SIGNIFICANT SCIENCE ON ANTIBIOTIC RESISTANCE: AN ANNOTATED BIBLIOGRAPHY

Overwhelming scientific evidence now indicates that bacteria are developing antibiotic resistance as a result of antibiotic use in animal agriculture. Evidence has accumulated despite the inadequate public health monitoring and surveillance programs in the United States. There is every reason to believe that as further studies are done, and as monitoring improves, the link between antibiotic use in agriculture and the emergence of difficult-to-treat disease will only become more evident. Since antibiotic resistance is worsening in the interim, many public health organizations and experts are calling for action now to limit antibiotic overuse in agriculture to protect public health.

- **Antibiotic Resistance Generally**
- **Agricultural Use of Antibiotics and Antibiotic Resistance**
- **Evidence for Resistant Bacteria Transferred from Animal Agriculture to Humans**
- **Evidence that Livestock Drug Use Puts Farmers and Rural Residents at Increased Risk for Resistant Infections and other Health Hazards**
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**Antibiotic Resistance Generally**--The following articles provide an overview of the general problem of antimicrobial resistance and its impacts on public health.


**Agricultural Use of Antibiotics and Antibiotic Resistance**-- The following articles provide a good overview of the link between animal drug use and the public health risk.


10. Collignon, P. *The Use of Antibiotics in Food Production Animals: Does This Cause Problems in Human Health?* A review by Peter Collignon, Infectious Diseases Physician and Microbiologist, Director Infectious Diseases Unit and Microbiology Department, The Canberra Hospital.


15. National Academy of Sciences/Institute of Medicine Global Board on Health, Microbial Threats to Health: Emergence, Detection, and Response. National Academies Press. 2003. The report succinctly summarizes data on agricultural use of antibiotics, concluding that "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 of antimicrobials in animals and agriculture as well.”


17. Alliance for the Prudent Use of Antibiotics, The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences. Clinical Infectious Diseases 2002; 34: S71-144. Over a two-year period, a panel of experts in human and veterinary medicine, public health, microbiology, and other disciplines reviewed more than 500 studies relating to agricultural uses of antibiotics. The panel concluded that "elimination of nontherapeutic use of antimicrobials in food animals and agriculture will lower the burden of antimicrobial resistance.”


21. Salyers A. How are human and animal ecosystems interconnected? Ontario Ministry of Agriculture, Food and Rural Affairs. Discusses the debate over agricultural use of
antibiotics as growth promoters, whether antibiotic use in agriculture selects for resistant bacteria, the potential impact on farmers and their animals, antibiotic-resistant bacteria in the food supply, and the transfer of resistance genes in the human colon.

Evidence for Resistant Bacteria Transferred from Animal Agriculture to Humans-- These articles provide some of the evidence showing that resistance in bacteria from animals can lead to resistant infections in humans.


4. Unicomb, Leanne E. et al. Low-Level Fluoroquinolone Resistance among *Campylobacter jejuni* Isolates in Australia. CID 2006. 42:1368-1374. Australia never approved the use of fluoroquinolone drugs for use in livestock and this is reflected in low resistance to the drug in Campylobacter isolated from humans. Two percent of Australian campylobacter isolates are resistant to fluoroquinolones. This is in contrast to the U.S. where 20% of isolates were resistant or Southern European countries where resistance is much higher.

5. Ramchandi, Meena et al. Possible Animal Origin of Human-Associated, Multidrug-Resistant, Uropathogenic *Escherichia coli*. CID 2005. 40:251-7. In response to a multistate outbreak of drug resistant urinary tract infections, the authors examined E. coli from animals and found the same strain supporting the view that the bacteria were transmitted from animal to people through food.

6. Gupta, Amita et al. Emergence of Multidrug-Resistant Salmonella enterica Serotype Newport Infections Resistant to Expanded-Spectrum Cephalosporins in the United States. JID 2003; 188:1707-1716. Reports on CDC field investigation of multistate outbreak of multi-drug resistant Salmonella infections. The researchers found that exposure to a dairy farm or food contaminated from the farm was the major risk factor for acquiring this resistance infection.


8. Van der Bogaard Anthony, Ellen E. Stobberingh. Epidemiology of resistance to antibiotics: Links between animals and humans. International J. Antimicrobial Agents. 2000. 14:327-335. Discusses avoparcin (an antibiotic similar to human vancomycin) use in animals in certain countries, and the discovery of enterococcal bacteria resistant to vancomycin not only in the exposed animals, but in the surrounding
human population outside of the hospital. Discusses ban on avoparcin in E.U. and significant decreases in vancomycin resistance enterococci in animals and humans.

Shows evidence for transfer of resistance genes between bacteria in humans and animals.


10. Molbak Kare, Dorte Lau Baggesen, Frank Moller Aarestrup, Jens Munk Ebbesen, Jørgen Engvæg, Kai Frydendahl, Peter Gerner-Smidt, Andreas Munk Petersen and Henrik C. Wegener. An outbreak of Multidrug-resistant, Quinolone-resistant Salmonella enterica serotype typhimurium DT104. New Engl J Med. November 4, 1999. Study details an outbreak of multidrug-resistant Salmonella in Denmark where 25 culture-confirmed cases were found; 11 patients were hospitalized and 2 patients died. The primary source of the resistant strain was a Danish swine herd.


13. Ojenyi A.A. Direct transmission of Escherichia coli from poultry to humans. Epidem. Inf. 1989. 103: 513-22. Tested 864 Escherichia coli isolates from workers at a poultry research farm in Denmark and 216 strains from poultry attendants in a commercial poultry farm in the city and poultry isolates were studied. Similar resistance patterns were found in the workers and the birds they worked with.

Evidence that Livestock Drug Use Puts Farmers and Rural Residents at Increased Risk for Resistant Infections and other Health Hazards— These articles provide further evidence of the link between animal drug use and the public health risk. Rural residents and farm workers are at the greatest risk for acquiring resistant infections from animals. While farm workers are at greatest individual risk, because many more people consume animal products than work directly with animals, each farm-related case may be associated with many more food-related cases.
6. van Dijke, B. et al. **Methicillin-resistant *Staphylococcus aureus* and pig-farming.** Presented at 16th European Congress of Clinical Microbiology and Infectious Diseases Nice, France, April 1-4 2006. Report of transfer of MRSA from swine to family of pig farmers that resulted in clinical mastitis in mother.
8. Merchant, James A. et al. **Asthma and Farm Exposures in a Cohort of Rural Iowa Children.** EHP 2005. 113(3):350-356. Found rural children on farms that used feed additives are at greater risk of asthma. This is consistent with other studies that have found antimicrobial exposure in children to be associated with asthma.
9. Voss, Andreas et al. **Methicillin-resistant *Staphylococcus aureus* in Pig Farming.** EID 2005. 11(12):1965-1966. Study showed transmission of MRSA between pig and human, between family members, and between a nurse and patient in a hospital. This is consistent with other studies that have found pig farmers to be at higher risk of MRSA.
10. Aubrey-Damon, Helene et al. **Antimicrobial resistance in Commensal Flora of Pig Farmers.** EID 2005. 10(5):873-879. Study compared pig farmers to matched group of non-farmers and found farmers at greater risk of being colonized with *Staphylococcus aureus* and at greater risk for resistant *Staphylococcus aureus*.
12. Ojeniyi A.A. **Direct transmission of *Escherichia coli* from poultry to humans.** Epidem. Inf. 1989. 103: 513-22. Tested 864 Escherichia coli isolates from workers at a poultry research farm in Denmark and 216 strains from poultry attendants in a commercial poultry farm in the city and poultry isolates were studied. Similar resistance patterns were found in the workers and the birds they worked with.
to human spread. JAMA. Feb. 8, 1980. 243(6). The case of a pregnant woman, infected with Salmonella heidelberg, who worked on a farm until 4 days before delivery. Her baby subsequently developed mild diarrhea, as did 2 others sharing the hospital nursery. Salmonella heidelberg was isolated from each, and in all cases was resistant to chloramphenicol, sulfamethoxazole, and tetracycline. The strain originated from a herd of infected farm animals.

14. Levy Stuart B, George B FitzGerald, and Ann B Macone. Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. New Engl. J Medicine. Sept. 9, 1976. 295(11): 583-588. In this controlled study, chickens were fed tetracycline-supplemented feed. Within 1 week the chicken's intestinal flora included organisms almost entirely resistant to tetracycline. Within 5-6 months 31.3% of farm dwellers had fecal samples with organisms more than 80 percent tetracycline-resistant; increased bacterial resistance to multiple antibiotics was also observed.

Evidence that Resistant Bacteria Lead to Increased Illness and Poorer Health Outcomes--

These articles explore the impact of resistance when it occurs in bacteria that come from farm animals. Most of this research focuses on bacteria known to be transmitted through foods of animal origin. While the connection to animal drug use is most clear in foodborne pathogens, there may be an even more significant human health impact from bacteria that do not normally cause disease but may transfer resistance to pathogenic bacteria or cause illness in immunocompromised patients. The direct negative impacts of resistance in foodborne pathogens described in these articles is just a small part of a much larger problem.


2. Cosgrove, Sara E. The Relationship between Antimicrobial resistance and Patient Outcomes: Mortality, Length of Hospital Stay, and Health Care Costs. CID 2006. 42:S82-S89. This article reviews research on reduced patient outcomes from resistant pathogens. While this article does not discuss the connection to animal agriculture many of the pathogens discussed MRSA, VRE, resistant Escherichia coli have been shown to have a link to drug use in animals. Resistant infections are associated with increases in mortality, length of hospitalization, and cost of health care.

3. Helmes, Morten et al. Adverse Health Events Associated with Antimicrobial Drug Resistance in Campylobacter Species: A Registry-Based Cohort Study. JID 2005. 191(1):1050-1055. This study compared outcomes of patients with Campylobacter infections resistant to erythromycin and quinolones with patients infected with susceptible pathogens. Erythromycin and quinolones are the drugs of choice for treating Campylobacter. Patients with resistant infections had a more than five times greater chance of suffering from invasive illness or death than patients infected with susceptible infections.

5. Varma, Jay K. et al. **Antimicrobial-Resistant Nontyphoidal Salmonella Is Associated with Excess Bloodstream Infections and Hospitalizations.** JID 2005. 191:554-561. Study found patients with resistant Salmonella infections are more likely to have bloodstream infections and be hospitalized than patients with susceptible infections.

6. Helms, Morten et al. **Quinolone Resistance Is Associated with Increased Risk of Invasive Illness or Death during Infection with Salmonella Serotype Typhimurium.** JID 2004. 190(1):1652-1654. Authors compared patients with resistant Salmonella infections with patients with susceptible infections and found that the patients with resistant infections had over three times the risk of invasive illness or death.


8. Nelson, Jennifer M. et al. **Prolonged Diarrhea Due to Ciprofloxacin-Resistant Campylobacter Infection.** JID 2004. 190(6):1150-7. This case control study found that patients with quinolone resistant Campylobacter infections had longer mean duration of diarrhea than patients with susceptible infections.

9. Barza, Michael and Karen Travers. **Excess Infections Due to Antimicrobial Resistance: The “Attributable Fraction.”** CID 2002. 34(Suppl 3):S126-S130. Patients taking antibiotics for an unrelated cause are more likely to contract a resistant foodborne illness. The presence of resistance to antibiotics in foodborne pathogens leads to an additional 30,000 Salmonella infections and an additional 20,000 Campylobacter infections each year.

**Resistant Bacteria, Antibiotics & Resistance Genes in Food, Water, Air, and Earth**


6. Kuldip Kumar, Satish C. Gupta, Yogesh Chander and Ashok K. Singh. **Antibiotic Use in Agriculture and Its Impact on the Terrestrial Environment.** Advances in Agronomy, 2005 87:1-54. This study found that repeated application of antibiotic-laden manure can provide an environment in which selection of antibiotic-resistant bacteria can occur.
7. Chee-Sanford J.C., R.I. Aminov, I.J. Krapac, N. Garrigues-Jeanjean, and R.I. Mackie. *Occurrence and Diversity of Tetracycline Resistance Genes in Lagoons and Groundwater Underlying Two Swine Production Facilities*. Applied and Env. Microbiology. April 2001. 67(4): 1494-1502. This study looked at evidence for tetracycline resistant bacteria in lagoons underlying hog farms using tetracycline antibiotics in feed, as well as in the groundwater beneath these lagoons. Determinants of tetracycline resistance were found in the lagoon, in the groundwater up to 250 meters downstream from the lagoons, and in the soil microbiota.

**Transfer of Resistance Genes Between Bacteria**

1. Lester, Camilla H. et al. *In Vivo Tranfer of the vanA Resistance Gene from an Enterococcus faecium Isolate of Animal Origin to an E. faecium Isolate of Human Origin in the intestines of Human Volunteers*. AAC 2006. 50(2):596-599. This experiment showed that resistance could be transferred from animal bacteria to human bacteria in the gut after being consumed by volunteers.

2. Shoemaker N.B., H. Vlamakis, K. Hayes, and A.A. Salyers. *Evidence for Extensive Resistance Gene Transfer among Bacteroides spp. and among Bacteroides and Other Genera in the Human Colon*, Applied And Environmental Microbiology, 2001, 67: 561—568. Provides evidence that bacteria transfer resistance genes extensively in the human colon. The gram negative bacteria, Bacteroides, accounts for around 25% of bacteria isolated from the colon. Over three decades, the prevalence of Bacteroides strains carrying a certain gene resistant to tetracycline went from 30% to 80%. Evidence also was found that resistant genes are transferred between Bacteroides and gram positive bacteria.

**Reversal of Antibiotic Resistance**

1. World Health Organization. *Impacts of antimicrobial growth promoter termination in Denmark*. 2003: Report number WHO/CDS/CPE/ZFK/2003.1. WHO convened an international panel of experts to conduct an in-depth review of the experience of Denmark, the world's largest pork exporter, which has pioneered reductions in agricultural use of antibiotics and has developed the world's most comprehensive data on antibiotic use and antibiotic-resistant bacteria. The panel, which included US experts on agriculture and public health, concluded that Denmark's phase-out of antibiotic feed additives led to an overall drop in the use of antibiotics in food animals by 54%, and "dramatically reduced" levels of resistant bacteria in animals. The panel also concluded that the phase-out did not adversely affect food safety, environmental quality, or consumer food prices.

2. Aarestrup Frank Moller, and Anne Mette Seyfarth. *Effect of intervention on the occurrence of antimicrobial resistance*. Acta. Vet scand. 2000; Suppl. 93: 99-103. Discusses reversals of antibiotic resistance following decreased antibiotic use observed in the Netherlands (tetracycline), Germany (VRE reduction), Denmark (avoparcin ban and VRE reduction). Authors note that to date there have not been major negative consequences of removing growth promoter antibiotics from use.
Alternatives/Complements to Agricultural Use of Antibiotics

1. Graham J.P, Boland J.J, and Silbergeld E. Growth Promoting Antibiotics in Food Animal Production: An Economic Analysis. Public Health Reports, 2006 121(1): 79-87. Researchers at Johns Hopkins University, using data from poultry giant Perdue, found that antibiotics slightly accelerated chicken growth. The benefit, however, was offset by the cost of purchasing antibiotics, with the total cost rising by about one cent per chicken.

2. Dritz, Tokach, Goodband, and Nelssen. Effects of administration of antimicrobials in feed on growth rate and feed efficiency of pigs in multisite production systems. J. American Veterinary Medical Association, 2002, 220: 1690-1695. This study, which was conducted at Kansas State University, found that adding antimicrobials to feed resulted in only a 5% improvement in growth rate among nursery pigs (typically the first 6 to 8 weeks after weaning), and no improvement in growth rate among finishing pigs (the remaining 14 to 18 weeks of production). Adding antimicrobials to feed did not improve feed efficiency (the amount of food needed to result in weight gain) in either nursery or finishing pigs.

3. Wierup Martin. The control of microbial diseases in animals: alternatives to the use of antibiotics. International Journal of Antimicrobial Agents. 2000. 14: 315-319. Discusses various means to control bacterial infections in farm animals by other means than antibiotic use, including improved hygiene, isolation of sick animals, replacing live breeding animals by semen and embryos, etc.

Other countries


10. Engberg Jorgen, Frank M. Aarestrup, Diane E. Taylor, Peter Gerner-Smidt, and Irving Nachamkin. **Quinolone and Macrolide Resistance in Campylobacter jejuni and C. coli: Resistance Mechanisms and Trends in Human isolates**. Emerging Infectious Diseases. Jan-Feb. 2001; 7(1). Review of macrolide and quinolone resistance in Campylobacter strains and tracking of the resistance trends in human clinical isolates in relation to use of these agents in food animals. Good synopsis of when antibiotics were licensed in many countries (for food animals) and good bar graph depicting resistances in many countries.


13. Smith Kirk E., Jeffrey B. Bender and Michael T. Osterholm. **Antimicrobial Resistance in animals and relevance to human infections**. In Campylobacter, 2nd edition; 2000; Chapter 25. Edited by Martin Blaser and Irving Nachamkin. American Society for Microbiology, Washington, D.C. Study focuses on combinations of bacteria resistant to particular antimicrobials looking especially at fluoroquinolone-resistant Campylobacter, and relates the latter to approval in many countries of the fluoroquinolones, sarafloxacin and enrofloxacin, for use in food animals.
