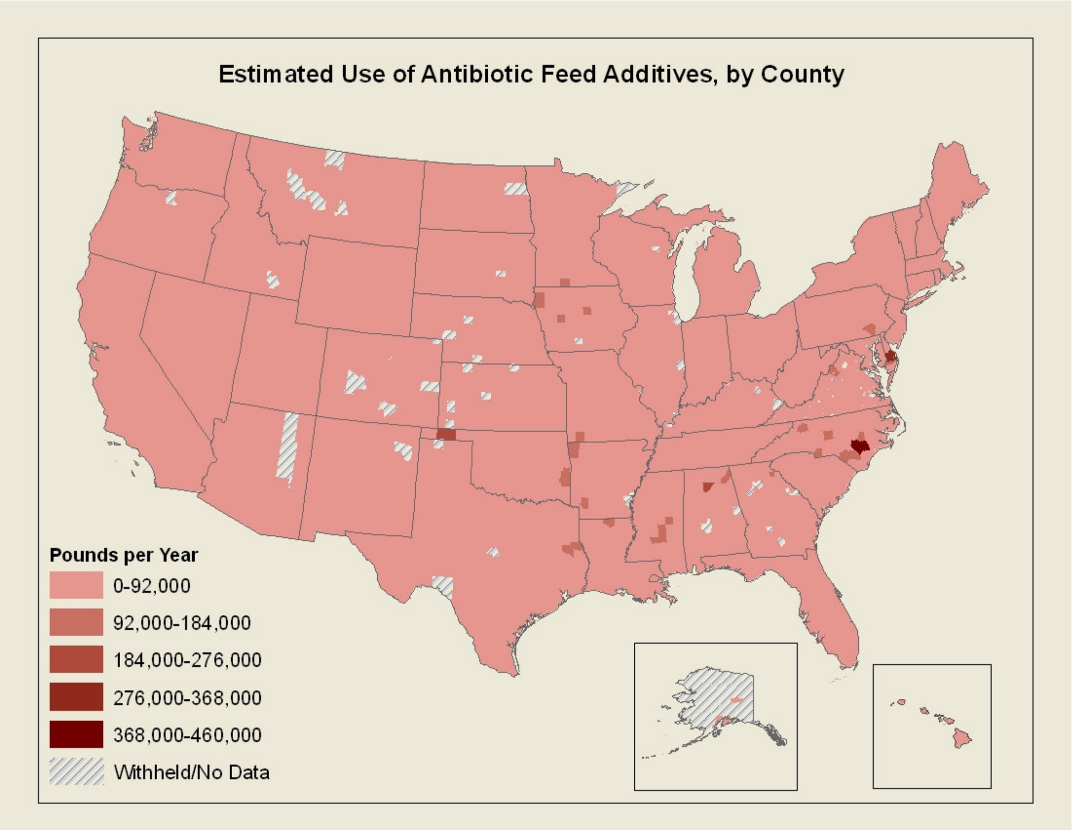
MAP A

Estimated use of antibiotic feed additives, by state



MAP B

Estimated use of antibiotic feed additives, by county



B. Area-adjusted estimates of antibiotics in agricultural feed

States and counties both vary dramatically in area. For example, the nation's largest state, Alaska, is nearly 600 times bigger than its smallest, Rhode Island. Likewise, California's San Bernardino County is almost 900 times larger than New York's New York County. Thus, some of the variation in quantities of antibiotics used and excreted in different states and counties simply reflects the fact that some jurisdictions are bigger.

To gain a clearer indication of relative *intensity* of use, the use estimates presented above can be "normalized" by dividing each jurisdiction's use estimate by its area. The resulting area-adjusted estimates, which are expressed in pounds per 1,000 square miles, have both similarities to and differences from the unadjusted estimates (see Table 4 and Map C):

- Delaware is estimated to be by far the most intensive user of all antibiotic feed additives. Almost all of this use occurs in Delaware's Sussex County. In 2002, Delaware was estimated to use almost three times as many antibiotics per thousand square miles (187,000 pounds) as the next closest state, North Carolina (64,000 pounds).

- Some other smaller states, notably Maryland and Indiana, join the ranks of the top 10 states when area is taken into account.

- North Carolina's Duplin County still tops the county rankings, at almost 570,000 pounds/year. North Carolina and Georgia each account for seven of the top 30 counties; Maryland accounts for an additional four.

Likewise, the area-adjusted rankings for use of medically important antibiotics vary somewhat from the unadjusted rankings (see Table 5 and Map D):

- Using area-adjusted estimates, Iowa and North Carolina remain two of the top three users of medically important antibiotic feed additives. But Delaware, with its small total area, jumps to number two with almost 39,000 pounds per thousand square miles. These three states are estimated to account for 44% of area-adjusted usage nationwide.

- As with the area-adjusted estimates for all feed-additive antibiotics, some smaller states—namely Maryland and Arkansas—show up as top-ranked users of medically important antibiotics.

- On a county basis, Iowa, Minnesota and North Carolina account for the greatest intensity of use of medically important antibiotic use when area is taken into consideration (26 of the top 30 counties). Iowa alone accounts for 16 of the top 30 counties.

(All units are pounds per 1,000 square miles per year)

Table 4. **Estimated area-adjusted use of all antibiotic feed additives in chicken, hogs and beef cattle in a) Top 10 states; b) Top 30 counties**

State	Rank	All Antibiotics Used
Delaware	1	186,729
North Carolina	2	63,774
Iowa	3	53,274
Maryland	4	44,467
Arkansas	5	31,726
Georgia	6	31,443
Alabama	7	27,811
Mississippi	8	26,132
Indiana	9	19,308
Minnesota	10	15,148

County	State	Rank	All Antibiotics Used
Duplin	North Carolina	1	568,335
Franklin	Georgia	2	423,065
Sampson	North Carolina	3	419,925
Sussex	Delaware	4	337,729
Greene	North Carolina	5	322,708
Madison	Georgia	6	301,756
Somerset	Maryland	7	299,652
Camp	Texas	8	292,775
Habersham	Georgia	9	292,557
Hardin	Iowa	10	290,968
Banks	Georgia	11	278,271
Wicomico	Maryland	12	278,042
Cullman	Alabama	13	253,805
Wayne	North Carolina	14	246,611
Hart	Georgia	15	234,348
Union	North Carolina	16	230,460
Scott	Mississippi	17	224,384
Sioux	Iowa	18	218,141
Caroline	Maryland	19	215,284
Jackson	Georgia	20	209,855
Smith	Mississippi	21	205,783
Page	Virginia	22	201,195
DeKalb	Alabama	23	197,343
Bladen	North Carolina	24	197,151
Benton	Arkansas	25	195,399
Wilkes	North Carolina	26	194,441
Worcester	Maryland	27	190,646
Barrow	Georgia	28	187,156
Carroll	Iowa	29	175,866
McLean	Kentucky	30	175,738

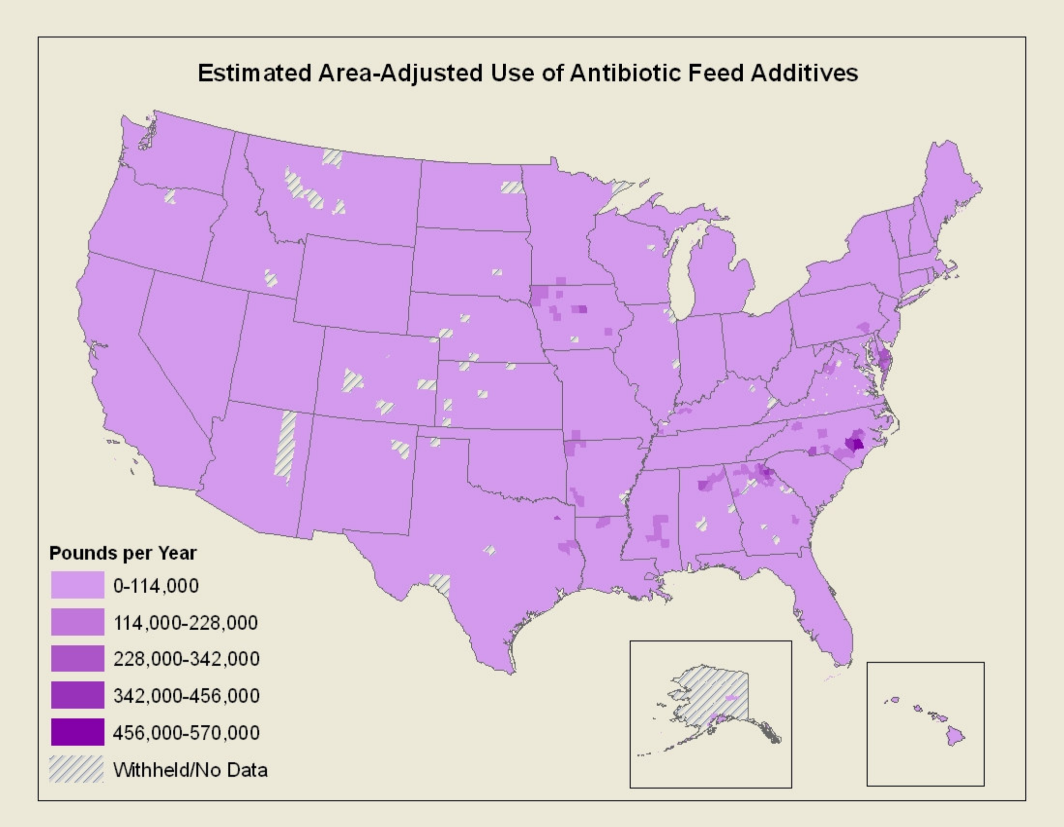
Table 5. **Estimated area-adjusted use of medically important antibiotic feed additives in chicken, hogs and beef cattle in a) Top 10 states; b) Top 30 counties**

State	Rank	Medically Important Antibiotics Used
Iowa	1	39,971
Delaware	2	38,929
North Carolina	3	34,258
Indiana	4	14,048
Minnesota	5	11,144
Illinois	6	10,674
Maryland	7	9,240
Missouri	8	8,074
Arkansas	9	7,487
Georgia	10	7,292

County	State	Rank	Medically Important Antibiotics Used
Duplin	North Carolina	1	398,932
Sampson	North Carolina	2	307,918
Greene	North Carolina	3	233,487
Hardin	Iowa	4	223,107
Sioux	Iowa	5	164,218
Wayne	North Carolina	6	156,702
Bladen	North Carolina	7	142,473
Carroll	Iowa	8	134,217
Martin	Minnesota	9	124,594
Hamilton	Iowa	10	115,189
Lyon	Iowa	11	107,216
Washington	Iowa	12	106,762
Sac	Iowa	13	103,694
Lenoir	North Carolina	14	100,706
Palo Alto	Iowa	15	98,100
Plymouth	Iowa	16	95,015
O'Brien	Iowa	17	89,404
Osceola	Iowa	18	89,187
Franklin	Georgia	19	88,063
Carroll	Indiana	20	86,207
Jones	North Carolina	21	82,461
Franklin	Iowa	22	80,215
Wright	Iowa	23	76,745
Buena Vista	Iowa	24	75,601
Blue Earth	Minnesota	25	75,098
Texas	Oklahoma	26	73,635
Mitchell	Iowa	27	72,902
Delaware	Iowa	28	72,796
Nicollet	Minnesota	29	72,709
Lancaster	Pennsylvania	30	71,174

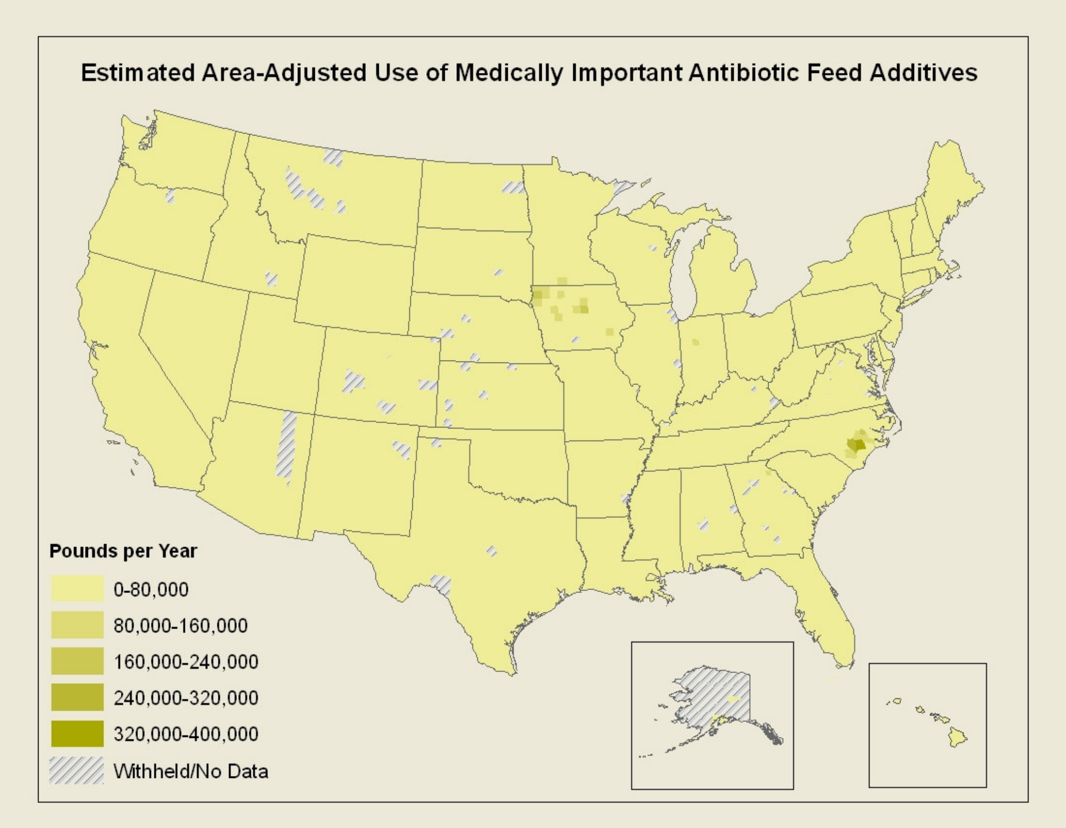
MAP C

Estimated area-adjusted use of all antibiotic feed additives, by county



MAP D

Estimated area-adjusted use of medically important antibiotic feed additives, by county



C. State and county estimates of antibiotics in animal waste

Animals excrete a significant fraction of the antibiotics they consume in feed. These wastes, and the antibiotics and resistant bacteria in them, are typically transferred to soil or water—both through intentional land spreading (the primary way that animal waste is disposed of in the United States) and sometimes through unintentional releases following storms or mishaps. These antibiotics in the environment can promote development of resistance in bacteria naturally present in the soil and water. (Resistant bacteria are also found in animal waste, but are not quantified in this report.)

As with the use estimates discussed above, we present two sets of estimates of quantities of antibiotics in waste from use of antibiotics as feed additives: one for all antibiotics (see Table 6), the other covering only medically important antibiotics (see Table 7). Key findings include the following:

- Nationwide, an estimated 13.5 million pounds of total antibiotics are excreted annually in animal wastes as a result of using antibiotic feed additives. This is nearly half of the quantity used as feed additives.
- Iowa and North Carolina account for an estimated 25% of this total, or 3.3 million pounds annually.
- Hogs account for an estimated 47% of *all* antibiotics that are excreted (compared with 39% for broiler chickens and 14% for beef cattle). For *medically important* antibiotics in waste, however, hogs account for 72% of the total (compared with 14% for broiler chickens and 13% for beef cattle).

(All units are pounds per year)

Table 6. Estimated quantity of antibiotics in waste from use of all antibiotic feed additives in chicken, hogs and beef cattle in a) Top 10 states; b) Top 30 counties

State	Rank	All Antibiotics Excreted
Iowa	1	1,703,769
North Carolina	2	1,636,908
Georgia	3	846,769
Arkansas	4	773,093
Minnesota	5	723,869
Texas	6	715,562
Alabama	7	659,995
Mississippi	8	573,924
Missouri	9	554,498
Oklahoma	10	498,587

County	State	Rank	All Antibiotics Excreted
Duplin	North Carolina	1	253,620
Sampson	North Carolina	2	223,116
Sussex	Delaware	3	152,022
Texas	Oklahoma	4	114,494
Bladen	North Carolina	5	97,942
Sioux	Iowa	6	94,202
Hardin	Iowa	7	94,107
Cullman	Alabama	8	87,355
Benton	Arkansas	9	75,281
Wayne	North Carolina	10	74,363
Lancaster	Pennsylvania	11	71,276
DeKalb	Alabama	12	70,737
Washington	Arkansas	13	70,239
Martin	Minnesota	14	68,469
Wilkes	North Carolina	15	67,704
Union	North Carolina	16	66,547
Rockingham	Virginia	17	65,139
Scott	Mississippi	18	61,537
Plymouth	Iowa	19	61,363
Nacogdoches	Texas	20	60,508
Robeson	North Carolina	21	59,880
Smith	Mississippi	22	58,628
Shelby	Texas	23	57,986
Union	Louisiana	24	57,327
Carroll	Iowa	25	56,862
Franklin	Georgia	26	50,923
Greene	North Carolina	27	49,588
Hamilton	Iowa	28	49,521
Le Flore	Oklahoma	29	48,694
Wicomico	Maryland	30	48,319

Table 7. Estimated quantity of antibiotics in waste from use of medically important antibiotic feed additives in chicken, hogs and beef cattle in a) Top 10 states; b) Top 30 counties

State	Rank	Medically Important Antibiotics Excreted
Iowa	1	1,065,461
North Carolina	2	761,577
Minnesota	3	445,330
Illinois	4	285,061
Missouri	5	262,258
Indiana	6	241,507
Nebraska	7	240,466
Texas	8	233,783
Oklahoma	9	219,064
Georgia	10	156,170

County	State	Rank	Medically Important Antibiotics Excreted
Duplin	North Carolina	1	149,652
Sampson	North Carolina	2	136,592
Texas	Oklahoma	3	72,536
Hardin	Iowa	4	59,771
Bladen	North Carolina	5	59,219
Sioux	Iowa	6	58,957
Martin	Minnesota	7	43,461
Wayne	North Carolina	8	40,249
Plymouth	Iowa	9	38,748
Carroll	Iowa	10	35,997
Hamilton	Iowa	11	31,452
Lancaster	Pennsylvania	12	30,845
Greene	North Carolina	13	30,016
Robeson	North Carolina	14	29,515
Lyon	Iowa	15	29,042
Washington	Iowa	16	28,984
Sac	Iowa	17	28,634
Kossuth	Iowa	18	28,633
Blue Earth	Minnesota	19	27,271
Palo Alto	Iowa	20	25,548
Sussex	Delaware	21	23,848
Yuma	Colorado	22	23,786
O'Brien	Iowa	23	23,683
Franklin	Iowa	24	22,502
Wright	Iowa	25	21,710
Buena Vista	Iowa	26	21,241
Nobles	Minnesota	27	20,780
Delaware	Iowa	28	19,991
Pender	North Carolina	29	19,636
Lenoir	North Carolina	30	19,040

D. Area-adjusted estimates of antibiotics in animal waste

As with the antibiotic-use estimates, rankings for estimated quantities of antibiotics in waste change when presented on an area-adjusted basis (see Table 8 and Map E for all antibiotics, and Table 9 and Map F for medically important antibiotics):

- On an area-adjusted basis, Delaware is the top-ranked state in terms of estimated quantity of all antibiotics in animal waste (85,000 pounds).
- For all antibiotics in waste from feed-additive use of antibiotics, North Carolina, Georgia, Maryland and Iowa account for 20 of the top 30 counties on an area-adjusted basis.
- For medically important antibiotics in waste from feed-additive use of antibiotics, Iowa, Minnesota and North Carolina account for 26 of the top 30 counties on an area-adjusted basis.

(All units are pounds per 1,000 square miles per year)

Table 8. Estimated area-adjusted quantity of antibiotics in waste from use of all antibiotic feed additives in chicken, hogs and beef cattle in a) Top 10 states; b) Top 30 counties

State	Rank	All Antibiotics Excreted
Delaware	1	84,757
North Carolina	2	33,374
Iowa	3	30,285
Maryland	4	20,185
Arkansas	5	14,611
Georgia	6	14,443
Alabama	7	12,762
Mississippi	8	12,052
Indiana	9	10,884
Minnesota	10	8,564

County	State	Rank	All Antibiotics Excreted
Duplin	North Carolina	1	317,040
Sampson	North Carolina	2	237,026
Franklin	Georgia	3	192,085
Greene	North Carolina	4	181,482
Hardin	Iowa	5	166,276
Sussex	Delaware	6	153,282
Madison	Georgia	7	136,819
Somerset	Maryland	8	135,827
Wayne	North Carolina	9	134,106
Camp	Texas	10	133,135
Habersham	Georgia	11	132,743
Banks	Georgia	12	126,354
Wicomico	Maryland	13	126,042
Sioux	Iowa	14	124,036
Cullman	Alabama	15	115,327
Bladen	North Carolina	16	110,832
Hart	Georgia	17	107,241
Union	North Carolina	18	104,560
Scott	Mississippi	19	101,686
Carroll	Iowa	20	100,389
Caroline	Maryland	21	97,651
Jackson	Georgia	22	95,444
Smith	Mississippi	23	93,368
Martin	Minnesota	24	92,917
Page	Virginia	25	91,478
DeKalb	Alabama	26	91,446
Benton	Arkansas	27	88,976
Wilkes	North Carolina	28	88,249
Worcester	Maryland	29	86,428
Hamilton	Iowa	30	85,847

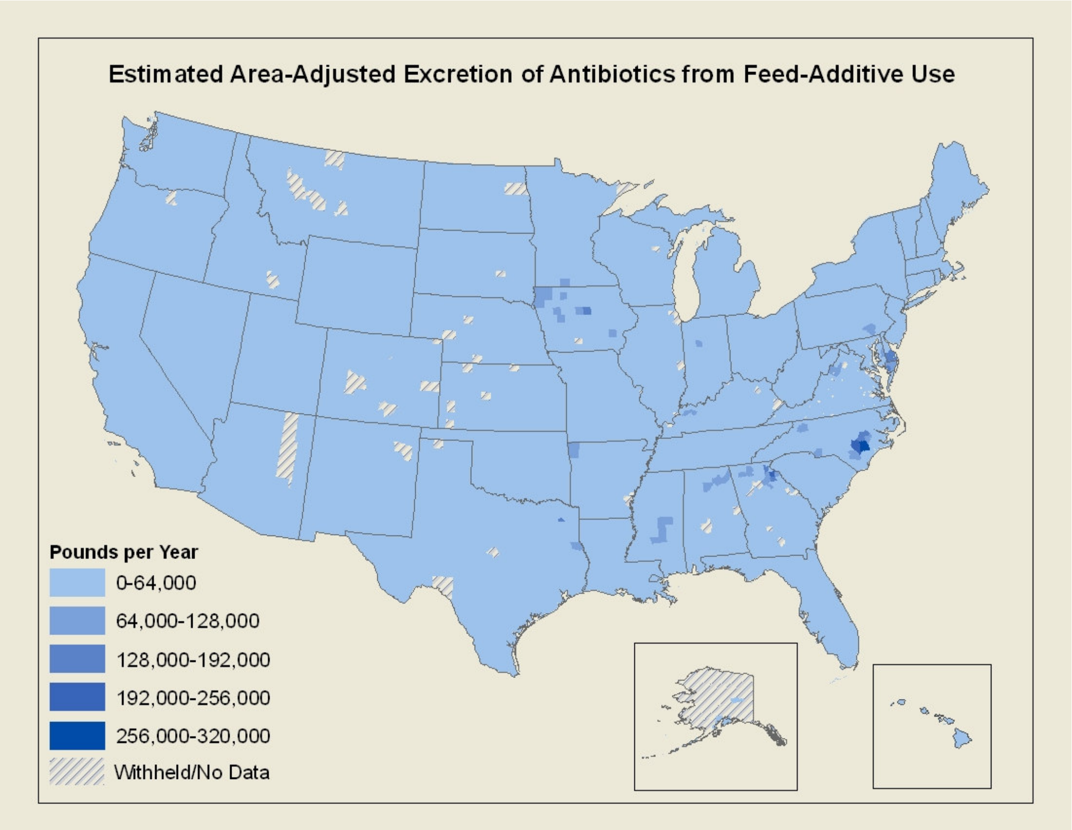
Table 9. Estimated area-adjusted quantity of antibiotics in waste from use of medically important antibiotic feed additives in chicken, hogs and beef cattle in a) Top 10 states; b) Top 30 counties

State	Rank	Medically Important Antibiotics Excreted
Iowa	1	18,939
North Carolina	2	15,527
Delaware	3	13,314
Indiana	4	6,635
Minnesota	5	5,269
Illinois	6	5,063
Missouri	7	3,756
Maryland	8	3,173
Oklahoma	9	3,129
Nebraska	10	3,110

County	State	Rank	Medically Important Antibiotics Excreted
Duplin	North Carolina	1	187,074
Sampson	North Carolina	2	145,108
Greene	North Carolina	3	109,851
Hardin	Iowa	4	105,608
Sioux	Iowa	5	77,629
Wayne	North Carolina	6	72,585
Bladen	North Carolina	7	67,013
Carroll	Iowa	8	63,553
Martin	Minnesota	9	58,979
Hamilton	Iowa	10	54,525
Lyon	Iowa	11	50,777
Washington	Iowa	12	50,551
Sac	Iowa	13	49,095
Lenoir	North Carolina	14	47,140
Palo Alto	Iowa	15	46,444
Plymouth	Iowa	16	45,003
O'Brien	Iowa	17	42,334
Osceola	Iowa	18	42,229
Carroll	Indiana	19	40,812
Jones	North Carolina	20	38,834
Franklin	Iowa	21	37,980
Wright	Iowa	22	36,331
Buena Vista	Iowa	23	35,797
Blue Earth	Minnesota	24	35,551
Texas	Oklahoma	25	34,865
Mitchell	Iowa	26	34,516
Delaware	Iowa	27	34,477
Nicollet	Minnesota	28	34,417
Lancaster	Pennsylvania	29	31,849
Robeson	North Carolina	30	31,335

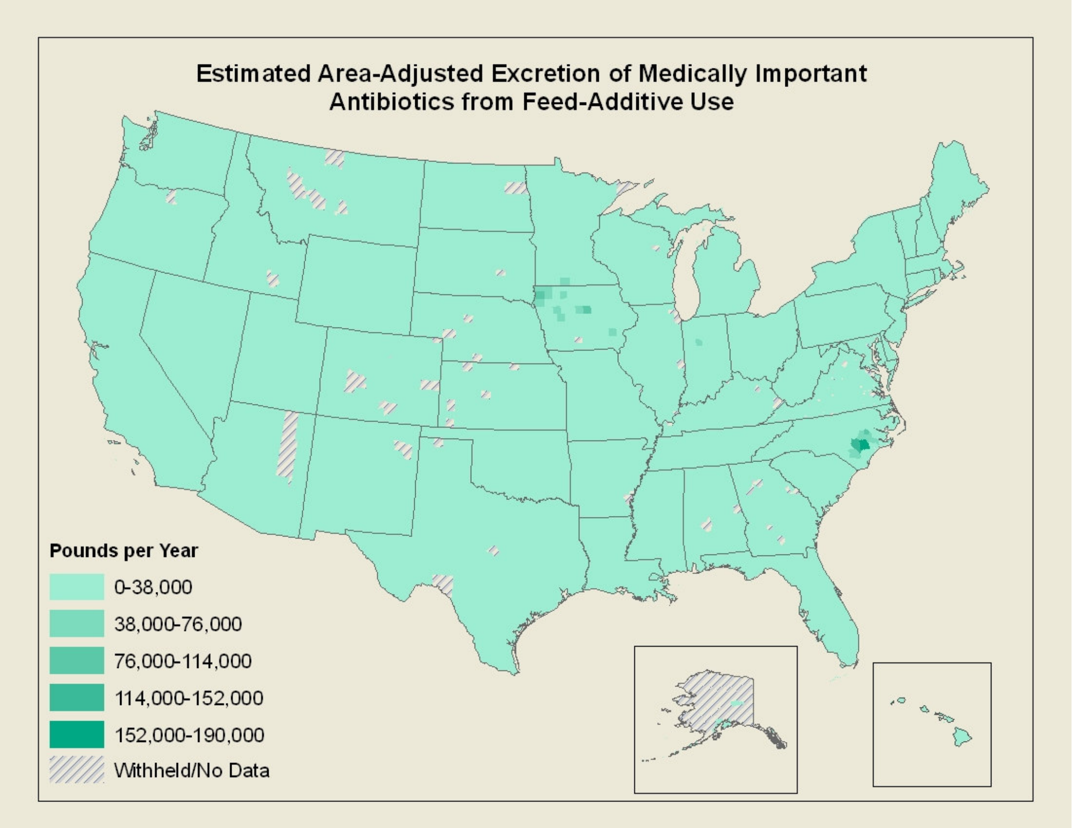
MAP E

Estimated area-adjusted excretion of antibiotics from feed-additive use



MAP F

Estimated area-adjusted excretion of medically important antibiotics from feed-additive use, by county



CHAPTER 3

Preserving human medicines for the future

The use of medically important antibiotics as feed additives is as unnecessary as it is unwise. The National Academy of Sciences noted in a 1999 report that "the beneficial effects of subtherapeutic drug use are found to be greatest in poor sanitary conditions."[40] Even the National Pork Board has acknowledged that "The level of performance improvement [from feeding of antibiotics] depends on management and housing conditions. As sanitation improves on the farm, there are smaller increases in performance response."[41] When animals are subjected to poor hygienic conditions—overcrowding, environmental extremes, malfunctioning water- or waste-handling systems, poorly mixed or contaminated feed—the animals become more susceptible to disease, and the risk of one animal becoming sick and then rapidly infecting the entire herd is much greater.

Where animals are raised under better conditions, use of antibiotic feed additives provides little benefit even on industrial-scale farms. For example, Denmark, the world's leading exporter of pork, ended the use of antibiotic feed additives in 1999 resulting in a 54% reduction in the overall use of antibiotics in agriculture. After an in-depth review of Denmark's experience, an expert panel convened by the World Health Organization concluded that there had been no impact on food safety or consumer meat prices, and only a very minimal (1%) impact on production costs for hogs and none for chicken.[42]

In October 2003, FDA released Guidance #152,[43] which "outlines a comprehensive evidence-based approach to preventing antimicrobial resistance

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[40] National Academy of Sciences/National Research Council. *The Use of Drugs in Food Animals, Benefits and Risks*. Washington, DC: National Academy Press, p. 157. Available at www.nap.edu/books/0309054346/html/157.html (accessed Apr. 19, 2005).

[41] Pork Checkoff (a project of the National Pork Board) (no date). Non-Antimicrobial Production Enhancers: A Review, p. 1. Available at www.porkscience.org/documents/Other/NAPESbook.pdf (accessed Apr. 19, 2005).

[42] World Health Organization (2003). Impact of antimicrobial growth promoter termination in Denmark. WHO/CDS/CPE/ZFK/2003.1, p. 42. Available at www.who.int/salmsurv/en/Expertsreportgrowthpromoterdenmark.pdf (accessed Apr. 19, 2005).

[43] Food and Drug Administration (2003). Guidance for Industry #152 – Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern, pg. 15. Available at www.fda.gov/cvm/guidance/fguide152.pdf (accessed Apr. 19, 2005). Although issuance of the Guidance constitutes a significant step forward, it has some key weaknesses, including its complete disregard of all pathways other than food by which resistant bacteria (and their genes) can move from agricultural settings to humans. While the Guidance acknowledges that such pathways exist, in it FDA simply asserts (without discussion) its belief that examining only the food-borne pathway "is the best way to qualitatively assess the risk" of antibiotic use in agriculture (though noting that "uncertainties regarding the contribution of other exposure pathways may be considered during the development of appropriate risk management strategies"). Guidance, p. 15.

that may result from the use of antimicrobial drugs in animals."[44] The Guidance sets out appropriate management conditions depending on whether the overall "risk estimate" for the drug is high, medium or low based on a qualitative risk assessment. In April 2005, health and environmental organizations, including the American Academy of Pediatrics and Environmental Defense, petitioned FDA to implement the Guidance with regard to seven classes of antibiotics that are currently used as feed additives.[45] As the Petition explains in detail, the Guidance rates those seven classes of antibiotics as "highly important" or "critically important;" accordingly, their use as feed additives for chicken, hogs, and beef cattle violates the Guidance's safety criteria.

Although the Guidance as written applies only to future drug approvals, FDA has stated that the Guidance's "principles will also be applied in determining whether to remove approved products from the market."[46] Unfortunately, the Guidance does nothing to streamline FDA's extremely cumbersome process for withdrawing drugs from the market. In the past, it has taken FDA from six to 20 years to remove a single drug or drug class from agricultural use *after* the agency formally concluded that continued use was unsafe.

In light of FDA's apparent inability to act on a timely basis, the U.S. Congress must act to set a strict timeline for ending uses of medically important antibiotics as feed additives (unless such uses are affirmatively shown to be safe based on contemporary scientific understanding). Bipartisan legislation to accomplish this objective, The Preservation of Antibiotics for Medical Treatment Act, was introduced in April 2005.[47] The measure also requires collection of data on sales of agricultural antibiotics. In addition, the Senate version provides funding for demonstration projects, as well as financial assistance to help farmers curtail the use of medically important antibiotics as feed additives. Similar legislation has been endorsed by more than 380 groups, including the American Medial Association, American Academy of Pediatrics, and American Public Health Association.

Consumers also have an important role to play. High-volume meat purchasers are beginning to adopt procurement policies aimed at reducing the use of antibiotics in meat production. In June 2003, for example, McDonald's adopted a procurement policy under which its "direct" suppliers (primarily

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[44] Food and Drug Administration (2003). "FDA Issues Guidance on Evaluating the Safety of Antimicrobial New Animal Drugs to Help Prevent Creating New Resistant Bacteria" (press release). Available at www.fda.gov/bbs/topics/NEWS/2003/NEW00964.html (accessed Apr. 19, 2005).

[45] Environmental Defense, American Academy of Pediatrics, American Public Health Association, Food Animal Concerns Trust, Union of Concerned Scientists (April 7, 2005). *Citizen Petition Seeking Withdrawal of Approvals of Certain Herdwide/Flockwide Uses of Critically and Highly Important Antibiotics Pursuant to Guidance #152.* FDA docket no. 2005P-0139/CP1. Available at www.environmentaldefense.org/article.cfm?ContentID=4310 (accessed Apr. 19, 2005).

[46] Food and Drug Administration, Center for Veterinary Medicine. Annual Report – Fiscal Year 2003 (October 1, 2002 - September 30, 2003), p. 20. Available at www.fda.gov/cvm/Documents/CVMFY03AnnRpt.pdf (accessed Apr. 19, 2005).

[47] S. 742 and H.R. 2562. Available at http://thomas.loc.gov/ (accessed May 24, 2005).

chicken suppliers) cannot use medically important antibiotics for growth promotion as of the end of 2004. McDonald's policy also provides a purchase preference for all other meat suppliers that minimize overall antibiotic use. In December 2003, Bon Appétit—one of the nation's leading food-service companies—adopted a policy that bars the use of medically important antibiotics for growth promotion *and* routine disease prevention in chickens, and that provides a purchase preference for suppliers that minimize antibiotic use. Health-based organizations have adopted resolutions urging businesses and institutions—including state and local governments—to adopt similar procurement policies.[48]

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[48] American Public Health Association Resolution 2004-13, "Helping Preserve Antibiotic Effectiveness by Stimulating Demand for Meats Produced Without Excessive Antibiotics." Available at www.apha.org/legislative/policy/policysearch/index.cfm?fuseaction=view&id=1299 (accessed Apr. 19, 2005). The American Nurses Association adopted a similar resolution in June 2004.

APPENDIX 1

Estimation Methods

This report presents two primary sets of state-by-state and county-by-county estimates relating to agricultural antibiotics: first, estimates of the quantities of antibiotics administered to broiler chickens (those produced for human consumption), hogs and beef cattle as feed additives for nontherapeutic purposes;[49] and second, estimates of the quantities of key antibiotics that are expected to be found in these animals' waste as a result of such feed-additive use. We developed these estimates as follows.

A. Animals per county and per state

We obtained state- and county-level data on the numbers of broiler chickens,[50] hogs, and beef cattle from the Census of Agriculture compiled by the U.S. Department of Agriculture (USDA) every five years. We used the 2002 data set, which was publicly released in June 2004 and is the most recent available.

The Census of Agriculture only reports the following two types of animal counts:

1) The standing <u>inventory</u> of a given animal type present on December 31st of the reporting year (the latest year being 2002). This is not an annual production estimate because more than one (in the case of broilers and hogs) or less than one (in the case of beef cattle) "crop" of animals is typically produced every year.
2) The <u>number of animals sold annually</u>, again the latest data being for 2002. While this figure is an annualized count, animals may be sold more than once in their lifetimes, so these figures include some double counting. In addition, for cattle, the "number sold" data do not distinguish between beef cattle and other cattle (e.g., dairy); in contrast, the inventory data for cattle do make this distinction.

Data are also available from USDA statistical bulletins, which include annual national animal production and slaughter estimates for each animal type.

To estimate annual county- and state-level production totals for each animal type, we started with the Census of Agriculture's inventory data for December 2002 (available at www.nass.usda.gov/census/ (select "U.S. State Level Data") (accessed Apr. 19, 2005). Each state's and county's inventory data were retrieved by downloading the following county-level data tables for each state: Table 11 (Cattle and Calves—Inventory and Sales: 2002 and 1997), Table 12 (Hogs and

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[49] As noted in the body of this report, nontherapeutic uses are those that do not treat overt illness, but rather promote faster growth or prevent disease that could otherwise result from the crowded and stressful conditions common at large-scale animal production facilities.

[50] We included chickens raised for human consumption (termed "broilers and other meat-type chickens") but not chickens raised to produce eggs ("layers").

Pigs—Inventory and Sales: 2002 and 1997), and Table 13 (Poultry—Inventory and Sales: 2002 and 1997). Within each of these tables, the following rows of data were extracted:

Table 11 – Beef cows, number, 2002, for each county in each state, as well as the state total
Table 12 – Total hogs and pigs, number, 2002, for each county in each state, as well as the state total
Table 13 – Broilers and other meat-type chickens, number, 2002, for each county in each state, as well as the state total

We then adjusted the Census of Agriculture data to provide estimates of the number of a given animal type produced in a given county or state per year, in this case 2002, based on discussions with USDA experts about various Census of Agriculture data sets and related issues.[51]

Potential data sources for deriving our county- and state-level estimates for annual production included the agricultural census data, which provide inventory and annual sales estimates for each animal type, and the USDA statistical bulletins, which provide annual production and annual slaughter estimates for the animal types. Both sources include animal-specific data on broiler chickens, hogs and beef cattle, the three animal types of interest.

BROILER CHICKENS

Based on our conversation with USDA staff, our understanding is as follows:

- The national estimate for the number of animals slaughtered includes not only broilers, but also layers and other chickens (e.g., roosters); for poultry, this figure corresponds closely to the "number sold" estimate from the Census of Agriculture. A small percentage of the slaughter estimate is comprised of chickens that are not broilers, while a small fraction of the number sold estimate is comprised of double counts, e.g., because a single farmer might not raise the broilers for the full cycle and instead sells them to another farmer who later sells them for slaughter.
- The national estimate for the annual number of animals produced includes "domestic chickens of meat-type strain for meat production;" this number effectively includes only broilers, excluding layers and other chickens.
- Broiler chickens have a typical turn-around time of 5.5–6 cycles of chickens raised/year.

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[51] Personal communications on Sept. 1, 2004, between Environmental Defense staff scientist Terri Stiffler and Tom Krutchen, Dan Lofthus and Mike Miller of USDA's National Agricultural Statistics Service, respectively regarding poultry, swine and beef. These individuals, however, were not asked to review the adjustment methodology.

To derive county- and state-level data on annual production of broilers, we considered using the "sold data" reported for each county and state available in the 2002 Census of Agriculture. Because the "number sold" can double-count broilers sold more than once, however, and to be consistent with the approach taken for hogs and beef cattle (see below), we instead chose the following approach.

Given that the inventory data count only how many animals are present in a county as of the end of the year, it is necessary to estimate how many "crops" of broiler chickens were produced during the entire year. To do so, we divided the overall national annual "produced number" for broilers, which in 2002 was 8,590,180,000,[52] by the national inventory of broilers and other meat-type chickens as of December 2002, which is 1,389,279,047.[53] We applied the resulting ratio of 6.18 as a multiplier to the county- and state-level inventory data for broilers and other meat-type chickens, taken from the 2002 Census of Agriculture. This 6.18 multiplier is fairly consistent with estimates by USDA staff of 5.5–6 cycles of chickens raised per year. Considering that the average length of the production cycle is approximately 42 days,[54] the annual theoretical maximum number of cycles would be 365/42 = 8.7 cycles; given that there are some down days between production cycles, our 6.18 multiplier seems reasonable if not conservative.

HOGS

Based on our conversation with USDA staff, our understanding is that the "sold number" available from the Census of Agriculture double-counts many animals, as there are often multiple sales of a given animal over its lifetime (from farmer to farmer, between feedlots, etc.), and hence it is not a good indicator of the actual number of animals raised.

Given this, we opted to divide the national estimate for the number of hogs slaughtered in 2002, which is 100,262,600,[55] by the national estimate for the inventory of hogs as of December 2002, which is 60,405,103.[56] We then applied the resulting ratio of 1.66 as a multiplier to the county- and state-level inventory

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[52] National Agricultural Statistics Service (2003). *Poultry - Production and Value, 2002 Summary*, p. 5, table titled "Broilers: Production, Price, and Value by State and Total, 2002." Available at http://usda.mannlib.cornell.edu/reports/nassr/poultry/pbh-bbp/plva0403.pdf (accessed Apr. 20, 2005).

[53] National Agricultural Statistics Service (2002). Census of Agriculture, U.S. National Level Data, Table 27 titled "Poultry—Inventory and Number Sold: 2002 and 1997." Available at www.nass.usda.gov/census/census02/volume1/us/st99_1_027_029.pdf (accessed Apr. 19, 2005).

[54] National Academy of Sciences/National Research Council (1999). The Use of Drugs in Food Animals: Benefits and Risks (National Academy Press, Washington, DC), p. 29. Available at www.nap.edu/books/0309054346/html/29.html (accessed Apr. 19, 2005).

[55] National Agricultural Statistics Service (2003). *Livestock Slaughter, 2002 Summary*, table titled "Number of Head Slaughtered: By Species, Commercial and Farm, United States, 2002," p. 3. Available at http://usda.mannlib.cornell.edu/reports/nassr/livestock/pls-bban/lsan0303.pdf (accessed Apr. 19, 2005).

[56] National Agricultural Statistics Service (2002). Census of Agriculture, U.S. National Level Data, Table 21 titled "Hogs and Pigs Herd Size by Inventory and Sales: 2002." Available at www.nass.usda.gov/census/census02/volume1/us/st99_1_020_022.pdf (accessed Apr. 19, 2005).

data for hogs, taken from the 2002 Census of Agriculture, in order to generate an annual production estimate for hogs. This multiplier is roughly consistent with statements by USDA staff that there are up to two pig crops each year, and with other estimates that the length of the typical hog production cycle is approximately 180 days;[57] our multiplier will yield conservative estimates of the number of hogs annually produced in each county and state.

BEEF CATTLE

Based on our conversation with USDA staff, our understanding is as follows:

- The typical turnover for a feedlot is approximately 2.25 per year, with animals kept on a feedlot for approximately 90-120 days.
- In terms of total production, the "number sold" is probably the best overall indicator of production. However, the "number sold" for cattle and calves does not distinguish between beef and dairy animals, which is necessary to our analysis. The national estimates for number of cattle slaughtered do make this distinction.

Given the above information, we opted to divide the national estimate for the number of beef cattle slaughtered in 2002, which is 29,373,841,[58] by the national estimate for the inventory of beef cattle as of December 2002, which is 33,398,271.[59] We then applied the resulting ratio of 0.88 as a multiplier to the county- and state-level inventory data for beef cattle, taken from the 2002 Census of Agriculture. This multiplier is roughly consistent with the typical production cycle for beef cattle of approximately 15 months.[60]

B. Antibiotic use per animal

No "hard data" on antibiotic use in agricultural animals are publicly available, much less any indicating the quantities of antibiotics administered as feed additives for nontherapeutic purposes. Although some figures have been released by the Animal Health Institute (AHI), the trade association for animal-drug

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[57] Mellon M, et al. (2001), *op. cit*. Table B-2.

[58] A figure for total cattle slaughtered in 2002 of 35,734,600 head was taken from National Agricultural Statistics Service, *Livestock Slaughter, 2002 Summary*, March 2003, table titled "Commercial Cattle Slaughter: Number of Head by Month, State, and United States, 2002," p. 31. Available at http://usda.mannlib.cornell.edu/reports/nassr/livestock/pls-bban/lsan0303.pdf (accessed Apr. 20, 2005). That total includes dairy cows (7.4% of total), other cows (8.7%), and bulls (1.7%) (see p. 1). Because it is appears that at least some of these animals are not likely to receive antibiotic feed additives for nontherapeutic purposes, we adjusted the total to exclude these categories of cattle, yielding a figure of 29,373,841.

[59] National Agricultural Statistics Service (2002). *Census of Agriculture*, U.S. National Level Data, Table 12 titled "Cattle and Calves Inventory 2002 and 1997." Available at www.nass.usda.gov/census/census02/volume1/us/st99_1_012_013.pdf (accessed Apr. 19, 2005).

[60] Mellon M, et al. (2001), *op. cit*. Table B-1.

producers,[61] those figures have several serious limitations. First, they fail to distinguish between therapeutic and nontherapeutic uses. Second, they do not provide species-specific information; indeed, they commingle data from antibiotic use in companion animals (pets) as well as agricultural animals, even though use patterns between the two are highly dissimilar. Third, they are not necessarily comprehensive, as they are compiled from AHI's survey of its members; it is neither clear whether all animal-drug manufacturers are AHI members, nor what fraction of the members responded to the survey. Fourth, AHI lumps antibiotics together in seven large classes, including one comprised of more than five distinct types of antibiotics. Finally, the figures lack independent verification; because these numbers are not provided to a governmental entity, there is no penalty for misreporting nor is there any other indicator of reliability. For all these reasons, these figures are of limited value and utility.

The most detailed figures currently available are estimates published by the Union of Concerned Scientists (UCS) in 2001.[62] We used figures from Table 14 (p. 54) of the UCS report to derive an estimate of the average amount of each feed additive used in producing the total number of animals (separate estimates were developed for each animal type). UCS's Table 14 does not directly present such figures; instead, it presents the total quantity of each drug used nontherapeutically in each animal type. Accordingly, we divided those totals by the 1997 number of animals of each animal type as presented in the UCS report: 92.6 million hogs, 29 million beef cattle, and 7.8 billion chickens.[63] We then multiplied the resulting values by the 2002 figures for the total number of animals of each type produced annually (see above), to yield updated totals for each drug used nontherapeutically in each animal type. See Table A-2 below.

By definition, then, changes in the national totals that we report compared to those reported by UCS reflect *only* the updating of the estimates for the numbers of animals produced. We did *not* attempt to update UCS's calculations for the average amount of feed-additive antibiotics used.

C. Antibiotics in waste

In order to estimate the quantity of each antibiotic present in waste, we determined an "excretion" factor for each drug and each animal type—i.e., the percentage of the parent antibiotic that is not metabolized by the animal and, hence, is present in the feces or urine. It should be noted that excretion factors were not available for all drugs in all animal types. Where possible, we extrapolated from data for similar animal types. If no data at all were available, we used a default value of 50%.

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[61] Animal Health Institute (2004). Survey Shows Antibiotic Use in Animals Declines (press release of Oct. 6, 2004). Available at www.ahi.org/Documents/Antibioticuse2003.pdf (accessed Apr. 19, 2005). The survey reports an 8% decline in total use of antibiotics for all purposes (therapeutic and nontherapeutic) on a combined basis for pets and agricultural animals.

[62] Mellon M, et al. (2001), *op. cit*. Table 14.

[63] The UCS report generally used 1997 data, as those were the most recent then available. The figures are found on the following pages: hogs, p. 37; cattle, p. 29, and chickens, p. 44.

After determining an excretion factor for each drug, we multiplied it by the use-per-animal value (see section B above) to estimate the quantity of each antibiotic expected to be present in each animal's waste. We then multiplied this figure by the number of each animal type per county or state (see section A above) to calculate the total estimated quantity of each antibiotic in waste, per county or state.

For example, if 1,000,000 broiler chickens are raised in a particular county, the total quantity (in pounds) of chlortetracycline estimated to be excreted in the waste of those 1,000,000 broiler chickens is calculated as follows: 1) 0.000182 pounds/chicken (from Table A-2 below) *x* 45% (excretion factor, also from Table A-2 below) = 0.00008185, representing the amount in pounds of chlortetracycline excreted per chicken. 2) This is then multiplied *x* 1,000,000 chickens to yield 81.85 pounds. We made analogous calculations for each of the drugs used as a nontherapeutic feed additive for chickens, hogs and beef cattle. The resulting estimates are presented in three ways: for individual antibiotics in each animal type, summed across all antibiotics used for a given animal type, and summed across the subset of "medically important" antibiotics. Key findings are presented in this report, and the full set of data is available in the spreadsheets posted at www.environmentaldefense.org/go/antibiotic.estimates.

D. Definition of medically important antibiotics and their relationship to feed-additive antibiotics

"Medically important" antibiotics are those that the Food and Drug Administration (FDA) has designated (individually or as a member of a drug class) as "critically important" or "highly important" in human medicine:[64]

- Penicillins[65]
- Aminoglycosides
- Macrolides
- Sulfonamides [67]
- Tetracyclines
- Streptogramins
- Clindamycin/lincomycin[66]

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[64] FDA (2003). *Guidance for Industry #152: Guidance on Evaluating the Safety of Antimicrobial New Animal Drugs with regard to their Microbiological Effects on Bacteria of Human Health Concern.* Available at www.fda.gov/cvm/guidance/fguide152.pdf (accessed Apr. 19, 2005). In our view, this criterion is insufficiently protective of the public health, inasmuch as it fails to capture valuable drugs simply because there are more than a "few" alternative drugs. Given that resistance to existing antibiotics is spreading far more rapidly than new drugs are being developed, this approach is shortsighted. For purposes of this analysis, however, we employ Guidance's categorization of drugs.

[65] The Guidance includes four categories of penicillins: natural penicillins, penase resistant penicillins, antipseudomonal penicillins and aminopenicillins.

[66] Table A1 in Guidance #152 lists clindamycin, which is essentially identical to lincomycin. Clindamycin is the primary form of the human drug, while lincomycin is primarily used in animals. They differ by a single atom group: lincomycin's hydroxyl (OH) group is a chlorine atom in clindamycin. "Antimicrobial Chemotherapy," www.bmb.leeds.ac.uk/mbiology/ug/ugteach/icu8/antibiotics/protein.html (accessed Apr. 19, 2005).

[67] Table A1 of the Guidance designates one member of the sulfonamides class—namely trimethoprim/sulfamethoxazole, abbreviated as "trimeth/sulfameth"—as critically important.

FDA categorizes drugs' importance in human medicine as "critically" or "highly" important based on the following criteria (Guidance #152, Table A1, pp. 30-33):

Critically Important: Antimicrobial drugs which meet BOTH criteria 1 and 2 below.
Highly Important: Antimicrobial drugs which meet EITHER criteria 1 or 2 below.

1. ***Antimicrobial drugs used to treat enteric [gut] pathogens that cause food-borne disease.***

2. ***Sole therapy or one of few alternatives to treat serious human disease or drug is essential component among many antimicrobials in treatment of human disease.***

Specifically, macrolides are "critically important," while penicillins, aminoglycosides, clindamycin/lincomycin, tetracyclines, glycopeptides, and streptogramins are "highly important." One sulfonamide combination drug—namely trimethoprim/sulfamethoxazole—is also designated as "critically important." Human uses of these drugs are described in Appendix 5.

The feed-additive antibiotics discussed in this report are members of these medically important classes as follows:

TABLE A-1
Feed-additive antibiotics by antibiotic class

Antibiotic Class	**Feed-additive antibiotic(s)**
Penicillins	Penicillin
Tetracyclines	Chlortetracycline, Oxytetracycline
Aminoglycosides	Apramycin
Streptogramins	Virginiamycin
Macrolides	Erythromycin, Oleandomycin, Tylosin
Clindamycin (Lincosamide class)	Lincomycin
Sulfonamides	Sulfamethazine, Sulfathiazole

With the exception of one drug (bacitracin), the non-medically important antibiotics included in our estimates are not themselves used in human medicine nor are they members of classes of antibiotics used in human medicine.

TABLE A-2

Excretion Factors

Animal Type	Antibiotic used	Antibiotic Class	Total Use	Per animal use estimate (lbs.):	Excretion factor**	Range of excretion (if applicable)	Excretion per animal (lbs.)	Source of excretion information
Broiler Chickens	Chlor-tetracycline	Tetracycline	1,418,675	1.82×10^{-4}	45.0%	35-55%	8.185×10^{-5}	Van Houweling CD (1978). Draft Environmental Impact Statement Subtherapeutic Antibacterial Agents in Animal Feed. Food and Drug Administration. Prepared by Feinman SE and Matheson III JC, p. A-30 & A-31 (Note: this number is for tetracycline, rather than chlortetracycline in swine).
Broiler Chickens	Bacitracin	Polypeptide	96,728	1.24×10^{-5}	38.25%	.5-77%	4.74×10^{-6}	Van Houweling CD (1978), op. cit., p. A-71 (see BMD on poultry worksheet).
Broiler Chickens	Penicillin	Beta lactam	141,867	1.82×10^{-5}	0.0%		0.00	Van Houweling CD (1978), op. cit., p. A-4.
Broiler Chickens	Lincomycin	Lincosamide	25,794	3.31×10^{-6}	100.0%		3.31×10^{-6}	Van Houweling CD (1978), op. cit., p. A-92 (Note: assumption made in report – excretion is in humans)
Broiler Chickens	Erythromycin	Macrolide	381,753	4.89×10^{-5}	10.0%		4.89×10^{-6}	Calamari E, Zuccato E, Castiglioni S, Bagnati R, and Fanelli R (2003). Strategic survey of therapeutic drugs in the rivers Po and Lambro in Northern Italy. *Environmental Science and Technology* 37: 1241-1248 (Note: excretion rate of erythromycin is for humans).
Broiler Chickens	Virginiamycin	Streptogramin	192,682	2.47×10^{-5}	15.5%	0-31%	3.83×10^{-6}	No data available for virginiamycin in poultry. Used hog excretion number from Van Houweling, CD (1978), op. cit., p. A-83.
Broiler Chickens	Monensin	Ionophore	1,923,723	2.47×10^{-4}	94.0%		2.32×10^{-4}	Donoho AL et al (1982). Excretion and Tissue Distribution of C14 Monensin in Chickens. *Journal of Agriculture and Food Chemistry* 30: 909-913.
Broiler Chickens	Lasalocid	Ionophore	2,238,514	2.87×10^{-4}	12.0%		3.44×10^{-5}	Environmental Assessment 096-298. Available at www.fda.gov/cvm/FOI/096-298EA.pdf.
Broiler Chickens	Roxarsone	Arsenical	1,972,443	2.53×10^{-4}	43.5%	42-45%	1.1×10^{-4}	Van Houweling CD (1978), op. cit., p. A-123.
Broiler Chickens	Amprolium	Vitamin B analogue	789,299	10.12×10^{-5}	50.0%		5.06×10^{-5}	No data available for amprolium - used 50%.

Animal Type	Antibiotic used	Antibiotic Class	Total Use	Per animal use estimate (lbs.):	Excretion factor**	Range of excretion (if applicable)	Excretion per animal (lbs.)	Source of excretion information
Broiler Chickens	Arsanilic acid	Arsenical	371,435	$4.76\text{x}10^{-5}$	76.5%	74-79%	$3.64\text{x}10^{-5}$	Van Houweling CD (1978), op. cit., p. A-122.
Broiler Chickens	Zoalene	Nitrobenzamide	702,631	$9.01\text{x}10^{-5}$	50.0%		$4.50\text{x}10^{-5}$	No data available for zoalene - used 50%.
Broiler Chickens	Salinomycin	Ionophore	232,147	$2.98\text{x}10^{-5}$	2.0%		$5.95\text{x}10^{-7}$	Environmental Assessment 128-686. Available at www.fda.gov/cvm/FOI/128-686EA.pdf.
Broiler Chickens	Ethopabate	Vitamin B analogue	25,072	$3.21\text{x}10^{-6}$	50.0%		$1.61\text{ x}10^{-6}$	No data available for ethopabate - used 50%.
Broiler Chickens	Bambermycin (also known as flavosphopholipol or moenomycin)	Amino-glycoside complex - (phosphorglycolipid.)	23,163	$2.97\text{ x}10^{-6}$	100.0%		$2.97\text{ x}10^{-6}$	Botsoglou NA and Fletouris DJ (2001). *Drug Residues in Foods - Pharmacology, Food safety and Analysis*, p. 33 (Basel, Switzerland: Marcel Dekker, Inc.). (Note: states that studies proved bambermycin is not absorbed and is excreted in feces as intact, biologically active drug).
	Total:		10,535,926					
Hogs	Chlor-tetracycline	Tetracycline	4,007,632	$4.33\text{ x}10^{-2}$	45.0%	35-55%	$1.95\text{ x}10^{-2}$	Van Houweling CD (1978), op. cit., p. A-30 & A-31(Note: this number is for tetracycline, rather than chlortetracycline).
Hogs	Bacitracin	Polypeptide	1,894,450	$2.04\text{ x}10^{-2}$	94.0%		$1.92\text{ x}10^{-2}$	Van Houweling CD (1978), op. cit., p. A-72. See also Donoso J (1970), The distribution and excretion of zinc bacitracin C14 in rats and swine. *Toxicolology & Applied Pharmacology* 17: 366-374. (Note: study noted that couldn't id if bacitracin was parent compound or metabolites in excreta).
Hogs	Tylosin	Macrolide	943,635	$1.02\text{ x}10^{-2}$	67.0%		$6.83\text{ x}10^{-3}$	Van Houweling CD (1978), op. cit., p. A-77.
Hogs	Oxytetracycline	Tetracycline	964,581	$1.04\text{ x}10^{-2}$	60%		$6.25\text{ x}10^{-3}$	WHO Food Additive Series 27. Available at www.inchem.org/documents/jecfa/jecmono/v27je06.htm
Hogs	Sulfathiazole	Sulfonamide	901,251	$9.73\text{ x}10^{-3}$	45%		$4.38\text{ x}10^{-3}$	Koritz G (1975). The pharmacokinetics of sulfathiazole in sheep, cattle and swine. Thesis submittal - Univ. Illinois. (p. 125).
Hogs	Sulfamethazine	Sulfonamide	455,434	$4.92\text{ x}10^{-3}$	25.0%		$1.23\text{ x}10^{-3}$	Van Houweling CD (1978), op. cit., p. A-62 & A-63.
Hogs	Penicillin	Beta lactam	528,777	$5.71\text{ x}10^{-3}$	20.0%		$1.14\text{ x}10^{-3}$	Van Houweling CD (1978), op. cit., p. A-4 (Note: extrapolated from testing in humans).

Animal Type	Antibiotic used	Antibiotic Class	Total Use	Per animal use estimate (lbs.):	Excretion factor**	Range of excretion (if applicable)	Excretion per animal (lbs.)	Source of excretion information
Hogs	Lincomycin	Lincosamide	53,685	5.80 x10^{-4}	100.0%		5.80 x10^{-4}	Van Houweling CD (1978), op. cit., p. A-92. See also Environmental Assessment 097-505. Available at www.fda.gov/cvm/FOI/097-505EA.pdf. (Note: in humans 70-85% excreted – see Van Houweling, p. A-92).
Hogs	Apramycin	Amino-glycoside	39,425	4.26 x10^{-4}	100.0%		4.26x x10^{-4}	Environmental Assessment 126-050. Available at www.fda.gov/cvm/FOI/126-050 EA.pdf. (EA states that very little metabolism of apramycin occurs, so can assume 100% excretion of unchanged product).
Hogs	Virginiamycin	Streptogramin	7,492	8.09 x10^{-5}	15.5%	0-31%	1.25 x10^{-5}	Van Houweling CD (1978), op. cit., p. A-83.
Hogs	Arsanilic acid	Arsenical	169,440	1.83 x10^{-3}	70.0%		1.28 x10^{-3}	Overby, LR and Frost, DV (1960). Excretion Studies in Swine Fed Arsanilic Acid. *J. Animal Science* 19:140-144 (Note: low end number cited in the study was used)
Hogs	Carbadox	Quinoxaline	299,135	3.23 x10^{-3}	74.0%		2.39 x10^{-3}	WHO Food additive series 27 www.inchem.org/documents/jecfa/jecmono/v27je06.htm
Hogs	Efrotomycin	Elfamycin	42,953	4.64 x10^{-4}	68.5%	60-77%	3.18 x10^{-4}	Environmental Assessment 140-818. Available at www.fda.gov/cvm/FOI/140-818EA.pdf (Note: structurally, Elfamycin is an N–methyl hydroxypyridone glucoside)
Hogs	Oleandomycin	Macrolide	33,156	3.58 x10^{-4}	67.0%		2.40 x10^{-4}	Van Houweling, CD (1978), op. cit., p. A-115 (no data available for Oleandomycin, but similar absorption to erythromycin; used excretion rate of tylosin, a macrolide)
Hogs	Bambermycin, also known as Flavosphopho-lipol or moenomycin	Amino-glycoside complex (phospho-glycolipid.)	7,550	8.15 x10^{-5}	100.0%		8.15 x10^{-5}	Botsoglou, NA and Fletouris, DJ (2001), op. cit., p. 33 (Note: stating that studies proved bambermycin is not absorbed and is excreted in feces as intact, biologically active drug).
	Total:		10,348,596					

Animal Type	Antibiotic used	Antibiotic Class	Total Use	Per animal use estimate (lbs.):	Excretion factor**	Range of excretion (if applicable)	Excretion per animal (lbs.)	Source of excretion information
Beef Cattle	Chlor-tetracycline	Tetracycline	588,042	2.02×10^{-2}	75.0%		1.52×10^{-2}	Van Houweling, CD (1978), op. cit., p. A-33. See also Elmund, GK, et al. (1971). Role of excreted chlortetracycline in modifying the decomposition process in feedlot waste. *Bulletin of Environmental Contamination and Toxicology* 6(2): 129-132.
Beef Cattle	Bacitracin	Polypeptide	25,885	8.91×10^{-4}	100.0%		8.91×10^{-4}	Environmental Assessment 046-592. Available at www.fda.gov/cvm/FOI/046-592EA.pdf. (EA states that in experiments with chicken, swine, and other species, bacitracin is largely excreted in feces). See also Botsoglou, NA and Fletouris, DJ (2001), op. cit., p. 185.
Beef Cattle	Tylosin	Macrolide	356,999	1.23×10^{-2}	40.0%		4.92×10^{-3}	Van Houweling, CD (1978), op. cit., p. A-77.
Beef Cattle	Oxytetracycline	Tetracycline	143,478	4.94×10^{-3}	45.0%	35-55%	2.22 x10-3	Van Houweling, CD (1978), op. cit., p. A-30 (Note: this number is for tetracycline rather than oxytetracycline in swine.)
Beef Cattle	Sulfamethazine	Sulfonamide	344,400	1.19×10^{-2}	22.0%		2.61 x10-3	Huber W (1977). Sulfonamides (Chapter 46) in *Veterinary Pharmacology and Therapeutics*, 4th ed. Jones, LM ed. Iowa State University Press, p. 902 (note – figure given is for sulfamethazine in sheep intravenously).
Beef Cattle	Erythromycin	Macrolide	18,181	6.26×10^{-4}	60.0%		3.76×10^{-4}	Environmental Assessment 012-123. Available at www.fda.gov/cvm/FOI/012-123EA.pdf (specifically for injectable Erythromycin).
Beef Cattle	Monensin	Ionophore	1,343,900	4.63×10^{-2}	50.0%		2.31×10^{-2}	Environmental Assessment 95-735. Available at www.fda.gov/cvm/FOI/095-735EA.pdf.
Beef Cattle	Lasalocid	Ionophore	841,823	2.90×10^{-2}	50.0%		1.45×10^{-2}	No data available for lasalocid - used 50%.
Beef Cattle	Amprolium	Vitamin B analogue	29,049	1.00×10^{-3}	50.0%		5.00×10^{-4}	No data available for amprolium - used 50%.
	Total***:		3,691,757					

*** Note: the total for cattle listed in this table does not match the total listed in table 14 of Mellon et al. 2001 (*Hogging It*) because totals for decoquinate are not included since this drug is only used in veal, and the calculations presented here do not include veal.
All URLs cited in this table were accessed Apr. 20, 2005.

APPENDIX 2

Bacteria, antibiotics and antibiotic resistance—the basics[68]

Bacteria are everywhere. They are found by the millions on our skin, in our digestive tract, throughout the environment (in air, water and soil), and on the things we touch every day. Most are harmless, and many are helpful because they compete with disease-causing bacteria, known as *pathogens*.

It is pathogenic bacteria that get most of the attention. They cause a remarkable variety of ailments, ranging from pneumonia, ear infections, meningitis, urinary tract infections and food poisoning, to skin, bone and bloodstream infections. Many types of bacteria are able to cause a range of different illnesses depending on what part of the body they invade. For example, *Streptococcus pneumoniae* causes not only pneumonia, as its name suggests, but also ear infections and meningitis. Conversely, some infections can be caused by several different bacteria and other microorganisms. Pneumonia, for instance, is a lung infection that can be caused not only by *Streptococcus pneumoniae* but also *Staphylococcus aureus, Legionella*, *Hemophilus influenzae* and many other microorganisms.[69] This is one reason that it is difficult to combat infectious diseases: different organisms can produce similar symptoms but must be treated with different antibiotics.

Most bacterial diseases are short-term but researchers continue to discover that bacteria cause or contribute to certain chronic conditions as well. For example, many ulcers are caused by bacteria and can be treated with antibiotics.[70] Researchers are currently examining the role bacteria may play in other chronic conditions such as some types of arthritis[71] and heart disease.[72]

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[68] This is a brief summary of a complex topic. For additional information see Levy, SB (1998). The Challenge of Antibiotic Resistance. *Scientific American* March 1998: 46-53. Available at www-biology.ucsd.edu/classes/bild30.FA04/antibiotic_resistance.pdf (accessed Apr. 19, 2005). See also Goforth RL and Goforth CR (2000). Appropriate Regulation of Antibiotics in Livestock Feed. *Boston College Environmental Affairs Law Review* 28: 39–77.

[69] Levison ME (2001). "Pneumonia, Including Necrotizing Pulmonary Infections (Lung Abscess)," in *Harrison's Principles of Internal Medicine*, 15th ed., Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, and Jameson JL, eds. New York: McGraw-Hill, p. 1475.

[70] De Boer WA and Tytgat GN (2001). "Regular Review: Treatment of *Helicobacter pylori* Infection," *British Medical Journal* 320: 31–34. Available at http://bmj.com/cgi/content/full/320/7226/31?view=full&pmid=10617524 (accessed Apr. 19, 2005).

[71] Wilkinson NZ, Kingsley GH, Jones HW, Sieper J, Braun J, and Ward ME (1999). "The Detection of DNA from a Range of Bacterial Species in the Joints of Patients with a Variety of Arthritides Using a Nested, Broad-Range Polymerase Chain Reaction," *Journal of Rheumatology* 38: 260-66. Available at http://rheumatology.oupjournals.org/cgi/reprint/38/3/260 (accessed Apr. 19, 2005)

[72] Campbell LA, Kuo CC, Grayston JT (1998). *Chlamydia pneumoniae* and Cardiovascular Disease. *Emerging Infectious Disease* 4(4): 571-9. Available at www.cdc.gov/ncidod/eid/vol4no4/adobe/campbell.pdf (accessed Apr. 19, 2005).

To fight bacteria, antibiotics target specific parts of their structure or machinery. While over 100 antibiotics are now available in the United States for use in treating human illness, most of the clinically important antibiotics fall into about a dozen classes of fairly similar compounds.[73] Often, if a strain of bacteria develops resistance to one member of the class, it develops at least partial resistance to some or all other members of that class as well. Typically, antibiotics affect not only the "target" bacteria—those causing the illness that the antibiotic is intended to treat or prevent—but also a wide array of bacteria that are just innocent bystanders.[74] Some antibiotics, known as broad-spectrum drugs, kill a particularly wide array of bacteria, while narrow-spectrum drugs are more targeted in their action.

Bacteria become resistant to antibiotics when they change, or mutate, in ways that reduce or erase the antibiotics' effect on them (it is the bacteria, not the host, that become resistant to antibiotics).[75] Put another way, resistance is the ability of bacteria to survive and even multiply despite the presence of an antibiotic at levels that previously could kill the bacteria or inhibit their growth.

When bacteria are first exposed to an antibiotic, those most susceptible to it die quickly, but the bacteria that survive pass on their ability to resist to succeeding generations. As noted above, bacteria are remarkably numerous; they are also astonishingly prolific. Indeed, in some species, a single bacterium can produce a *billion* offspring in a single day under optimal conditions. Thus, even if initially no bacteria are able to survive the onslaught of an antibiotic, the random mutation of the bacteria's DNA will produce a wide variety of genetic changes, some of which—sooner or later—will almost inevitably confer resistance. This may happen in one of several ways:

- The bacteria's outer membranes may change in such a way that it no longer allows the antibiotic to enter the cell.
- The bacteria may develop biochemical pumps that remove the antibiotic from the bacteria before it can reach its target within the bacterial cell.
- The bacteria's receptors may change so that the antibiotic can no longer engage them.
- The bacteria may create enzymes that deactivate the antibiotic.[76]

The problem of resistance is exacerbated by the fact that, unlike higher organisms, bacteria can transfer their DNA to other bacteria that are not their offspring—even to members of entirely unrelated species. Most frequently, such

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[73] Alliance for Prudent Use of Antibiotics (2001). "Table of Common Antibiotics." Available at www.tufts.edu/med/apua/Miscellaneous/common_antibiotics.html (accessed Apr. 19, 2005).

[74] Levy, SB (1998). The Challenge of Antibiotic Resistance. *Scientific American* March 1998: 46-53. Available at www-biology.ucsd.edu/classes/bild30.FA04/antibiotic_resistance.pdf (accessed Apr. 19, 2005).

[75] Centers for Disease Control and Prevention (July 2000). "Antimicrobial Resistance—Glossary," Available at www.cdc.gov/drugresistance/glossary.htm (accessed Apr. 19, 2005).

[76] Barker KF (1999). "Antibiotic Resistance: A Current Perspective," *British Journal of Clinical Pharmacology 48*: 109–24.

transfer occurs via a *plasmid*, a small circle of DNA that is not part of the bacteria's regular DNA (which is found in its chromosomes). In effect, bacteria can teach one another how to outwit antibiotics. Plasmid transfer is by no means rare. In fact, as one leading expert noted, "The exchange of genes is so pervasive that the entire bacterial world can be thought of as one huge multicellular organism in which the cells interchange their genes with ease."[77] This phenomenon can occur in the environment and has been documented in the human intestine.[78]

Thus, even if the bacteria that first become resistant do not cause disease, they can transfer their resistance genes to other types of bacteria that do. In short, the problem of antibiotic resistance is not just confined to resistant *germs*, but rather encompasses *all* resistance *genes*, in any type of bacteria. Moreover, many plasmids carry several resistance genes, leading to "superbugs" that are able to simultaneously withstand three, four, or even more classes of antibiotics. These superbugs pose some of the toughest challenges to disease treatment today.

Given that resistance to antibiotics is already so widespread, an important question is whether antibiotic resistance is reversible. That is, once resistant bacteria become prevalent, will they become less so if the use of antibiotics is reduced? Fortunately, the answer seems to be yes, at least in some instances. For example, a campaign in Finland to lower the resistance to erythromycin in certain kinds of infections by reducing its use almost halved the incidence of resistance in those bacteria to that drug.[79] Similarly, researchers in Denmark compared the levels of resistant bacteria in chickens just before and shortly after antibiotic use in chickens was sharply restricted in that country. The researchers found that the fraction of bacteria in chickens resistant to one drug (avoparcin) plummeted from nearly 73% to just over 5% in a five-year period. Resistance to another drug (virginiamycin) dropped from more than 66% in 1997 to less than 35% in 2000.[80]

Although even the most careful use of antibiotics can eventually produce antibiotic-resistant bacteria, the widespread, indiscriminate or inappropriate use of an antibiotic hastens the moment when it loses its ability to treat disease. Put more colloquially, the more you use them, the faster you lose them. Thus, a key strategy in combating antibiotic resistance is using antibiotics as sparingly as possible—and only where truly needed.

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[77] Levy (1998), *op. cit.*, p. 3.

[78] Shoemaker NB, Vlamakis H, Hayes K, and Salyers AA (2001). "Evidence for Extensive Resistance Gene Transfer among *Bacteroides* spp. and among *Bacteroides* and Other Genera in the Human Colon," *Applied and Environmental Microbiology* 67: 561–68. Available at www.pubmedcentral.nih.gov/articlerender.fcgi?artid=92621 (accessed Apr. 19, 2005).

[79] Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, et al. (1997). "The Effect Changes in the Consumption of Macrolide Antibiotics on Erythromycin Resistance in Group Streptococci in Finland," *New England Journal of Medicine* 337(7): 441–46. Available at http://content.nejm.org/cgi/content/abstract/337/7/441 (accessed Apr. 19, 2005).

[80] Aarestrup FM, Seyfarth AM, Dorth-Emborg H, Pedersen K, Hendriksen RS, and Bager F. (2001). "Effect of Abolishment of the Use of Antimicrobial Agents for Growth Promotion on Occurrence of Antimicrobial Resistance in Fecal Enterococci from Food Animals in Denmark," *Antimicrobial Agents and Chemotherapy* 45: 2054–59. Available at www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=11408222 (accessed Apr. 19, 2005).

Food as a pathway for resistance-gene spread[81]

Resistant bacteria can contaminate carcasses during slaughter and wind up on raw meat that reaches the consumer (whether in a private home, restaurant or institutional kitchen).[82] If the meat is not cooked thoroughly, if cutting boards or knives are not thoroughly washed before being used for other food, or if raw meat juices are splashed onto other food or utensils, these bacteria can infect people who eat the food or use the utensils.[83]

Contamination of raw meat with resistant bacteria is by no means rare, as shown by studies of meat and poultry purchased in locations around the United States.[84] Moreover, avoiding exposure to bacteria on meat is no easy feat. Even cleaning the kitchen can spread bacteria,[85] and experts now advise consumers not to rinse meat before it is cooked, because rinsing can spread potentially dangerous microbes.[86]

Similarly, foodborne illness is not uncommon. For example, *Salmonella* and *Campylobacter* from foodborne sources cause millions of illnesses and hundreds of

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[81] The problem of resistant bacteria *on* meat is sometimes confused with the issue of antibiotic residues *in* meat. FDA has established maximum levels for the amount of antibiotic residues allowed in meat and poultry; the scant data now available suggest that residues are not generally a problem. However, this in no way alleviates concern about the spread of resistant bacteria via food, workers or the environment.

[82] Barkocy-Gallagher GA, Arthur TM, Siragusa GR, Keen JE, Elder RO, Laegreid WW, and Koohmaraie (2001). Genotypic Analysis of *Escherichia coli* O157:H7 and O157 Nonmotile Isolates Recovered from Beef Cattle and Carcasses at Processing Plants in the Midwest States of the United States. *Applied and Environmental Microbiology* 67: 3810–18. Millemann Y, Gaubert S, Remy D, and Colmin C (2000). Evaluation of IS*200*-PCR and Comparison with Other Molecular Markers to Trace *Salmonella enterica* subsp. *enterica* Serotype typhimurium Bovine Isolates from Farm to Meat. *Journal of Clinical Microbiology* 38(6): 2204–09.

[83] World Health Organization (1999). Basic Food Safety for Health Workers, p.33, 40-41. Available at www.who.int/foodsafety/publications/capacity/en/3.pdf (accessed Apr. 19, 2005).

[84] Price LB, Johnson E, Vailes R, and Silbergeld EK (2005). Fluoroquinolone-Resistant Campylobacter Isolates from Conventional and Antibiotic-Free Chicken Products. *Environmental Health Perspectives* 113(5):557-560. Available at http://ehp.niehs.nih.gov/members/2005/7647/7647.pdf (accessed May 15, 2005). Donabedian SM, Thal LA, Hershberger E, Perri MB, Chow JW, and Bartlett P (2003). Molecular characterization of gentamicin-resistant Enterococci in the United States: evidence of spread from animals to humans through food. *Journal of Clinical Microbiology* 41(3):1109-13. Hayes JR, English LL, Carter PJ, Proescholdt T, Lee KY, Wagner DD, and White, DG (2003). Prevalence and antimicrobial resistance of enterococcus species isolated from retail meats. *Applied and Environmental Microbiology* 69(12):7153-7160. Available at http://aem.asm.org/search.dtl (accessed Apr. 19, 2005). White DG, Zhao S, Sudler R, Ayers S, Friedman S, Chen S, McDermott PF, McDermott S, Wagner DD, and Meng J (2001). The isolation of antibiotic-resistant salmonella from retail ground meats. *New England Journal of Medicine* 345(16):1147-1154.

[85] Hesser, "Squeaky Clean? Not Even Close," *New York Times*, Jan. 28, 2004.

[86] U.S. Department of Agriculture, 2005 Dietary Guidelines Advisory Committee, Food Safety section. Available at www.health.gov/dietaryguidelines/dga2005/report/ (accessed Apr. 19, 2005).

deaths annually in the United States;[87] while recent data suggest that rates of foodborne illness are falling, the proportion of resistant illnesses is continuing to rise.[88]

The data required to trace an outbreak of resistant illness back to a specific facility are seldom collected. However, some data have been collected in Denmark. There, eleven patients were hospitalized and 2 died in a 1998 outbreak of multidrug-resistant *Salmonella* food poisoning that was traced back to a swine herd.[89]

While most food-borne illnesses are of the "stomach bug" variety, recent research indicates that resistant bacteria that cause urinary tract infections may in some instances be transmitted by food.[90] The authors of one of these studies noted that "the possibility that human drug-resistant UTI could be a foodborne illness has serious public health implications," given that urinary tract infections may result in permanent kidney damage.

Moreover, a growing body of data indicates that resistant illnesses are often more virulent as well. As one group of experts recently noted, "Recent studies have demonstrated that anti[biotic] resistance among foodborne bacteria, primarily *Salmonella* and *Campylobacter*, may cause prolonged duration of illness, bacteremia [the presence of bacteria in blood], hospitalization, and death."[91]

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[87] Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, Griffin PM, and Tauxe RV (1999). Food-Related Illness and Death in the United States. *Emerging Infectious Diseases* 5:607–25. Available at www.cdc.gov/ncidod/EID/vol5no5/mead.htm (accessed Apr. 19, 2005).

[88] Vugia D, Cronquist A, Hadler J, Tobin-D'Angelo M, et al. (2005). Preliminary FoodNet Data on the Incidence of Infection with Pathogens Transmitted Commonly Through Food – 10 Sites, United States, 2004. *CDC Morbidity and Mortality Weekly Report,* 54(14):352-356 (April 15, 2005). Available at www.cdc.gov/mmwr/preview/mmwrhtml/mm5414a2.htm (accessed April 20, 2005).

[89] Molbak K, Baggesen DL, Aarestrup FM, et al. (1999). An outbreak of Multidrug-resistant, Quinolone-resistant *Salmonella enterica* serotype typhimurium DT104. *New England Journal of Medicine* 341(19): 1420-1425.

[90] Manges AR, Johnson JR, Foxman B, O'Bryan TT, Fullerton KE, and Riley LW (2001). Widespread Distribution of Urinary Tract Infections Caused by a Multidrug-Resistant Escherichia coli Clonal Group. *New England Journal of Medicine* 345(14):1007–13. Ramchandani M, Manges AR, DebRoy C, Smith SP, Johnson JR, and Riley LW (2005). Possible Animal Origin of Human-Associated, Multidrug-Resistant, Uropathogenic Escherichia coli. *Clinical Infectious Diseases*. 40(2): 251. Available at www.journals.uchicago.edu/CID/journal/issues/v40n2/34442/brief/34442.abstract.html (accessed Apr. 12, 2005).

[91] Department of Health and Human Services, comments included as Appendix VII (p.89 ff) in Government Accountability Office (2004), *Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals*, Report no. GAO-04-490. Available at www.gao.gov/new.items/d04490.pdf (accessed Apr. 19, 2005).

APPENDIX 4

Waste-management practices[92]

The 8.6 billion chickens, 100 million hogs and 29 million beef cattle produced in the United States each year[93] generate more than three times as much biological waste as the nation's human population.[94] But while human waste is generally treated in sewage-treatment or septic systems, most animal waste is directly applied to land with only minimal treatment. Agricultural waste-management practices differ by type of animal, and to some extent, in response to state and local requirements.

In theory, most animal waste is utilized as "fertilizer." While animal waste contains nutrients such as nitrogen and phosphorous, in many locations the quantity of waste far exceeds the capacity of the available land to absorb it.[95] All too often, waste is over-applied on nearby land simply to get rid of it as inexpensively as possible. The unabsorbed material can then contaminate surface waters—not only with nutrients but also with antibiotic-resistant bacteria and with undigested antibiotics. Even if waste is not over-applied on land (i.e., application rates properly reflect the land's ability to absorb the nutrients), such application nonetheless disperses resistant bacteria and undigested antibiotics in the soil. Resistant bacteria have also been detected in air at animal-agriculture facilities,[96] suggesting that airborne releases may also occur after land application of wastes.

Broiler Chickens

Production of broiler chickens (those raised for human consumption) is "vertically integrated," meaning that large poultry companies control nearly every

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[92] Except where otherwise noted, materials in Appendix 4 are drawn from the following source: EPA (2001), *Development Document for the Proposed Revisions to the National Pollutant Discharge Elimination System Regulation and the Effluent Guidelines for Concentrated Animal Feeding Operations.* EPA-821-R-01-003.

[93] See Appendix 1 for description of the derivation of these figures.

[94] Environmental Protection Agency (2003). Final Rule: National Pollutant Discharge Elimination System Permit Regulation and Effluent Limitation Guidelines and Standards for Concentrated Animal Feeding Operations (CAFOs). 70 Fed. Reg. 7176, 7180 (Feb. 12, 2003). Available at www.epa.gov/npdes/regulations/cafo_fedrgstr.pdf (accessed Apr. 19, 2005).

[95] For example, more than 50% of large swine facilities lack sufficient land for absorbing the nitrogen content of the waste.

[96] Chapin A, Rule A, Gibson K, Buckley T, and Schwab K (2004). Airborne Multi-drug Resistant Bacteria Isolated from a Concentrated Swine Feeding Operation. Environmental Health Perspectives Online 22 November 2004, doi:10.1289/ehp.7473. Available at http://ehp.niehs.nih.gov/members/2004/7473/7473.pdf (accessed Apr. 19, 2005). Zahn JA, Anhalt J, Boyd E (2001). Evidence for transfer of tylosin and tylosin-resistant bacteria in air from swine production facilities using sub-therapeutic concentrations of tylan in feed. *Journal of Animal Science* 79 (supplement 1):189 (abstract #783). Available at www.asas.org/jas/jointabs/iaafsc83.pdf (accessed Apr. 10, 2005).

part of the process.[97] In this system, the farmer supplies the buildings, electricity, water, fuel, bedding material, his or her labor, and the management and disposal of the waste. The poultry company supplies the chicks, feed and medication. Broilers are generally raised for 42 to 56 days. Typically, 25,000 – 30,000 broilers are housed in a structure approximately 40 feet wide by 400 to 500 feet long. The floor is usually an impermeable surface, over which bedding derived from wood shavings, rice hulls, chopped straw, peanut hulls or other materials is spread. Most newer houses have automatic feed and water systems and some sort of ventilation system. Between flocks, the top one-inch or so of the bedding material, called the "cake," is removed and a thin layer of new bedding material is added. The cake is typically stored for six months or more outdoors in an uncovered pile. Some states regulate manure storage to some degree (though compliance with such regulations is not necessarily complete). Virginia, for example, requires the stockpiled poultry litter to be covered and protected from storm water runoff as well as located away from the high-water table. In general, litter is only completely cleaned out after an average of 12-15 flocks have occupied the house.[98]

The great majority of chicken waste is utilized as "fertilizer."[99] The material is usually removed with a front-end loader or bobcat and then spread on the field by a truck. Alternative technologies may be used. For example, in some instances, the waste is heat-treated and pelletized prior to use as fertilizer,[100] though data on the extent of use of this and other practices are not available.

Hogs

The swine industry is approaching the degree of vertical integration found in poultry, with large swine companies controlling most aspects of the process.[101] As with poultry, waste management is the responsibility of the individual farmer. Swine are raised in various stages. Breeders or farrowing operations have sows (female swine) that give birth to the piglets, generally in confinement operations. Between three and four weeks of age, piglets are typically weaned from the mothers and moved to a nursery operation where they reach approximately 50 pounds. They are finally transferred to a grower-finisher operation where they are

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[97] National Academy of Sciences/National Research Council (1999). *The Use of Drugs in Food Animals: Benefits and Risks,* p. 30. Washington, DC: National Academy Press. Available at www.nap.edu/books/0309054346/html/30.html (accessed Apr. 19, 2005).

[98] Williams CM, Barker JC, and Sims JT (1999). Management and Utilization of Poultry Wastes. *Reviews of Environmental Contamination and Toxicology* 162: 105-157.

[99] A percentage of poultry litter was previously fed to cattle as a feedstuff, but this practice has been recently banned in light of concerns about BSE. U.S. Department of Health and Human Services. January 26, 2004. Press Release: Expanded "Mad Cow" Safeguards Announced To Strengthen Existing Firewalls Against BSE Transmission. Available at www.hhs.gov/news/press/2004pres/20040126.html (accessed Apr. 19, 2005).

[100] Delaware Division of Natural Resources (no date). Perdue-AgriRecycle Poultry Manure Pelletization Plant. Available at www.dnrec.state.de.us/water2000/Sections/Watershed/ws/trib_times_2003_2_nc_perdue.htm (accessed Apr. 19, 2005).

[101] National Academy of Sciences/National Research Council (1999), *op. cit.*

raised to slaughter weight (usually between 240 and 280 pounds), at approximately 26 weeks of age. There are also combined operations that are known as “farrow-to-finish” operations where all stages are conducted on the same site, as well as “wean-to-finish” operations that handle animals only from weaning to slaughter.

A typical confinement farrowing facility houses 3,000 sows, although some house as many as 10,000. The typical size of a farrowing pen is 5 by 7 feet, with the sow separated from the piglets by guardrails low enough to allow for suckling by piglets. Floors are usually slatted underneath or to the rear of the sow’s area to provide for waste removal. In contrast to chicken facilities, which are usually fully cleaned only once every 12-15 flocks as noted above, nursery operations are typically fully cleaned between each group of piglets. In most large grower-finisher facilities, concrete flooring with open slats allows the waste to drop through to pits or troughs below the pen. The waste is then moved to a storage area either via a pit recharge system, where the waste is periodically drained by gravity and recharged with new or recycled water, or a flush system where fresh or recycled water is used to flush out the waste several times a day. At small facilities, waste is typically gathered from pens by hand.

The type of manure storage and application system used varies between regions of the country. In the Southeast, open lagoons are the most common type of storage, though some larger operations have below-floor pit storage from which waste is periodically transferred outside to lagoons or aboveground storage containers. As a lagoon or storage container becomes full, it is pumped out and a sprinkler irrigation system is used to spread manure onto fields.[102]

In the Midwest, larger operations typically use lagoon storage systems, while medium ones typically use deep pit storage with transfer to aboveground storage (smaller operations, ones with fewer than 500 pigs, primarily utilize hand labor).[103] The manure from the storage pits or lagoons is transferred to slurry spreaders and spread onto the field and/or injected into the soil. Open anaerobic lagoons are the most common types of lagoons and involve anaerobic breakdown of wastes. They are usually designed to fill to capacity within two to three years. Deep pit manure storage facilities are approximately six to eight feet deep and provide for up to six months of storage underneath the swine house. Most of the manure is spread onto land owned or rented by the operator.

In addition to intentional application of manure to land, leakage or overflow from hog lagoons is common. During the past several years, lagoons in North Carolina, Iowa, Illinois, Minnesota, Virginia and several other states have experienced major spills or leaks. For example, in 1995, a lagoon in North Carolina broke and spilled 20 million gallons of hog waste into the New River.[104]

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[102] Economic Research Service/USDA (no date). Economic and Structural Relationships in U.S. Hog Production. AER-818. Available at www.ers.usda.gov/publications/aer818/aer818f.pdf (accessed Apr. 19, 2005).

[103] *Ibid.*

[104] *Ibid.*

Beef Cattle

Beef is the least vertically integrated of the animal sectors. Cattle production consists of two primary stages: the first occurs at the "cow-calf" operation and the second at the feedlot. Most cow-calf operations are operated as stand-alones (i.e., not in conjunction with a particular feedlot). After birth, cows nurse their calves until weaning, which occurs when the calves are approximately seven months old. During this time, cows typically graze on open pasture, and calves begin to do so as they approach weaning. Once weaned, calves are put through a "backgrounding" process lasting about 45 days; they continue to graze but also receive a high-protein, high-energy diet to accustom them to the high-grain diet they will receive at the feedlot. Although cows and their calves spend most of their time outdoors, barns or windbreaks may be available to protect them from extreme weather. After backgrounding, animals are usually shipped to beef feedlots—typically hundreds of miles away—where they are fed to maximize growth for a period of about a year.[105]

Most beef feedlots are open, unpaved areas, though some are partially or entirely paved. Most feedlots are on mounded areas to improve drainage. Cattle are usually fed two or three times a day, by truck, automated system, or (in smaller operations) by manual distribution of feed.

Much of the waste on feedlots is concentrated around the water and feed troughs. Feedlot waste is usually collected between herds. The most common method used to clean out the waste involves using a scraper with a front-end loader. Less frequently, a flushing system may be used. In this system a large amount of water is used to flush the manure down the sloped surface to a storage area where the waste may be transferred to a storage lagoon or basin.

After collection, the waste is transported to storage, treatment, use or disposal areas. Most feedlots have a settling basin to allow the liquid to separate from the solids, before it enters a storage pond. (At some facilities, composting or mechanical solids separation is employed but these techniques do not appear to be widely used.) Subsequently, the waste is spread as "fertilizer." As with chicken and swine facilities, many beef feedlots do not own enough land to absorb all of the waste generated, and over-application is not uncommon.

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[105] National Academy of Sciences/National Research Council (1999), *op. cit.*

APPENDIX 5

Important clinical uses of feed-additive antibiotics[106]

Drugs belonging to seven classes of antibiotics that are used as agricultural feed additives have been designated by the U.S. Food and Drug Administration as "critically important" or "highly important" in human medicine: penicillins, tetracyclines, macrolides, lincosamides, streptogramins, aminoglycosides, and sulfonamides.[107] Significant human clinical uses of drugs in these classes are described below.

Penicillins

For the past sixty years, penicillins have been effective treatments for bacterial infections. The penicillin class includes not only natural penicillins, but also penicillinase-resistant penicillins, antipseudomonal penicillins, and aminopenicillins. (Guidance 152 explicitly lists all four types of penicillins as "highly important" for human medical use.) The latter three categories have been developed in part to treat bacterial infections already resistant to the original, natural penicillins.

NATURAL PENICILLINS remain the antibiotic of choice for certain types of bacterial meningitis (infection of the membranes that line the brain and nervous system), neurosyphilis (syphilis infection of the brain and spinal tract), and strep throat. They are also the antibiotic of choice for serious infections such as endocarditis (infection of heart valves), toxic shock syndrome, and tetanus.

PENICILLINASE-RESISTANT PENICILLINS are vital to treating infections of the skin, including burn wounds, and for serious infections of bones, joints and heart valves.

ANTIPSEUDOMONAL PENICILLINS are essential for treating skin infections in diabetics, hospital-acquired infections, infections in cancer patients with neutropenia (low white-cell counts), and burn patients, among other uses.

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[106] This Appendix was compiled primarily from Medline and the Merck Manual, both of which are widely used reference sources. Medline, a service of the U.S. National Library of Medicine, is available at www.nlm.nih.gov/medlineplus/druginfo/uspdi/202027.html (accessed Apr. 19, 2005). The Merck Manual of Diagnosis and Therapy is available at www.merck.com/mrkshared/mmanual/home.jsp (accessed Apr. 19, 2005). The assistance of Tamar Barlam, M.D., of Boston University School of Medicine in preparing this Appendix is gratefully acknowledged. Dr. Barlam is board-certified in Infectious Disease.

[107] Food and Drug Administration (2003). Guidance for Industry #152: Guidance on Evaluating the Safety of Antimicrobial New Animal Drugs with regard to their Microbiological Effects on Bacteria of Human Health Concern. Available at www.fda.gov/cvm/guidance/fguide152.pdf (accessed Apr. 19, 2005).

AMINOPENICILLINS are first line treatments for respiratory tract infections, urinary tract infections, bacterial meningitis, septicemia (blood-stream infections), and endocarditis if caused by susceptible organisms.

Tetracyclines

Tetracyclines are used primarily in treating upper respiratory tract infections. They are also the drugs of choice for Lyme disease, atypical pneumonia, certain sexually transmitted diseases, and sometimes for prevention of anthrax in people potentially exposed to anthrax spores.

Macrolides

Macrolides, which include erythromycin, are first line treatments for upper respiratory infections like sinusitis or bronchitis, and are often used in patients with penicillin allergies, such as allergic children with strep throat. Macrolides are also essential for treatment of diarrheal disease due to *Campylobacter* (bacteria that can cause severe food poisoning), treatment of community-acquired pneumonia including pneumonia *Legionella pneumophila* (Legionnaire's Disease), treatment of whooping cough in children and adults, and treatment and prevention of certain secondary infections (e.g., Mycobacterium avium) in patients with AIDS.

Lincosamides

Clindamycin, the human-use drug in the lincosamide class, is vital in the treatment of skin infections, respiratory tract infections, toxic shock syndrome, abdominal infections, and gynecologic infections. It is also used for the topical treatment of severe acne. (The animal-use drug lincomycin is essentially identical to clindamycin, differing only by one atom).

Streptogramins

The streptogramin class contains Synercid, the human drug closely related to the animal drug virginiamycin. It is one of the very few drugs that can be used in patients with infections due to highly resistant forms of *Staphylococcus aureus* and *Streptococcus pyrogenes,* as well as vancomycin resistant *Enterococcus faecium.* These bacteria cause infections of the skin, gastrointestinal tract and abdominal cavity, as well as systemic sepsis (blood poisoning).

Aminoglycosides[108]

Aminoglycosides are used for the treatment of severe infections of the abdomen and urinary tract, as well as bacteremia (invasion of the bloodstream by bacteria), and endocarditis (an infection of the heart's inner lining or the heart valves). Aminoglycosides may also be given for treatment of tuberculosis (TB).

Sulfonamides

Sulfonamides are currently used to treat urinary tract infections (UTIs) and to treat skin infection in burn patients. Sulfonamides are also used in combination with the drug trimethoprim to treat several types of bacterial diarrhea, *Nocardia* infection (a disorder that affects the lungs, brain, and skin and occurs primarily in individuals with weakened immune systems), ear infections (otitis media), acute exacerbations of chronic bronchitis and are drugs of choice to treat pneumocystis pneumonia in HIV-infected patients and other immunocompromised patients.

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[108] Gonzalez and Spencer (1998). Aminoglycosides: A Practical Review. *American Family Physician* 58(8). Available at www.aafp.org/afp/981115ap/gonzalez.html (accessed Apr. 19, 2005).