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, 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.

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 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. (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


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


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.

### Additional studies


  Fecal enterococci isolated from 122 dairy cattle operations demonstrated widespread resistance, highest percentage to lincomycin (92.3%), flavomycin (71.9%) and tetracycline (24.5%).

Sixty-nine enterococci isolated from nine commercial poultry farms were analyzed for antibiotic susceptibility. Multidrug resistance of public health significance was evident in *E. faecium* and *E. faecalis* isolates, most commonly of the phenotype Bac Ery Tyl Lin Str Tet Cip. Available at http://aem.asm.org/content/76/24/8033.


Exposed to sublethal doses of antibiotics, such as are put into animal feed, cell production of radical oxygen species (ROS) occurred, leading to increased rate of mutation in *E. coli*. Such mutations potentially could confer resistance, including to antibiotics different from those being administered. Available at http://www.sciencedirect.com/science/article/pii/S1097276510000286.


This study proves *Enterococcus* bacteria in French cattle continued to acquire glycopeptide (VanA)-resistant genes a decade after the glycopeptide, avoparcin, was banned as a feed additive. Because French calves are recurrently exposed to antibiotics, it may signify glycopeptide resistance is reemerging due to co-selection via physical linkage of resistance genes for glycopeptide and other antibiotics.


Seventy-two percent of 58 *S. enterica* serovar Heidelberg isolates from food animals displayed resistance, with 24 percent resistant to eight or more antimicrobial agents. Tetracycline resistance was the most commonly observed.


Indicates fluoroquinolone (FQ)-resistant *Campylobacter* may persist as contaminants of poultry products after on-farm FQ use has ceased. FDA's ban on FQ use in poultry may be insufficient to reduce FQ-res *Campylobacter* in poultry products. Available at http://ehp03.niehs.nih.gov/article/info:doi/10.1289/ehp.10050.


Avoparcin, an antibiotic feed additive related to vancomycin, was used and then banned in Europe. Seven years post-ban, Van-res *E. faecium* persist in multiple broiler flocks from two UK production facilities, 99 percent of them resistant to at least five antibiotics.


*Enterococcus* bacteria from organic and conventional chicken and turkey meat in Spain were tested for resistance to eight different antibiotics. Bacteria counts were higher on organic chicken meat, but resistance and multidrug resistance was higher in isolates from conventional chicken or turkey meat than from organic chicken.


Examines virginiamycin use in poultry and its effect on cross-resistance to quinupristin-dalfopristin, another streptogramin intended for treating vancomycin-resistant *E. faecium* infections in humans. “[C]ontinue use of virginiamycin may increase the potential for streptogramin-resistant *E. faecium* infection in humans.” Available at http://jid.oxfordjournals.org/content/194/9/1200.full.


Veterinary review states “[A] review of outbreaks of *Salmonella* infections indicated that outbreaks caused by antimicrobial-resistant *Salmonella* were more likely to have a food animal source than outbreaks caused by antimicrobial-susceptible *Salmonella*.” Available at http://www.colby.edu/biology/BI402B/Angulo%20et%20al%202004.pdf.

CDC investigation into a multi-state outbreak found exposure to a dairy farm or food contaminated from the farm was the major risk factor for acquiring multidrug-resistant Salmonella infection. Available at http://jid.oxfordjournals.org/content/188/11/1707.full.


Evaluates the likelihood that emergence of several resistant strains of bacteria occurred first in animals rather than humans. Reviews studies that correlate antimicrobial use on farms to the occurrence of colonization and infection of farm workers and residents of the surrounding communities. Discusses the trend in antibiotic resistance in commensal microorganisms and their opportunistic infection of hospitalized patients. Available at http://cid.oxfordjournals.org/content/34/Supplement_3/S111.full.


Poultry was withdrawn in Belgium in June 1999 after a contaminant was found in feed. By using the ban as an epidemiologic tool, the rate of Campylobacter infections attributable to poultry was determined to be greater than 40 percent. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2730260.


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) with a bar graph depicting resistances in many countries. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2631682/.


This review article finds that use of antimicrobial growth promoters greatly influences the prevalence of resistance in animal bacteria and poses a risk factor for emergence of antibiotic resistance in human pathogens. Resistance genes can be transferred from animal bacteria to human pathogens in the intestinal flora of humans.

Studies On Farms Comparing Animals Fed and Not Fed Antibiotics


E. coli were isolated from cattle fed or not fed subtherapeutic levels of chlorotetracycline, chloroxytracycline 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.


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 chlorotetracycline plus sulfamethazine.
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


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.


Additional studies


Reviewed factors associated with the high prevalence of livestock-associated MRSA in Dutch pork and veal production; herd treatment with antimicrobials appears to pose a risk.

Longitudinal study of two Danish and four Dutch pig herds finds that livestock-associated MRSA CC398 is endemic and able to spread and persist in herds. Use of antimicrobials as well as the age of pigs is found to affect transmission rates. Available at http://www.biomedcentral.com/content/pdf/1746-6148-8-58.pdf.

Nasal swabs of 178 pigs and 89 humans working on 25 pig farms not using antibiotics failed to detect livestock-associated ST398 previously found in conventional farm settings.


Analysis of resistance genes among livestock-associated MRSA (LA-MRSA) isolates reveals most were located on multiresistance plasmids. Co-selection enables LA-MRSA to both receive and donate multiple antimicrobial resistance genes with other Gram-positive organisms.


Among 35 pig farmers already colonized with LA-MRSA, colonization persisted among 59 percent even during periods of prolonged absence with the majority spending 7–14 days away from pig contact.

Among turkey farms in Germany, 18/20 (90%) flocks and 22/59 turkey workers (37.3%) tested positive for MRSA. Livestock-associated MRSA (CC 398) was detectable in most flocks. Available at http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=8488404.

Screening in four feedlots in Alberta, Canada of 491 feedlot cattle shortly before slaughter failed to isolate any MRSA.


Over half (152/290) of German finisher pig farms tested positive for MRSA. All isolates were resistant to tetracycline. Farm size was strongly correlated with risk of MRSA (OR 5.4). Available at http://www.biomedcentral.com/1746-6148/7/69.


Among several hundred porcine MRSA CC398 isolates from Europe and Canada, zinc resistance was observed in 74 percent, nearly all coding for the czaR resistance gene. The study concludes zinc in animal feed may have contributed to the emergence of livestock-associated MRSA. Available at http://www.biomedcentral.com/1746-6148/7/69.


This review article summarizes information about livestock-associated MRSA in Europe, China and North America. It concludes that MRSA control in animals should include farm hygiene and reductions in antimicrobial use, both of which contribute to MRSA occurrence on farms.


Among retail meats purchased in Washington, D.C. from March to August of 2008, 56 percent of 196 ground turkey samples, 28 percent of 198 ground beef samples and 12 percent of 300 ground pork samples tested positive for *S. aureus*. Concludes that *S. aureus* in retail ground meats is not uncommon, and all *S. aureus* from ground turkey, 89 percent from ground pork and 11 percent from ground beef were resistant to at least one antimicrobial agent. One sample was MRSA positive.


Reports on a new vga(A) found in livestock-associated MRSA in U.S. swine and swine farmers.


152 *S. aureus* isolates, including 22 MRSA, isolated from Louisiana retail meat, were analyzed for antimicrobial susceptibility, as well as the prevalence of enterotoxin and exotoxin genes.


Of 3687 MRSA isolates from persons in two Canadian provinces, five were identified as livestock-associated MRSA. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3321955/.


Human MRSA carriage in veal farmers is strongly associated with the number of MRSA-positive calves on the farm, and with intensity of animal contact. Farm hygiene appeared to lower MRSA prevalence among calves, while antibiotic use raised it. Available at http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0010990.


Summary of presentations at a 2009 Iowa conference elucidating the picture of livestock-associated MRSA in the American Midwest.

A review of an emerging sequence type of MRSA ST398, which has been isolated from various food animals observes that in a recent U.S. study, *S. aureus* contamination was found in 39.2 percent of retail meats and in that group 5 percent was MRSA. The spread of ST398 from animals to humans needs to be monitored as the potential threat from the retail food reservoir has widespread potential implications on human health. Available at http://onlinelibrary.wiley.com/doi/10.1111/j.1469-0691.2009.03110.x/full.


Among 402 samples of retail pork from four Canadian provinces, MRSA was isolated in 31 samples; 39 percent (12/31) were the most common Canadian epidemic clone, CMRSA, widely identified in horses and horse personnel but not in pigs. Thirty-two percent or 10/31, belonged to spa 539/034, a clone associated with food animals internationally. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2885117/.


Among hospital patients admitted with MRSA sequence type ST398, independent risk factors include pig, cattle contact. MRSA-carrying pigs were identified on 70 percent of 40 German pig farms, all ST398. Available at http://www.springerlink.com/content/d07291v16185374t/.


Finds that among *S. aureus* isolated from chickens in the 1970s compared to healthy chickens in 2006, resistance levels to eight of the drugs tested were significantly greater in 2006 samples. Available at http://aac.asm.org/content/52/10/3817.full.


Among Dutch patients identified as having had exposure to pigs or veal calves, up to 32 percent in some hospitals were positive for MRSA. Available at http://cid.oxfordjournals.org/content/46/2/261.full.


Reports that MRSA ST398, primarily a pathogen of pigs, appears to be quite virulent and can cause bacteremia in humans. States that if MRSA ST398 obtains this pathogenicity, care should be taken not to introduce this strain into humans. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2570802/.


Reports a new animal-associated MRSA strain that has entered the human population and is accounting for greater than 20 percent of all MRSA in the Netherlands. As most nontypable MRSA isolates are resistant to doxycycline, the spread of MRSA may be facilitated by the abundant use of tetracyclines in pig and cattle farming. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2876750/.

Pathogens Newly Tied to Food Animal Production – ExPEC E coli


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.


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.

Additional studies

Using antimicrobial susceptibility profiles for over 2202 human and avian E. coli isolates, this study finds that in ExPEC E. coli, multidrug resistance is most commonly associated with plasmids, and these are frequently found in E. coli from poultry production systems.


Antimicrobial resistance in E. coli from human blood stream infections strongly correlates with that in E. coli from poultry and pigs in 11 European countries.


Among nearly 1300 E. coli isolated from ground beef, turkey, chicken breasts and pork chops, about 16 percent overall were identified as ExPEC, including 23.5 percent of those in ground turkey and 20.2 percent in chicken breasts.


A small proportion of E. coli isolates from retail meats carry uropathogenic associated virulence genes and therefore may serve as a reservoir of these genes to uropathogenic E. coli in the human intestine.


The design of this study was to see if a food reservoir exists for E. coli that may cause UTIs. Sampling for E. coli from 2005 to 2007 comprised of clinical UTI samples, retail meats and restaurant/ready-to-eat foods. Upon comparison of these collected isolates by molecular methods, the authors report that E. coli identified from retail chicken and other food sources are identical or nearly the same as those from human UTIs. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2874376/.


Sixty-five percent of 207 E. coli isolates from cow-calf herds in western Canada were resistant to at least one antimicrobial. Patterns in this research suggest that when a bacterium acquires resistance to one antimicrobial, it likely becomes resistant to others because of the transfer of mobile genetic elements that harbor regions of multiple drug resistance. Available at http://aem.asm.org/content/74/12/3658.full.


Reports on UTIs from 1,667 patients over the course of six years. E. coli specimens were collected and characterized by molecular methods. Twelve percent of human UTI samples collected were found to be from a specific group, which from previous work has been shown to include E. coli collected from food animals or retail poultry products. The collected human isolates were also shown to be resistant to trimethoprim-sulfamethoxazole at a rate of 49 percent. The authors suggest that contaminated food products may be a source of drug resistant UTIs. Available at http://cid.oxfordjournals.org/content/46/5/689.full.


Given that ExPEC in meat may represent a new class of foodborne illness, this USDA study reviews various aspects of ExPEC prevalence, virulence, zoonotic properties and diseases association with it.


Resistant E. coli in humans appears to have a profile similar to that of resistant E. coli collected from chickens, suggesting that the use of antimicrobials in poultry production is leading to resistant E. coli that are being transferred to humans, possibly through contaminated meats. Available at http://jid.oxfordjournals.org/content/194/1/71.full.


In response to a multistate outbreak of drug resistant UTI infections, the authors examined E. coli from animals and found the identical strain supporting the view that the bacteria were transmitted from animal to people through food. Available at http://cid.oxfordjournals.org/content/40/2/251.full.

Studies community UTIs in the U.S. caused by *E. coli* resistant to trimethoprim-sulfamethoxazole as well as other antibiotics. Concludes that UTIs may be caused by contaminated foods, as the outbreaks appear to follow a pattern similar to that of *E. coli* O157 as they spread throughout a community. Available at http://www.nejm.org/doi/full/10.1056/NEJMoa011265.

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.

Additional studies


*E. faecalis* was found in over 94 percent of poultry samples, about 73 percent of beef and 86 percent of pork samples. Resistance to three or more antimicrobials was more common in *E. faecalis* from chicken and turkey (91%) than from pork (45%) or beef (14%). Resistance to aminoglycosides, macrolides, tetracyclines, streptogramin, bacitracin and lincosamide were most common.


Among *E. faecium* isolated from a poultry production environment, the extent of resistance found to quinupristin-dalfopristin, a drug reserved for human use to treat vancomycin-resistant enterococci, ranged from 51 percent to 78 percent. Available at http://jcm.asm.org/content/39/6/2298.full.


This study of 581 *Salmonella enterica* serotype Schwarzengrund isolates from persons, food and food animals suggests the bacteria pass from chickens to persons in Thailand, and from imported Thai food products to persons in Denmark and the United States. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2738437.

Salmonella was highly prevalent in more than 88 percent and over 84 percent of 480 pre- and post-chill whole chicken carcasses, respectively. 79.8 percent were resistant to at least one antimicrobial; 53.4 percent to three or more.

Comparison of more than 8,000 isolates from meat in Denmark shows higher rates of resistance, including multi-drug resistance, in Salmonella from imported vs. domestic meat. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725957/.


Salmonella were isolated from 41 out of 200 (20%) samples of ground chicken, pork, beef, and turkey purchased in Washington, DC. Eighty-four percent of Salmonella were resistant to one or more antibiotics; 53 percent were resistant to three or more antibiotics. Sixteen percent were resistant to ceftriaxone, drug of choice for treating salmonellosis in children. Available at http://www.nejm.org/doi/full/10.1056/NEJMoa010315#t=article.


Sixteen percent of samples taken from processed turkey plants in the Midwest over the course of a year detected *Salmonella*, which in turn demonstrated varying levels of antimicrobial resistance. The most common resistance was seen to tetracycline, streptomycin, sulfamethoxazole and ampicillin. Available at http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2672.2003.01815.x/full.


*Campylobacter* from humans and retail meats showed limited overlap, suggesting retail meat is not a unique route of *Campylobacter* transmission.


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Erythromycin is often the drug of choice for treating campylobacteriosis, while the similar macrolide antibiotic, tylosin, is FDA-approved in chicken feed at subtherapeutic levels to promote growth. In this feeding study, where chicks were raised with or without tylosin, it was found that tylosin in feed results in lower numbers of *Campylobacter*, but those remaining were erythromycin-resistant. Available at http://ps.fass.org/content/86/6/1229.full.


Demonstrated a reservoir of *Campylobacter* resistance in U.S. retail chicken. Available at http://aem.asm.org/content/71/8/4510.long.


Finds that while *Campylobacter* contamination does not significantly differ in poultry raised conventionally versus antibiotic-free, the former were more likely to harbor bacteria that were antibiotic-resistant. Available at http://ehp03.niehs.nih.gov/article/info:doi/10.1289/ehp.7647.

Specific *E. coli* phylogroups which are the main cause of UTIs in Denmark, also exist in *E. coli* samples of animal origin, such as from broiler chicken meat, pork meat, chickens and pigs. Animal isolates have similar antibiotic-resistance patterns as those collected from UTI patients and community-dwelling humans, suggesting that food animals and meat may be a source of such isolates to humans.

Of 340 antimicrobial-resistant and -susceptible *E. coli* isolates from retail meat and human stool in a single community, nearly 20 percent of meat-source resistant *E. coli* represented ExPEC. Resistant isolates from stool were more similar to resistance isolates from meat than to susceptible *E. coli* from stool, suggesting foodborne transmission. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3186705/.


Resistant and susceptible *E. coli* from NARMS retail meats demonstrated great variance by meat type, with chicken and turkey isolates having consistently higher virulence scores than beef and pork isolates. Supports the hypothesis that antimicrobial-resistant *E. coli* in retail meats emerge from a host species-specific lineage due to the direct effect of selection pressure from use of antimicrobials or as part of the organisms’ adaptations to their respective hosts. Available at http://cid.oxfordjournals.org/content/49/2/195.full.


Among *E. coli* isolated from 1,667 patients over six years with UTIs, 49 percent were resistant to trimethoprim-sulfamethoxazole at a rate of 49 percent. Twelve percent were found to be from a specific group previously collected from food animals or retail poultry products as well, suggesting contaminated food may be a source of drug-resistant UTIs. Available at http://cid.oxfordjournals.org/content/46/5/689.full.


Comparison of susceptible and resistant *E. coli* collected from hospital patients, healthy vegetarians, and poultry that were raised conventionally and without antibiotics suggests many resistant human isolates may originate from poultry. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2792839/.


Concludes that retail meats often are contaminated with resistant *E. coli*. A large portion of samples demonstrate *E. coli* resistant to tetracycline (59%), sulfamethoxazole (45%), streptomycin (44%), ampicillin (35%) and gentamicin (12%).

**Transmission via farmers, workers, veterinarians**


Of 341 Dutch pig slaughterhouse workers tested, 3.2 percent carried MRSA, of which 75 percent was the live-stock-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*. Available at http://ehp03.niehs.nih.gov/article/info/doi/10.1289/ehp.10191.

**Additional studies**


Enterococci bacteria appear prevalent in commercial beef processing plant settings and include a pool of resistance genes.

7.5 percent of Belgian and 1.4 percent of Danish veterinarians were colonized with livestock-associated MRSA (ST398), highlighting the importance of preventive measures.


Livestock-associated MRSA in farmers is strongly related to intensity and duration of animal contact. The fact that current LA-MRSA strains poorly colonize most humans is important for MRSA control strategies. Available at http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0016830.


An estimated 25 to 35 percent of pig and veal calf farmers in the Netherlands carry MRSA. MRSA-negative field workers were tested for MRSA before and after visiting MRSA-positive pig and veal farms. Seventeen percent of such visits resulted in workers converting to MRSA-positive status, but in most cases, workers lost the MRSA strain within 24 hours. Available at http://jcm.asm.org/content/49/3/1030.long.


3.7 percent of pork producers selected from the National Pork Board’s producer database reported being diagnosed with a MRSA infection. Available at http://www.aaem.pl/pdf/17331.htm.


Prevalence of MRSA colonization was 20 percent in farmers and 45 percent of pigs in Canadian pig farms studied. Humans residents of MRSA-free pig farms also were MRSA-negative. Available at http://www.apuabril.org.br/arquivos/veterinaria06.pdf.


Provides evidence that persons exposed to animals on farms in Denmark, particularly pig farms, have an increased chance of being colonized or infected with MRSA CC398. Available at http://wwwnc.cdc.gov/eid/article/14/9/07-1576_article.htm.


Reports a comprehensive evaluation of veterinary personnel for carriage of MRSA. Samples from veterinary personnel volunteers, from 19 different countries, indicated 6.5 percent were MRSA-positive; among those working with larger animals, prevalence was 15.6 percent. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3291342/.


Reports a mother and baby who were found to be carriers of MRSA. A case study followed; finding that the father was a pig farmer, a screening was done to test coworkers, pigs, and family members. Three coworkers, eight of 10 pigs and the father were found to be carriers of MRSA. Molecular characterization of the samples clearly revealed transmission of MRSA from pigs to humans. These findings show clonal spread and transmission of MRSA between humans and pigs in the Netherlands. Available at http://www.biomedcentral.com/1476-0711/5/26.


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. Reports that the frequency of MRSA among the group of regional pig farmers is more than 760 times higher than that among the general Dutch population. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3367632/.

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. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3323198/.


Resistant bacteria were more prevalent among residents or workers on farms where hogs were fed antibiotics. E. coli was obtained from 115 residents on 43 farms; 25.8 percent were resistant to at least one antibiotic. Farming feeding antibiotics to animals appears to have a heightened occupational hazard from exposure to resistant bacteria.


A survey of E. coli in poultry and in workers in close contact with animals strongly supports the transmission of resistant clones and resistance plasmids of E. coli from broilers and turkeys to humans. Available at http://jac.oxfordjournals.org/content/47/6/763.full.


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.

Additional studies


In measurement of water quality from locations impacted by confined animal feeding operations (CAFOs) compared to reference sites and sites located upstream and downstream of wastewater treatment facilities, agriculturally impacted sites had a significantly greater proportion of isolates that showed resistance to multiple antibiotics. Available at http://www.nocafos.org/EMUstudy.pdf.


Bovine fecal samples were screened for E. coli strains producing CTX-M, extended-spectrum β-lactamase enzymes that allow them to inhibit the antimicrobial effects of penicillins and cephalosporins. Six percent (3/50) of fecal samples harbored CTX-M genes. Cefotiofur use in cattle may provide the selection pressure for CTX-M genes to disseminate.


Selective pressures appear to exert an effect on the amount of resistant isolates recovered from waste lagoons on swine farms involving farrowing, nursery and finisher pigs. Elevated antibiotic use in nursery versus finisher pig environments correlates with more contamination with antibiotic-resistant bacteria in manure lagoons for the former. Available at https://www.soils.org/publications/jeq/articles/38/6/2431.

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.
Typical storage practices of poultry litter are not sufficient for eliminating drug-resistant enterococci and staphylococci, which may then be delivered to the environment by land application, aerosolization or water contamination during runoff.


Ninety-eight percent of bacteria from air samples from hog CAFOs had resistance to at least two antibiotics used in animal production and a greater potential for worker exposure to resistant bacteria, suggesting that exposure to air from swine operations may allow multidrug-resistant bacteria to be transferred from animals to humans. Available at http://ehp03.niehs.nih.gov/article/info:doi/10.1289/ehp.7473.


This study finds repeated applications of antibiotic-laden manure to soils provide an environment in which selection of antibiotic-resistant bacteria can occur. Available at http://www.moag.gov.il/NR/rdonlyres/5DAE251F-5653-4E3B-AD1D-EBA877F6989A/0/AntibioticuseinagricultureandimpactonterrestrialenvironmentAdvAgron_2005.pdf.


Determinants of tetracycline resistance were found in hog manure lagoons, in the groundwater up to 250 meters downstream from the lagoons, and in the soil microbiota. Available at http://aem.asm.org/content/67/4/1494.full.

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.

Additional studies


In environmental reservoirs where resistance to multiple antibiotics or to antibiotics plus heavy metals often co-exist and often are physically linked, reductions in the usage of a limited number of those agents may not quickly and fully reverse resistance as it can persist.


USDA surveys of producers find routine feed antibiotics are not necessary in many cases. In 2006, 42 percent of broiler producers don’t use them, and there was no correlation between size and antibiotic use. In contrast, about 20 percent of small feeder-to-finish hog producers surveyed in 2004 used routine low dose antibiotics in feed, versus 60 percent of the largest operations. Among pigs, size matters. Available at http://www.ers.usda.gov/publications/eib-economic-information-bulletin/eib43.aspx.


Reviews the effect on resistance in Campylobacter following withdrawal of enrofloxacin, a fluoroquinolone, from use in treating poultry. Concludes “judicious use of antimicrobial agents should be stressed to preserve the efficacy of these important chemotherapeutic agents.” Available at http://cid.oxfordjournals.org/content/44/7/977.full.


Observations show that it is possible to reduce the occurrence of antimicrobial resistance in a national population of food animals when the selective pressure is removed. Cases in which resistance to vancomycin was linked to resistance to erythromycin were exceptions. In such cases, resistance did not decrease until the use of both avoparcin and tylosin was limited. Available at http://aac.asm.org/content/45/7/2054.full.


Controlling bacterial infections in farm animals by other means than antibiotic use includes improved hygiene, isolation of sick animals, replacing live breeding animals by semen and embryos, etc.


Discusses some of the changes made in Swedish methods for raising farm animals after a ban on the use of antibiotics as growth promoters; the study also reviews some of the difficulties encountered, and the accomplishments. Also Wierup M. The Swedish experience of the 1986 year ban of antimicrobial growth promoters, with special reference to animal health, disease prevention, productivity, and usage of antimicrobials, in Microb Drug Resist.2001;7(2):183-90. Available at http://www.tufts.edu/med/apua/news/16__2a.html.

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.

Additional studies


Study of growth promoting antibiotics (GPA) in pork production: "Our results imply that antibiotics used for growth promotion are of value mainly when four or fewer different rations are used in finishing." Available at http://ageconsearch.umn.edu/bitstream/43146/2/Miller%20JAAE%20December%202003.pdf.


Removal of growth-promoting antibiotics from broiler chickens reduced livability by an average of only 0.2 percent on the Delmarva Peninsula and 0.14 percent in North Carolina. Livability varied, however, from a reduction of 0.5 percent to a positive impact of 0.3 percent. Removing growth promoting antibiotics resulted in no reports of field outbreaks of disease and did not affect total farm condemnations. Available at http://japr.fass.org/content/11/4/431.full.pdf.

Endnotes


