INSTITUTE FOR AGRICULTURE AND TRADE POLICY

Healthy Food Action

No Time to Lose

SCIENCE SUPPORTING PUBLIC HEALTH ACTION TO REDUCE ANTIBIOTIC OVERUSE IN FOOD ANIMALS*

1. Antibiotic resistance and why it occurs

Health professionals in training learn the basics of antibiotic resistance summarized, for example, in Levy (1999, 2002),[1,2] Tenover (2006)[3] and Courvalin (2006).[4]

As science evolves, it has become clear that resistance is fundamentally an ecological problem, spread via bacteria mutating or acquiring resistance from environmental reservoirs and then thriving.[5,6,7,8,9] Promiscuous bacteria can swap genetic "determinants" of resistance with other, often unrelated bacteria in the environment, between and within hospitals and communities, on farms, and in the guts of animals and humans.[7,10,11] Mothers may pass antibiotic-resistant bacteria from their own gut into their children.[12]

To expend energy for resistance genes, bacteria must derive some advantage. That advantage is explained by the huge volume of antibiotics used, and the selection pressure it exerts.[13] Pharmaceutical sales data (2010) collected by the Food and Drug Administration (FDA) indicate more than 80 percent of U.S. antimicrobials, over 29 million pounds, are sold for use in animal agriculture; 90 percent are added to water or animal feed not to treat sick animals but to promote growth, feed efficiency, or to control disease in otherwise healthy animals being raised in crowded or unhygienic conditions that promote disease. Exposure to antibiotics changes the microbial ecology in the animal gut, as it does in humans.[14]

Selection for resistant bacteria is now known to occur at antibiotic concentrations hundreds of times lower than those previously thought significant;[15] the lower levels of antibiotics put into animal feed compared to injections for sick animals therefore offer little basis for complacency. New science suggests feed antibiotics also can spur the spread of resistance by promoting new genetic mutations, which can give rise to it,[16] as well as by promoting the transfer among gut bacteria of genes (including, potentially, antibiotic resistance genes) via phages.[17] Transformation from benign to dangerous, multidrug-resistant bacteria can happen quickly, since resistance to a dozen or more drugs often sits —physically linked—on the same strand of transferable DNA.[18]

2. Why should we care?

There are rising numbers of disease-causing bacteria for which few, if any, antibiotics exist that might be effective treatments, nor are such treatments being newly developed.[19]

KEEP ANTIBIOTICS WORKING
The Campaign to End Antibiotic Overuse

*Prepared, in part, from a bibliography by the Keep Antibiotics Working coalition, of which IATP is a founding member.

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An estimated 900,000 antibiotic-resistant infections occur yearly, including 94,000 infections and 18,650 deaths from methicillin-resistant *Staphylococcus aureus* (MRSA) alone.[20,21] Ten-fold more MRSA infections afflict children in U.S. hospitals than in 1999.[22] Resistant infections generally cause more and longer hospitalizations—costing $18–29,000 per patient to treat—and more deaths.[23,24] Resistant infections cost $20 billion annually in direct treatment costs,[17] with an additional $35 billion or so in missed work or other costs to society.[21] More resistant infections mean more patients now receive antibiotics previously held in reserve that may be less potent or convenient, or inherently more toxic—like vancomycin.[25]

Ever-strengthening science—hundreds of studies to date—ties the spreading epidemic of resistant infections in humans to routine antibiotic use in food animals. This is a select summary of that science, across several critical strands of evidence. See an expanded version comprising 147 studies at iatp.org. (Web links indicate freely available studies; PubMed.org abstracts indicate non-public studies.)

Medical experts and public health agencies therefore agree: Routine antibiotic use in food animal production likely worsens the epidemic of resistance and action must be taken to reduce it. [26,27,28,29]

3. Connecting animal agriculture and antibiotic resistance

- Aarestrup FM, Wegener HC, Collignon P. **Resistance in bacteria of the food chain: epidemiology and control strategies.** *Expert Rev Anti Infect Ther.* 2008;6(5):733-750.

  Our favorite review article of bacterial resistance due to antimicrobial use in food animals, and its transferability to humans.

- Collignon P. Antibiotic resistance in human Salmonella isolates are related to animal strains. *Proc Biol Sci.* 2012;279(1740):2922-2923. Available at http://rspb.royalsocietypublishing.org/content/279/1740/2922.long.

- Hammerum AM. **Enterococci of animal origin and their significance for public health.** *Clin Microbiol Infect.* 2012 Jul;18(7):619-25.

- Davis MF, Price LB, Liu CM, et al. **An ecological perspective on U.S. industrial poultry production: the role of anthropogenic ecosystems in the emergence of drug-resistant bacteria from agricultural environments.** *Curr Opin Microbiol.* 2011;14(3):244-250.

  Rampant use of antibiotics in industrial food animal production has led to both an increased pressure on microbial populations as well as alterations of the ecosystems where antibiotics and bacteria interact.

- Marshall BM, Levy SB. **Food animals and antimicrobials: impacts on human health.** *Clin Microbiol Rev.* 2011 Oct;24(4):718-33. doi: 10.1128/CMR.00002-11.

- Silbergeld EK, Graham J, Price LB. **Industrial food animal production, antimicrobial resistance, and human health.** *Annu Rev Public Health.* 2008;29:151-169.

  Reviews four reasons why agricultural antimicrobial use is a major driver of resistance globally: agriculture is the primary use of antimicrobials; much of agricultural use results in subtherapeutic exposures for bacteria; drugs of every important clinical class are utilized in agriculture; and humans are exposed to resistant pathogens via consumption of animal products, and via widespread release into the environment.

- Barza M. Potential mechanisms of increased disease in humans from antimicrobial resistance in food animals. *Clin Infect Dis.* 2002;34(Suppl 3):S123-125.

  Summarizes five mechanisms by which resistance may adversely affect human health—two of which directly relate to animal antibiotic use. Available at http://cid.oxfordjournals.org/content/34/Supplement_3/S123.full.

Studies On Farms Comparing Animals Fed and Not Fed Antibiotics

- Mirzaagha P, Louie M, Sharma R, et al. Distribution and characterization of ampicillin- and tetracycline-resistant Escherichia coli from feedlot cattle fed subtherapeutic antimicrobials. *BMC Microbiology.* 2011;11:78.

  E. coli were isolated from cattle fed or not fed subtherapeutic levels of chlortetracycline, chlortetracycline and sulfamethazine (SMX), or virginiamycin over 9 months. Results: Administering chlortetracycline alone can lead to emergence of resistance to SMX, and to other antibiotics including ampicillin and chloramphenicol. Multidrug resistant strains were more frequently isolated from steers fed multiple, as opposed to single, antibiotics. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3103423/.

- Jackson CR, Lombard JE, Dargatz DA, et al. **Prevalence, species distribution and antimicrobial resistance of enterococci isolated from US dairy cattle.** *Lett Appl Microbiol.* 2011;52(1):41-48.

  Enterococci from 700+ fecal samples from 122 dairy cattle operations demonstrated widespread resistance, with the highest percentage of resistant isolates to lincomycin (92.3%), flavomycin (71.9%) and tetracycline (24.5%).

- Morley PS, Dargatz DA, Hyatt DR, et al. **Effects of restricted antimicrobial exposure on antimicrobial resistance in fecal *Escherichia coli* from feedlot cattle.** *Foodborne Pathog Dis.* 2011;8(1):87-98.

  Among *E. coli* collected from two feedlot cattle populations raised with and without antibiotics, no difference was found in resistance.

- Davis MA, Besser TE, Orfe LH, et al. Genotypic-phenotypic discrepancies between antibiotic resistance characteristics of Escherichia coli isolates from calves in management settings with high and low antibiotic use. *Appl Environ Microbiol.* 2011 May;77(10):3293-9. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3126435/?tool=pubmed.

- Alexander TW, Inglis GD, Yanke LJ, et al. **Farm-to-fork characterization of *Escherichia coli* associated with feedlot cattle with a known history of antimicrobial use.** *Int J Food Microbiol.* 2010;31;137(1):40-8.

  Compared to control animals fed no antibiotics, prevalence of amp- and tet-resistant *E. coli* was three-fold and four-fold greater, respectively, in feces from cattle fed diets containing chlortetracycline plus sulfamethazine.

- Harvey R, Funk J, Wittum TE, et al. **A metagenomic approach for determining prevalence of tetracycline resistance genes in the fecal flora of conventionally raised feedlot steers and feedlot steers raised without antimicrobials.** *Am J Vet Res.* 2009 Feb;70(2):198-202.

  Comparing feedlot steers raised conventionally and without antibiotics, the prevalence of fecal samples with 11 tet-resistant genes was significantly higher in the former (35/61, or 57%) than in the latter (16/61, or 26%).

- Vieira AR, Houe H, Wegener HC, et al. **Association between tetracycline consumption and tetracycline resistance in *Escherichia coli* from healthy Danish slaughter pigs.** *Foodborne Pathog Dis.* 2009 Jan-Feb;6(1):99-109.

  Study demonstrated the longer the time since the last administration of tetracycline, the lower the likelihood of isolating a tet-resistant *E. coli* from a pig's intestinal tract.

- Ladely SR, Harrison MA, Fedorka-Cray PJ, et al. **Development of macrolide-resistant *Campylobacter* in broilers administered subtherapeutic or therapeutic concentrations of tylosin**. *J Food Prot.* 2007;70(8)1945-1951.

  Chickens fed subtherapeutic and therapeutic doses of tylosin tested positive for resistant bacteria, but no resistant strains were found among tylosin-free flocks. Increased tylosin resistance was associated with birds given subtherapeutic relative to therapeutic doses.

Pathogens Newly Tied to Food Animal Production – MRSA, ExPEC E coli

- Price LB, Stegger M, Hasman H, et al. Staphylococcus aureus CC398: host adaptation and emergence of methicillin resistance in livestock. *MBio.* 2012;3(1):e00305-e00311.

  Whole genome sequence typing of 89 isolates from 19 countries suggests livestock-associated methicillin-resistant *Staphylococcus aureus* (MRSA) CC398 most likely originated as methicillin susceptible *S. aureus* in humans and jumped to livestock where it acquired tetracycline and methicillin resistance. Available at http://mbio.asm.org/content/3/1/e00305-11.long.

- Waters AE, Contente-Cuomo T, Buchhagen J, et al. Multidrug-resistant Staphylococcus aureus in US meat and poultry. *Clin Infect Dis.* 2011;52(10):1227-1230. Available at http://cid.oxfordjournals.org/content/52/10/1227.full.

- Bergeron CR, Prussing C, Boerlin P, et al. Chicken as reservoir for extraintestinal pathogenic Escherichia coli in humans, Canada. *Emerg Infec Dis.* 2012;18(3):415-421.

  Extraintestinal pathogenic *E. coli* (ExPEC) strains cause more than 85 percent of the several million community acquired urinary tract infections (UTIs) annually. Comparison of *E. coli* from humans with UTIs and from animals in slaughterhouses suggests ExPEC from the latter—most probably chickens—could be causing UTIs. Available at http://www.cdc.gov/eid/article/18/3/11-1099_article.htm.

- Manges AR, Johnson JR. **Food-borne origins of *Escherichia coli* causing extraintestinal infections.** *Clin Infect Dis.* 2012.

  A review suggesting many ExPEC strains responsible for UTIs, sepsis, and other extraintestinal infections may be transmitted from food animals or the food supply to humans, especially antimicrobial-resistant ExPEC.

Transmission of resistance via retail meat

- Cohen Stuart J, van den Munckhof T, Voets G, et al. **Comparison of ESBL contamination in organic and conventional retail chicken meat.** *Int J Food Microbiol.* 2012;154(3):212-214.

  Retail chicken contaminated with ESBL-producing bacteria likely contributes to the increasing incidence of human infection with these bacteria.

- Zhao S, Blickenstaff K, Bodeis-Jones S, et al. Comparison of the prevalences and antimicrobial resistances of Escherichia coli isolates from different retail meats in the United States, 2002 to 2008. *Appl Environ Microbiol.* 2012;78(6):1701-1707. Available at http://aem.asm.org/content/early/2012/01/06/AEM.07522-11.full.pdf+html.

- Dutil L, Irwin R, Finley R, et al. Ceftiofur resistance in Salmonella enterica serovar Heidelberg from chicken meat and humans, Canada. *Emerg Infect Dis.* 2010;16(1):48-54.

  From 2003 to 2008, ceftiofur, a 3rd-generation cephalosporin antibiotic, was removed from extra-label use in chicken hatcheries in Québec, coinciding with a dramatic decrease in ceftiofur resistance in *S.* Heidelberg and *E. coli* in retail chicken and a similar decrease in resistance in *S.* Heidelberg infections in humans. Reintroduction of ceftiofur into hatcheries in 2007 caused a rise in ceftiofur resistance in *E. coli*, but at lower levels than those seen in 2003-04. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2874360/.

- Zhao S, White DG, Friedman SL, et al. Antimicrobial resistance in *Salmonella* enterica serovar Heidelberg isolates from retail meats, including poultry, from 2002 to 2006. *Appl Environ Microbiol.* 2008;74(21):6656-6662.

  From more than 20,000 retail meat samples over four years, the FDA finds that multidrug-resistant strains of *S. enterica* serotype Heidelberg were common isolates. Available at http://aem.asm.org/content/74/21/6656.long.

- O'Brien AM, Hanson BM, Farina SA, et al. **MRSA in conventional and alternative retail pork products.** *PLoS One.* 2012;7(1):e300092.

  The largest sampling of retail pork to date found 64.8 percent with *S. aureus* and 6.6 percent with MRSA. 26.5 percent of MRSA had spa types associated with MRSA ST398. Available at http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0030092.

Transmission via farmers, workers, veterinarians

- Gilbert MJ, Bos ME, Duim B, et al. **Livestock-associated MRSA ST398 carriage in pig slaughterhouse workers related to quantitative environmental exposure.** *Occup Environ Med.* 2012;69(7):472-478.

  Of 341 Dutch pig slaughterhouse workers tested, 3.2 percent carried MRSA, of which 75 percent was the livestock-associated MRSA ST398 strain. Workers at the start of the slaughter line were at higher risk than those further down the line.

- Smith TC, Male MJ, Harper AL, et al. Methicillin-resistant *Staphyloccus aureus* (MRSA) strain ST398 is present in Midwestern U.S. swine and swine workers. *PLoS ONE.* 2009; 4(1): e4258.

  Prevalence of MRSA was 49 percent in swine and 45 percent in workers in two Midwest swine production operations. Available at http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0004258.

- Price LB, Graham JP, Lackey LG, et al. Elevated risk of carrying gentamicin-resistant *Escherichia coli* among U.S. poultry workers. *Environ Health Perspect.* 2007;15(12):1738-1742.

  Poultry workers examined were 32 times more likely to be colonized with gentamicin-resistant *E. coli* as community residents. Poultry workers also had an elevated risk of carrying multidrug-resistant *E. coli.*

Transmission via the broader environment (air, water, soil)

- McKinney CW, Loftin KA, Meyer MT, et al. ***tet* and *sul* antibiotic resistance genes in livestock lagoons of various operation type, configuration, and antibiotic occurrence.** *Environ Sci Technol.* 2010;44(16):6102-6109.

Water samples from the manure lagoons of various livestock facilities (dairy, chicken layer, swine) contained three to five times higher tetracycline resistance genes than did sediment samples upstream of such facilities.

- Chee-Sanford JC, Mackie RI, Koike S, et al. Fate and transport of antibiotic residues and antibiotic resistance genes following land application of manure waste. J *Environ Qual.* 2009;38:1086-1108.

  Feeding of antibiotics to food animals disseminates residues into the environment, and also likely leads to antibiotic resistance arising among commensal bacteria in the animal gut. Applying animal waste to the environment creates a reservoir of potentially significant antibiotic resistant genes in the area. Available at https://www.agronomy.org/publications/jeq/articles/38/3/1086.

- Gibbs SG, Green CF, Tarwater PM, et al. Isolation of antibiotic-resistant bacteria from the air plume downwind of a swine confined or concentrated animal feeding operation. *Environ Health Perspect.* 2006;114(7):1032-1037.

  Bacteria isolated from upwind, downwind and inside a confined hog operation revealed multidrug-resistant organisms; those inside the facility were most resistant. Available at http://ehp03.niehs.nih.gov/article/info%3Adoi%2F10.1289%2Fehp.8910.

4. Interventions and effective alternatives

- Aarestrup F. **Sustainable farming: get pigs off antibiotics.** *Nature.* 2012;486(7404):465-466.

- Sapkota AR, Hulet RM, Zhang G, et al. Lower prevalence of antibiotic-resistant enterococci on U.S. conventional poultry farms that transitioned to organic practices. *Environ Health Perspect.* 2011;119(11):1622-1628.

  Enterococci isolated from poultry litter, feed and water collected from 20 conventional and newly organic poultry houses leads to the conclusion that voluntary removal of antibiotics from large-scale poultry farms is associated with a lower prevalence of antibiotic-resistant and multidrug-resistant *Enterococcus*. Available at http://ehp03.niehs.nih.gov/article/info:doi/10.1289/ehp.1003350.

- Berge AC, Moore DA, Besser TE, et al. **Targeting therapy to minimize antimicrobial use in preweaned calves: effects on health, growth, and treatment costs.** *J Dairy Sci.* 2009 Sep;92(9):4707-14.

  This study showed the effect of raising preweaned dairy calves without routine antimicrobials in the milk was to save money and improve their health (less diarrhea).

- *Impacts of antimicrobial growth promoter termination in Denmark.* Report number WHO/CDS/CPE/ZFK/2003.1. Geneva, Switzerland: World Health Organization; 2003.

  WHO-convened experts concluded the phase out of antibiotic feed additives by Denmark—the world's largest pork exporter—led to an overall drop in antibiotic use by 54 percent, and "dramatically reduced" levels of resistant bacteria in animals without adversely affecting food safety, environmental quality or consumer food prices. Available at http://www.who.int/gfn/en/Expertsreportgrowthpromoterdenmark.pdf.

5. Production and economics

- Aarestrup FM, Jensen VF, Emborg HD, Jacobsen E, Wegener HC. **Changes in the use of antimicrobials and the effects on productivity of swine farms in Denmark.** *Am J Vet Res.* 2010;71(7):726-733.

  Despite a more than 50 percent decrease in antimicrobial use in Danish swine, 1992 to 2008, there was a 14-fold increase in swine production, increased mean number of pigs per sow for slaughter, increased average daily gain for weaning and finishing, and similar mortality rates.

- Dritz SS, Tokach MD, Goodband RD, et al. Effects of administration of antimicrobials in feed on growth rate and feed efficiency of pigs in multisite production systems. *J Am Vet Med Assoc.* 2002;220(11):1690-1695.

  Adding antimicrobials to feed leads to a five-percent improvement in growth rate among nursery pigs, but failed to improve feed efficiency (the amount of food needed to result in weight gain) in either nursery or finishing pigs (the latter 14 to 18 weeks of production). Available at http://www.avma.org/journals/javma/articles_public/020601_swine_Dritz.pdf?q=mf2301.

- Graham JP, Boland JJ, Silbergeld E. Growth promoting antibiotics in food animal production: an economic analysis. *Public Health Rep.* 2007;122(1):79-87.

  Using Perdue data, Johns Hopkins University researchers found antibiotic use can slightly accelerate chicken growth, but the gain is offset by increased production costs of about $.01 per chicken. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1804117.

Endnotes

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23. Varma JK, Greene KD, Ovitt J, et al. Hospitalization and antimicrobial resistance in Salmonella outbreaks, 1984-2002. *Emerg Infect Dis*. 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*.

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