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--The following articles provide an overview of the general problem of antimicrobial resistance and its impacts on public health.

1. Talbot, George H., et al. **Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America**. CID 2006, 42:657-668. The Infectious Diseases Society of America discusses six pathogens that are particularly difficult to treat because of resistance.
2. Tenover, Fred C. **Mechanisms of antimicrobial resistance in bacteria**. Am J Infect Control 2006. 34:S3-10. Describes how bacteria become resistant and gives three case examples of resistance arising in hospital settings.
3. Courvalin, Patrice. **Antimicrobial Drug Resistance: Prediction is Very Difficult, Especially about the Future**, EID 2005. 11(10):1503-1506. Short article discussing resistance, mechanisms of resistance, and how bacteria are able to transfer resistance between each other.

4. Barker, Keith F. **Antibiotic Resistance: A Current Perspective**. J. Clin. Pharmacol. 1999; 48: 109-124. Reviews various mechanisms of antibiotic resistance, and identifies current clinical problems along with possible solutions and future developments.
5. Levy, Stuart B. **The Challenge of Antibiotic Resistance**. Scientific Am. March, 1998. General discussion of antibiotic resistance, how bacteria become resistant, how antibiotic exposure promotes resistance, and how resistance might be reversed.

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.

1. Graham, J.P. et al. **Antibiotic Resistant Enterococci and Staphylococci Isolated From Flies Collected Near Confined Poultry Feeding Operations**. Science of the Total Environment, 2009, Volume 497(8): 2701-2710.
2. Silbergeld, Graham, and Price. **Industrial food animal production, antimicrobial resistance, and human health**. Annual Review of Public Health, Volume 29 (2008), pp. 151-169.
3. Nemati, M. et al. **Antimicrobial Resistance of Old and Recent *Staphylococcus aureus* Isolates from Poultry: First Detection of Livestock-Associated Methicillin-Resistant Strain ST398**. Antimicrobial Agents and Chemotheraphy, October 2008, Volume 52(10): 3817-3819.
4. Berrant, M.E. et al. **Subtherapeutic Tylosin Phosphate in Broiler Feed Affects *Campylobacter* on Carcasses During Processing**. Poultry Science, 2007, Volume 86: 1229-1233.
5. Gilchrist, M.J. et al. **The potential Role of Concentrated Animal Feeding Operations in Infectious Disease Epidemics and Antibiotic Resistance**. Environmental Health Perspectives, 2007, Volume 115(2): 313-316.
6. Ladely, Scott R. et al. **Development of Macrolide-Resistant *Campylobacter* in Broilers Administered Subtherapeutic or Therapeutic Concentrations of Tylosin**. Journal of Food Protection, Volume 70, Number 8, August 2007 , pp. 1945-1951(7).
7. Sapkota, Amy R. et al. **What Do We Feed to Food Production Animals? A Review of Animal Feed Ingredients and Their Potential Impacts on Human Health**. Environmental Health Perspectives 2007 (online Feb 8, 2007).
8. White, D.G. et al. **The Isolation of Antibiotic-Resistant Salmonella From Retail Ground Meats**. New England Journal of Medicine, 2007, Volume 345(16): 1147-1154.
9. Funk, Julie A. et al. **The Effect of Subtherapeutic Chlortetracycline on Antimicrobial Resistance in the Fecal Flora of Swine**. Microbial Drug Resistance, Volume 12, Number 3, 2006 , pp. 210-218.
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.
11. Nannapaneni, R. et al. **Concurrent Quantitation of Total Campylobacter and Total Ciprofloxacin Resistant Campylobacter Loads in Rinses From Retail Raw Chicken Carcasses from 2001 to 2003 by Direct Plating at 42 Degrees Celsius**. Applied and Environmental Microbiology, 2005, Volume 71(8): 4510-4515.

12. Smith, David L. et al. **Agricultural Antibiotics and Human Health: Does antibiotic use in agriculture have a greater impact than hospital use?**. PLoS Medicine 2005. 2(8):e232. Authors use mathematical model to examine spread of resistance in commensal bacteria from livestock to humans and finds that agricultural can have greater impact than human hospital use on resistance levels.
13. Shea, Katherine M. **Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics** . Pediatrics 2004. 114(3):862-868. Examines evidence of human health risks from animal antimicrobial use noting that children are at greater risk from resistant infections than the general population.
14. Anderson, Alicia D., et al. **Public health consequences of use of antimicrobial agents in agriculture**. Microb. Drug Resist 2003. 9(4): 373-379. *Risk management strategies: monitoring and surveillance. Excellent overview from CDC.*
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."
16. Catry, B. et al. **Antimicrobial resistance in livestock**. J Vet Pharmacol Therap. 2003. 26: 81-93. Good review of resistance in animals from a veterinary perspective. Notes that resistance could result in economic losses and animal welfare problems for livestock producers and that "the resistance level in a population is directly related to amount of antimicrobial drugs used."
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."
18. Goforth Robyn L., Carol R. Goforth. **Appropriate Regulation of Antibiotics in Livestock Feed**. Boston College Environmental Affairs Law Review. 2000. 28(1). Very good review of non-therapeutic uses of antimicrobials in food animals and the impact on human health. Discusses the regulatory process for approving new drugs for use in animal agriculture, and suggestions for how to curb the spread of antibiotic resistance.
19. Khachatourians George G. **Agricultural use of antibiotics and the evolution and transfer of antibiotic-resistant bacteria**. Canadian Medical Association Journal, 1998; 159: 1129-36. Excellent scientific review of trends in antibiotic use in animal husbandry and agriculture in general.
20. Levy Stuart B. **Antibiotic Use for Growth Promotion in Animals: Ecologic and Public Health Consequences**. J. Food Protection. July 1987. 50(7): 616-620. General discussion of sub-therapeutic use of antibiotics in animals, the cases of the spread of resistance from animals to man, reservoirs of resistance genes, multiple resistances and alternative measures.
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.

1. Johnson, J.R. et al. **Antimicrobial Drug Resistant *Escherichia coli* From Humans and Poultry Products, Minnesota and Wisconsin, 2002-2004**.Emerging Infectious Diseases, 2007, Volume 13(6): 838-846.
2. Johnson, J.R. et al. **Similarity Between Human and Chicken *Escherichia coli* Isolates In Relation to Ciprofloxacin Resistance Status**. The Journal of Infectious Diseases, 2006, Volume 194(1): 71-78.
3. Kieke, Amy L. et al. **Use of Streptogramin Growth Promoters in Poultry and Isolation of Streptogramin-Resistant Enterococcus faecium from Humans.** JID 2006. 194(9): 1200-1208.
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.
7. Dunne E.F., et al. **Emergence of Domestically Acquired Ceftriaxone-Resistant Salmonella Infections Associated with AmpC B-Lactamase**. J. American Medical Association. Dec. 27, 2000. 284(24): 3151-3154. Summarizes national surveillance data for Salmonella infections in the U.S. resistant to the antibiotic, ceftriaxone, and describes the mechanisms of resistance. Ceftriaxone is an important treatment for severe Salmonella infections, especially in children.
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.

9. Wegener HC, FM Aarestrup, P Gerner-Smidt and F. Bager. **Transfer of Antibiotic Resistant Bacteria From Animals to Man**. 1999. Acta. Vet. Scand. Suppl. 92: 51-57. Discusses antibiotic resistance in zoonotic bacteria — particularly in Salmonella, Campylobacter, Yersinia and enterohaemorrhagic E. coli (EHEC). Discusses that development of resistant bacteria primarily is driven by the use of antibiotics in animals and to a lesser extent due to use in humans.
10. Molbak Kare, Dorte Lau Baggesen, Frank Moller Aarestrup, Jens Munk Ebbesen, Jorgen Engverg, 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.
11. Smith K.E., J.M. Besser, C.W. Hedberg, F.T. Leano, J.B. Bender, J.H. Wicklund, B.P. Johnson, K.A. Moore, M.T. Osterholm. **Quinolone-Resistant Campylobacter jejuni Infections in Minnesota, 1992-1998**. New Engl J Med. May 20, 1999. 340(20): 1525-1532. The Minnesota Department of Health tested nearly 5,000 human isolates of Campylobacter for resistance to the quinolone antibiotic, nalidixic acid. Isolates found resistant to nalidixic acid then were tested for resistance to ciprofloxacin. Human isolates of C. jejuni resistant to quinolones rose from 1.3% in 1992 to 10.2% in 1998. Rising prevalence of resistant Campylobacter was temporally associated with the U.S. licensure of sarafloxacin in 1995 and enrofloxacin in 1996 for use in poultry.
12. Endtz HP, et al. **Quinolone resistance in Campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine**. J. Antimicrob. Chemother. 1991; 27(2): 199-208. Tested 883 strains of Campylobacter bacteria isolated between 1982 and 1989 from human stool and poultry products for quinolone resistance. Campylobacter isolated from poultry increased in resistance from zero to 14 percent in that time, while resistance in human isolates rose from zero to 11 percent. Results suggest that the increase is mainly due to use of the fluoroquinolone, enrofloxacin, in poultry.
13. Ojenyiyi 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.

1. Smith, T.C. et al. **Methicillin-Resistant *Staphyloccus aureus* (MRSA) Strain ST398 Is Present in Midwestern U.S. Swine and Swine Workers**. PLoS ONE, 2009, Volume 4(1): e4258.
2. Khanna, T. et al. **Methicillin-Resistant *Staphylococcus aureus* Colonization in Pigs and Pig Farmers**. Veterinary Microbiology, 2008, Volume 128: 298-303.
3. Rule, A.M, S.L. Evans and E.K. Silbergeld. **Food Animal Transport: A Potential Source of Community Exposure to Health Hazards From Industrial Farming (CAFOs)**. Journal of Infection and Public Health, 2008, Volume 1(1): 33-39.
4. Akwar, T.H. et al. **Risk factors for antimicrobial resistance among fecal Escherichia coli from residents on forty-three swine farms**. Microbial Drug Resistance 2007. Spring 13(1):69-76.
5. Price, L.B. et al. **Elevated Risk of Carrying Gentamicin-Resistant *Escherichia coli* among U.S. Poultry Workers**. Environmental Health Perspectives, 2007, Volume 15(12): 1738-1742.
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.
7. Hanselman, B.A. et al. **Methicillin-Resistant *Staphyloccus aureus* Colonization in Veterinary Personnel**. Emerging Infectious Diseases, 2006, Volume 12(12): 1933-1938.
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.
11. Fey Paul, Thomas J. Safranek, Mark E. Rupp, Eileen F. Dunne, Efrain Ribot, Peter C. Iwen, Patricia A. Bradford, Frederick J. Angulo, and Steven H. Hinrichs. **Ceftriaxone-resistant Salmonella infection acquired by a child from cattle**. New Engl. J. Medicine. April 27, 2000. Analysis of Salmonella enterica serotype typhimurium isolated from a 12-year old boy with fever, abdominal pain and diarrhea. Results indicated that the ceftriaxone-resistant bacteria isolated from the child was indistinguishable from a Salmonella isolate taken from cattle on his father's farm.
12. Ojenyiyi 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.
13. Lyons Robert W, Cathryn L Samples, Hema N DeSilva, Kathryn A Ross, Ernest M Julian, Patricia J. Checko. **An epidemic of Resistant Salmonella in a Nursery: Animal**

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 immuno-compromised patients. The direct negative impacts of resistance in foodborne pathogens described in these articles is just a small part of a much larger problem.

1. Klevens, R.M. et al. **Invasive Methicillin-Resistant *Staphylococcus aureus* Infections in the United States**. Journal of the American Medical Association, 2007, Volume 285(15): 1763-1771.
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.
4. Varma, Jay K. et al. **Hospitalization and Antimicrobial Resistance in Salmonella Outbreaks, 1984-2002**. EID 2005. 11(6):943-946. This review of Salmonella outbreaks in the U.S. found that outbreaks caused by resistant Salmonella were more likely to cause hospitalization than outbreaks caused by susceptible Salmonella.

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 blood stream 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.
7. Martin, Leah J. et al. **Increased Burden of Illness Associated with Antimicrobial-Resistant Salmonella enterica Serotype Typhimurium Infections**. JID 2004. 189(1):377-384. Study found increased hospitalization in patients with multidrug resistant Salmonella.
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 meand 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

1. Koike, S. et al. **Monitoring and Source Tracking of Tetracycline Resistance Genes in Lagoons and Groundwater Adjacent to Swine Production Facilities**. Applied and Environmental Microbiology, 73 (15):4813-4823 (2007).
2. Sapkota, A., et al. **Antibiotic-resistant enterococci and fecal indicators in surface water and groundwater impacted by a concentrated swine feeding operation**. Environmental Health Perspectives, (2007).
3. Gibbs S.E., et al. **Isolation of Antibiotic-Resistant Bacteria from the Air Plume Downwind of a Swine Confined or Concentrated Animal Feeding Operation**. Environmental Health Perspectives, 114:1032–1037 (2006).
4. Anderson, M.E. and M.D. Sobsey. **Detection and Occurrence of Antimicrobially Resistant *E. coli* In Groundwater On or Near Swine Farms in Eastern North Carolina**. Water Science and Technology, 54(3): 211-218 (2006).
5. Chapin, A. et al. **Airborne Multidrug-Resistant Bacteria Isolated from a Concentrated Swine Feeding Operation**. Environmental Health Perspectives, 113:137–142 (2005).
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 bacteris 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

1. Springer, B. et al. **Methicillin-Resistant *Staphylococcus aureus*: A New Zoonotic Agent?** The Middle European Journal of Medicine, 2009, Volume 121: 86-90.
2. Lewis, H.C. et al. **Pigs as a Source of Methicillin-Resistant *Staphylococcus aureus* CC398 in Pigs and Humans**. Emerging Infectious Diseases, Volume 14(9): 1383-1389.
3. van Belkum, A. et al. **Methicillin-Resistant and susceptible *Staphylococcus aureus* Sequence Type 398 in Pigs and Humans**. Emerging Infectious Diseases, 2008, Volume 14(3): 479-483.
4. van Duijkeren, E. et al. **Transmission of Methicillin-Resistant *Staphylococcus aureus* Strains Between Different Kinds of Pig Farms**. Veterinary Microbiology, 2008, Volume 136: 383-389.
5. van Rijen, M.M.L. et al. **Increase in a Dutch Hospital of Methicillin-Resistant *Staphylococcus aureus* Related to Animal Farming**. Clinical Infectious Diseases, 2008, Volume 16: 261-263.
6. van Loo, I et al. **Emergence of Methicillin-Resistant *Staphylococcus aureus* of Animal Origin in Humans**.Emerging Infectious Diseases, 2007, Volume 13(12): 1834-1839.
7. Witte, W. et al. **Methicillin-Resistant *Staphylococcus aureus* ST398 in Humans and Animals, Central Europe**. Emerging Infectious Diseases, 2007, Volume 13(2): 255-258.
8. Bager Flemming. DANMAP reports from Denmark (**DANMAP 2005**, **DANMAP 2004**, **DANMAP 2003**, **DANMAP 2002**, **DANMAP 2001, DANMAP 2000**, **DANMAP 1999**): The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme presents the results of resistance monitoring in food animals, foods and humans.

9. Huijsdens, X.W. et al. **Community-Acquired MRSDA and Pig-Farming**. Annals of Climinical Microbiology and Antimicrobials, 2006. 5(26).
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.
11. Martel Jean-Louis, Florence Tardy, Anne Brisabois, Renaud Lailler, Michel Coudert, Elisabeth Chaslus-Dancla. **The French antibiotic resistance monitoring programs**. International Journal of Antimicrobial Agents. 2000. 14: 275-283. Description of the French antibiotic resistance monitoring program involving testing non-human zoonotic Salmonella for antimicrobial susceptibilities, as well as testing of other bacteria strains pathogenic to beef cattle.
12. Moreno Miguel A., Lucas Dominguez, Tirushet Teshager, Inmaculada A. Herrero, M. Concepcion Porrero, The VAV Network. **Antibiotic resistance monitoring: the Spanish programme**. International Journal of Antimicrobial Agents. 2000. 14: 285-290. Description of the Spanish program to monitor antibiotic resistance, including isolates of bacteria from sick animals, as well as from healthy food animals.
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.
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