1. Antibiotic resistance and why it occurs

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

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. 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. Mothers may pass antibiotic-resistant bacteria from their own gut into their children.

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. 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.

Selection for resistant bacteria is now known to occur at antibiotic concentrations hundreds of times lower than those previously thought significant; 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, as well as by promoting the transfer among gut bacteria of genes (including, potentially, antibiotic resistance genes) via phages. Transformation from benign to dangerous, multiresistant bacteria can happen quickly, since resistance to a dozen or more drugs often sits—physically linked—on the same strand of transferable DNA.

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.

*Prepared, in part, from a bibliography by the Keep Antibiotics Working coalition, of which IATP is a founding member.
An estimated 900,000 antibiotic-resistant infections occur yearly, including 94,000 infections and 18,650 deaths from methicillin-resistant Staphylococcus aureus (MRSA) alone. Ten-fold more MRSA infections afflict children in U.S. hospitals than in 1999. Resistant infections generally cause more and longer hospitalizations—costing $18–29,000 per patient to treat—and more deaths. Resistant infections cost $20 billion annually in direct treatment costs, with an additional $35 billion or so in missed work or other costs to society. 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.

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.

3. Connecting animal agriculture and antibiotic resistance


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.


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.


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


E. coli were isolated from cattle fed or not fed subtherapeutic levels of chlorotetracycline, chlortetracycline and sulfamethazine (SMX), or virginiamycin over 9 months. Results: Administering chlorotetracycline 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/.
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%).


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


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%).


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.


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


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.


Extrainestinal 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.

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


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


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/.


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.


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


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.


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.


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)

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.


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.


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


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.


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).


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


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.


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.


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