Natural Resources Defense Council, November 18, 2013

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   a. In 1977, FDA determined that the use of penicillin and tetracycline in animal feed were "not shown to be safe" for human health because of the risks of antimicrobial resistance.
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      In preparing the Guidance, the FDA reviewed key scientific studies and reports and concluded that "the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health." (See id. at 13.) The FDA has not issued a single statement since the issuance of the 1977 NOOHs that undermines the original findings that the drugs have not been shown to be safe.

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      Nevertheless, the Agency has all but made a finding that the subtherapeutic use of antibiotics in food-producing animals has not been shown to be safe. In the course of this litigation, the Agency has conceded that "the phenomenon of antimicrobial resistance exists, [that] antimicrobial resistance poses a threat to public health, [and that] the overuse of antimicrobial drugs in food-producing animals can contribute to the development of antimicrobial resistance." (See Memorandum of Law in Support of the Government's Motion for Summary Judgment on Plaintiff's First Supplemental Complaint at 2.) The Agency has also stated that it "has reviewed the recommendations provided by ... various published reports and, based on this review, believes the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health." (See Rec. at 179.) These statements, while not the equivalent of a finding that triggers a withdrawal proceeding under the FDCA, indicate that the Agency recognizes that these drugs pose a risk (possibly a very serious risk) to human health. However, instead of taking the statutorily prescribed action—making a finding that the drugs are not shown to be safe and initiating withdrawal proceedings—the Agency has pursued a course of action not foreseen by Congress.

   e. Currently on appeal at the 2nd Circuit

3. FDA Guidance:
    a. Concerns about voluntary nature of guidance
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4. Science on antibiotic resistance and use of antibiotics in livestock
    a. Major scientific medical and scientific institutions agree that antibiotic use in livestock is contributing to the resistance crisis (Fact Sheet)
    b. The CDC recently stated, "Up to half of antibiotic use in humans and much of antibiotic use in animals is unnecessary and inappropriate and makes everyone less safe." (CDC, 2013)
    c. In 2010, the CDC wrote to the House Energy and Commerce Committee:

       There are multiple North American studies describing how:

       • *Use of antibiotics in animals results in resistant bacteria in food animals*
       • *Resistant bacteria are present in the food supply and transmitted to humans*
       • *Resistant bacteria result in adverse human health consequences (such as increased hospitalizations)*

    d. People living closer to fields treated with pig manure and near pig CAFOs had greater incidence of antibiotic-resistant skin infections in Pennsylvania. (Casey, 2013)
    e. Introduction of antibiotics on chicken farm led to increase in resistant bacteria in chickens and workers and subsequent removal of antibiotics led to decline in resistant bacteria. (Levy, 1976)
    f. Poultry workers in the eastern shore of Maryland and Virginia had 32 times the odds of being colonized with gentamicin-resistant *E. coli* as community residents and an elevated risk of carrying multidrug- resistant *E. coli.* (Price et al, 2007)
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       Studies indicate a strong link between E. coli found in poultry and ExPEC [E. coli] strains recovered from humans, including genetic similarities and common antimicrobial-resistance patterns. . . . Authors indicate that although there are no known studies that can prove direct transmission between humans and food-animals, the weight of available evidence supports the presence of a food-animal reservoir for ExPEC.

    h. WHO report summarizes the science and risks of antibiotic use in livestock (Chap. 4)
    i. Review study summarizes the science through 2011 (Marshall & Levy, 2011)
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        i. *However, even if health improves, it is not certain that established practices and consumption will change [without regulation requiring change], since most antimicrobial agents for growth promotion and prophylaxis are used*

without any evidence of the need for, or benefit from, their use. (WHO 2012, p. 59)

   ii. Although benefits of antibiotic use are often put forward and deserve consideration, most of the claims have not been substantiated and a body of literature exists that lends support to an association between antibiotic use in food animals and antibiotic resistance bacteria in humans. (Lander et al 2012)

5. Studies suggest small increases in cost from transitioning away from non-therapeutic uses of antibiotics
   a. Eliminating antibiotics in animal feed estimated to increase the costs of chicken by 1.5-2.5% and pork by 3-6% in 1999. This translates to an increase in cost for the average consumer of an additional $5-10 per year. In today's dollars, that's about $7-14 per year. (National Research Council, 1999)
   b. Other studies place the costs of removing antibiotics from feed in the range of 2% for chicken producers and in the range of 4% for pork producers (see GAO Summary)
   c. Data from farmer surveys estimates that broiler grow-out operations that are required to not use antibiotics in feed or water are paid grower fees that are 2.1% higher on average. They speculate that this is due to higher costs of production and management at the grower level when no antibiotics are used. (Macdonald and Wang 2011)
   d. The costs of switching practices for Danish pork producers to transition away from nontherapeutic use of antibiotics was estimated to be about 1%. This does not account for capital costs if physical improvements proved necessary, but industry representatives said that they "believed that changes to pig production systems other than those accounted for in the economic analysis presented above were driven by other factors and were not the result of withdrawal of antimicrobial growth promoters." (WHO 2003)
   e. Denmark has an industrial system of pork production and produces nearly 30 million pigs a year, close to the size of Iowa's pig industry. It has reduced antibiotic use, while increasing pork production, and all while maintaining food safety and with a negligible impact on the economy. (Aarestrup 2010)
6. Feasibility (MacDonald and McBride 2009):

   Other technologies, including better sanitation and testing procedures, can be substituted for these practices in some production stages especially in poultry production. These practices, used in most operations not providing their animals sub therapeutic antibiotics, include: the testing of feed for specific pathogens; testing of flocks routinely for disease; cleaning out and sanitizing houses after each flock; and typically were required to have a hazard analysis and critical control point plan in place to direct food safety measures. The farms that do not rely on sub therapeutic antibiotics for disease prevention were nearly twice as likely to follow these procedures as those farms that used sub therapeutic antibiotics.

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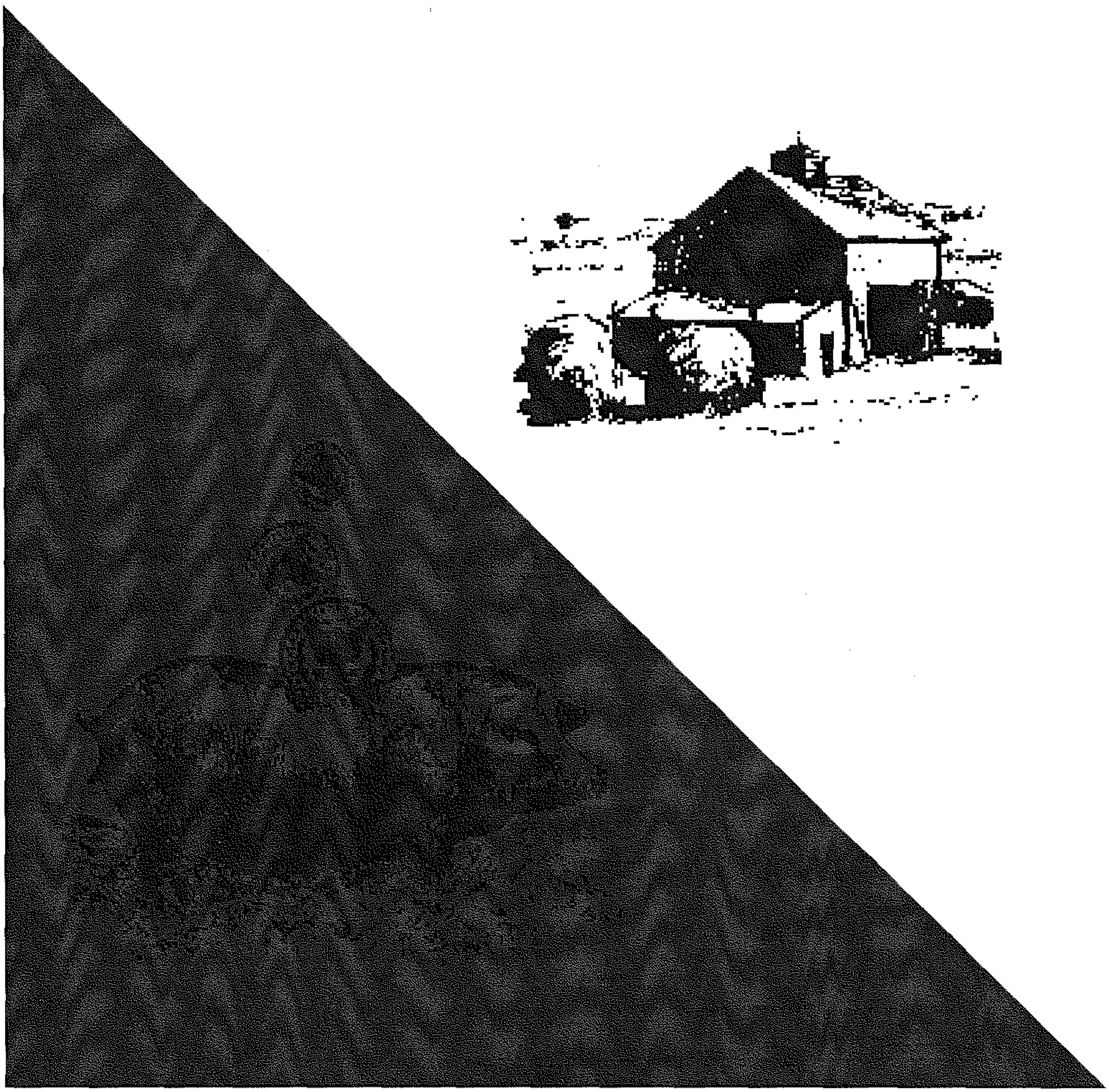
Industrial Food Animal Production in America:

Examining the Impact of the Pew Commission's Priority Recommendations



Industrial Food Animal Production in America: Examining the Impact of the Pew Commission's Priority Recommendations

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Fall 2013

Public Health Recommendations 1

1. Phase out and then Ban the Nontherapeutic Use of Antimicrobials

Summary and basis for recommendation

The practice of administering antimicrobials to food animals for purposes other than treatment of a diagnosed illness or control of an existing outbreak has been commonplace in IFAP for several decades. Many of the drugs used in this context are no different from those used in human medicine. In the context of food animal production, the use of antimicrobials continues to increase steadily and greatly surpasses uses in humans. Administering nontherapeutic antimicrobials to food animals is particularly problematic since chronic administration of low doses of antimicrobials contributes to the evolution and proliferation of antimicrobial-resistant strains of bacteria [3]. Accordingly, the widespread use of nontherapeutic antimicrobials in animals and the selection of genes conveying resistance can vastly diminish the effectiveness of antimicrobials to treat animal and human disease [4].

Data on antimicrobial administration in food animal production are extremely limited. Usage data are neither collected nor reported by the Food and Drug Administration (FDA). Instead, sales data are collected from pharmaceutical manufacturers and released in summary form by the FDA on an annual basis, starting in 2009. To date, these sales data serve as the only surrogate for antimicrobial use in food animal production.

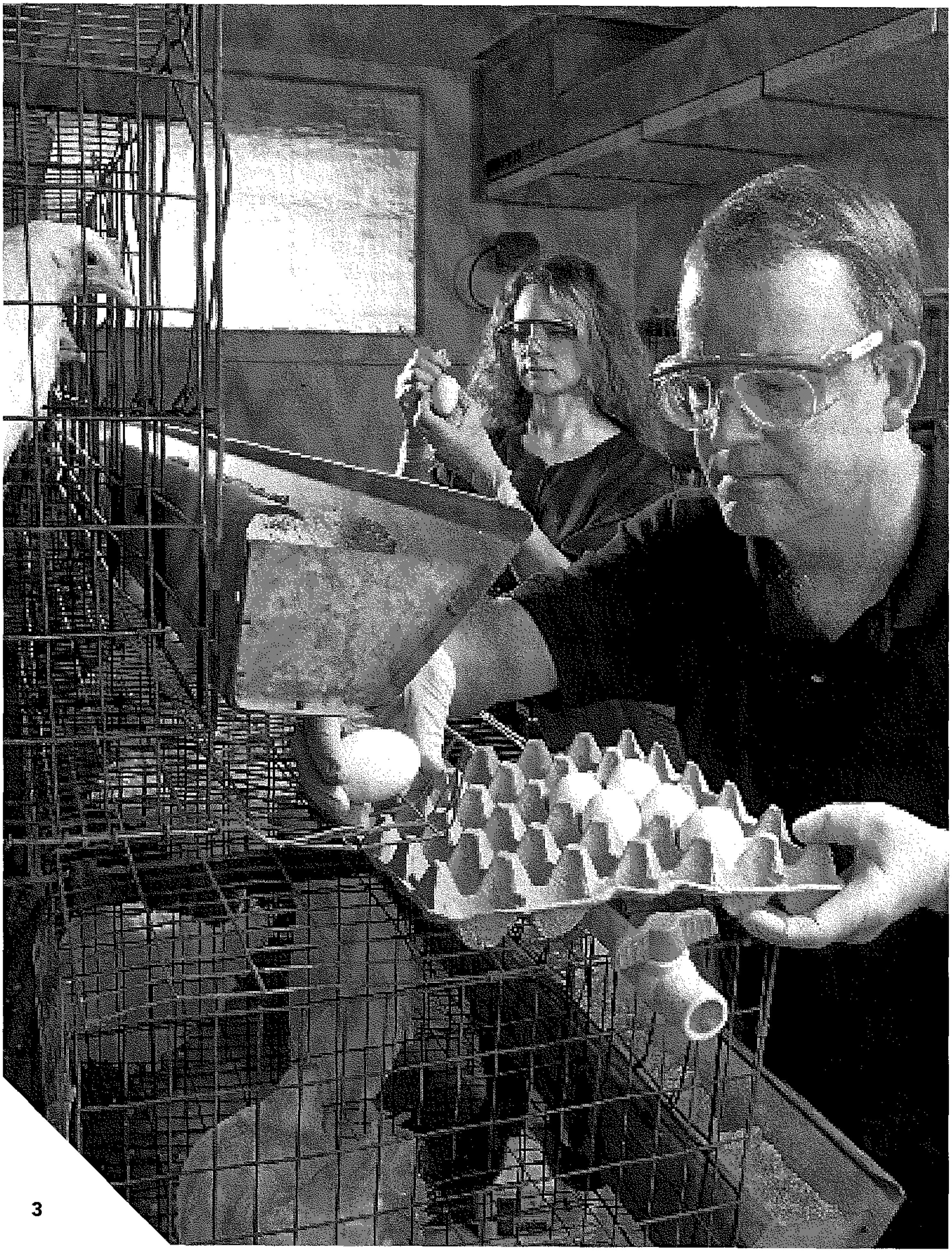
Based on FDA data, 29.9 million pounds of antibiotics were sold for use in meat and poultry production in 2011 [5], representing 80 percent of the total volume of antibiotics sold in the United States for any purpose [6]. Some 685 drugs are approved by the FDA for use in animal feed [7].Effects from these drugs, however, reach far beyond their direct administration to food animals. The use of animal byproducts can cause the drugs to be recycled back into food production, further contributing to antimicrobial pressure on bacteria present in the food animal production setting. A recent study, for example, has shown that feather meal, a poultry byproduct used as a feed additive in poultry, swine, ruminant, and fish feed, is a source of numerous antimicrobial (and other pharmaceutical) residues [8]. All samples tested had between two and ten measurable antibiotic residues. In addition, fluoroquinolones, a class of antibiotics banned from use in poultry in 2005, were found in the majority of samples tested.

Antibiotic-resistant bacteria easily migrate from animal production sites into the air, water, and soils surrounding these sites [9-12]. They can then be transported to members of rural communities and beyond through a variety of mechanisms, including land application of animal waste as fertilizer [13]. Workers at IFAP operations, food animal transport trucks, and nondomesticated animals (rats, birds of prey, flies) have been shown to carry antibiotic-resistant bacteria [14-19]; these vectors are capable of transporting bacteria off the farm site.

Humans may be exposed to antimicrobial-resistant bacteria originating from IFAP through a wide array of environmental and dietary pathways, including direct contact with animals, contact with soil, air, or water contaminated with animal waste, and consumption or handling of contaminated food [3].

Antimicrobial-resistant infections are of public health significance because they diminish the efficacy of medical treatment, resulting in increased morbidity and mortality as well as longer and costlier hospital visits [20]. The additional costs associated with antibiotic resistance have been studied most effectively via comparisons between methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) [21]. A study comparing hospitalization costs between patients with infections of these types found that even after accounting for the severity of the disease, the average hospitalization cost for a MRSA patient was $45,920 compared to $9,699 for a MSSA patient [22]. A Canadian study found that MRSA infection increased hospital stays by a mean of 14 days [23]. A study of patients of the Minneapolis Veterans Affairs Medical Center found that compared to MSSA patients, MRSA patients were 12 percent more likely to die [24].

After considering evidence linking animal agricultural antibiotic use practices to infection risks in humans, the



Commission recommended that the nontherapeutic use of antimicrobials begin to be phased out and eventually banned. As a first step, the Commission suggested an immediate ban on any new approvals of antimicrobials for nontherapeutic use in food animals and called for an FDA retroactive investigation of previously approved antimicrobials. Since the Commission issued this recommendation, new science has emerged that highlights the severity of the public health threat posed by this practice and reinforces the validity of the recommendation.

This section will briefly discuss key scientific developments in the understanding of the public health impacts related to the use of antimicrobials in IFAP that have occurred since the publication of the Commission report in 2008.

Antimicrobial-Resistant Bacteria in Retail Meat

The National Antimicrobial Resistance Monitoring System (NARMS) tracks antimicrobial resistance in bacteria isolated from food animals, retail meats, and humans. The FDA is responsible for testing retail meat isolates, while the U.S. Department of Agriculture and the Centers for Disease Control and Prevention focus on food animal and human isolates, respectively. NARMS is the primary source of information on antimicrobial resistance in foodborne pathogens available in the United States.

The FDA's retail meat program analyzes *Salmonella*, *Campylobacter*, *Escherichia coli*, and *Enterococcus* bacteria in collaboration with 11 state public health laboratories. Each month, participating laboratories purchase 40 meat and poultry samples, including 10 samples each of chicken breast, ground turkey, ground beef, and pork chops. All samples are cultured for *Salmonella* while only poultry (chicken breast and ground turkey) samples are cultured for *Campylobacter*. Four laboratories also culture samples for *E. coli* and *Enterococcus*. The FDA receives all bacterial isolates for analysis, including antimicrobial susceptibility testing.

NARMS has reported concerning levels of antimicrobial resistance in bacteria isolated from retail meat. In 2011, the most recent year reported, *E. coli* isolated from 37.5 percent of chicken breast samples and 64.4 percent of ground turkey samples were resistant to at least three antimicrobial classes. Similarly, 43.3 percent of *Salmonella* isolates from chicken breast, 33.7 percent of ground turkey isolates, 42.9 percent of ground beef isolates, and 50 percent of pork chop isolates were resistant to three or more classes. Similar results were reported for *Campylobacter* and *Enterococcus* isolates from chicken breast and ground turkey [25].

Another study, which reviewed 1,729 *E. coli* isolates from humans and food animals collected over six decades, found that multidrug-resistant pathogens increased from 7.2 percent in the 1950s to 63.6 percent in the early 2000s [26].

NARMS does not monitor *Staphylococcus aureus* in retail meat, though it has announced a pilot study that would do so. Recent literature suggests that multidrug-resistant *S. aureus* (MDRSA) is prevalent in U.S. meat and poultry products. Waters et al. (2011) reported that *S. aureus* contaminated 47 percent of 136 meat and poultry samples purchased from 26 grocery stores in five cities; a majority of isolates (52 percent) were resistant to three or more antimicrobial classes [27]. Separately, O'Brien et al. (2012) reported that 64.8 percent of 395 pork samples purchased from 36 stores in three states were contaminated with *S. aureus* and that 6.6 percent were contaminated with MRSA [28].

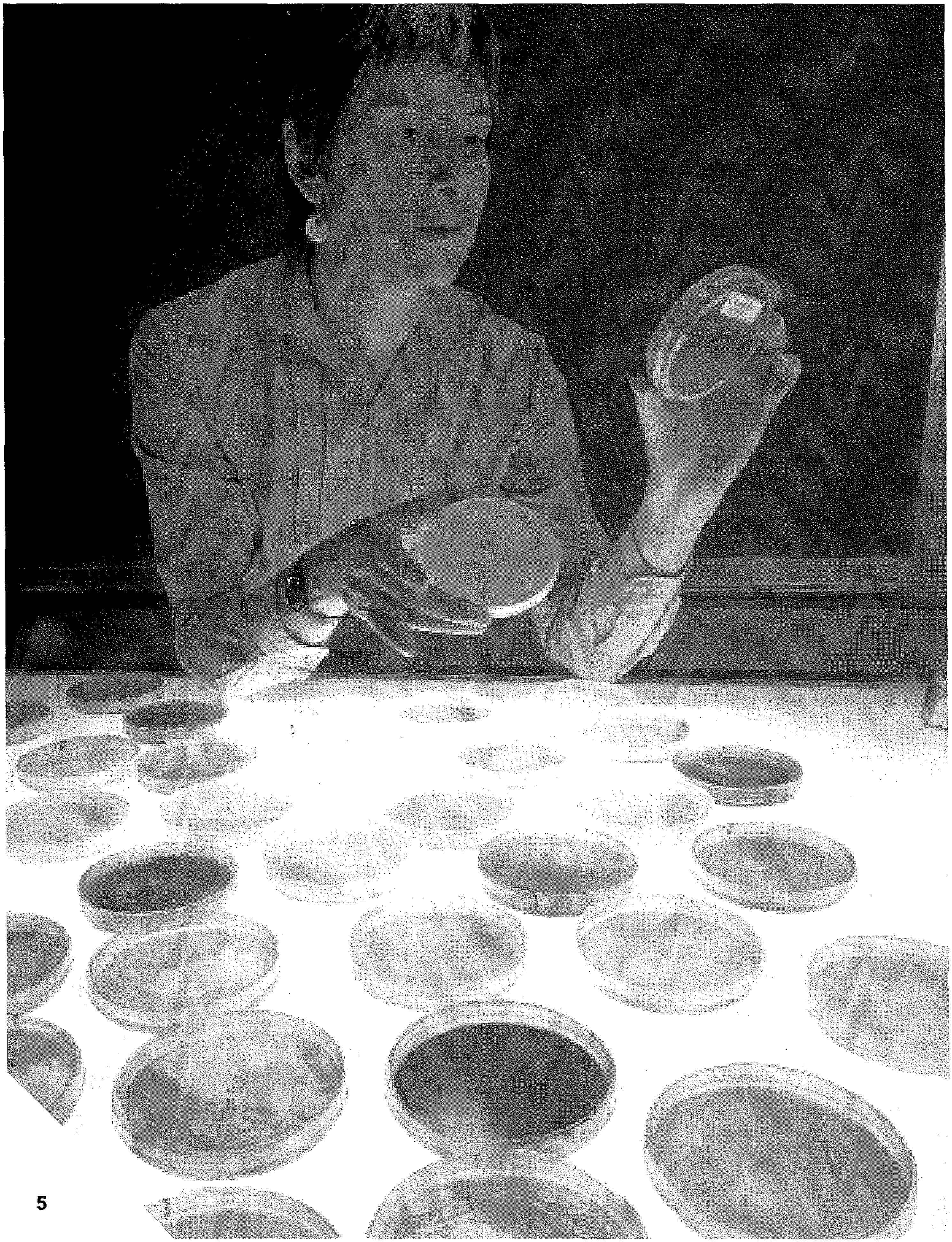
Foodborne Illness and Other Food-Related Exposures

Foodborne illness is responsible for significant morbidity and mortality in the United States, and in some cases, antimicrobial-resistant pathogens cause these illnesses. A 2013 report in *The Lancet Infectious Diseases* highlighted trends in drug-resistant *Salmonella* infections around the world and raised concerns about potentially untreatable infections in the future. Researchers estimated that these serious infections could cause an excess 1,000 deaths per year in the United States if antibiotic treatments were to become ineffective [29; 30].

A Canadian study of *Salmonella Heidelberg* isolates from retail chicken meat and from human infections found a strong correlation in rates of resistance to cetiofur, a cephalosporin drug that had been used in hatcheries around the time of the study. The authors asserted that cetiofur use in poultry production selects for broad spectrum cephalosporin resistance in bacteria present on chicken meat and humans [31].

Beyond gastrointestinal foodborne illness, a growing body of research has associated foodborne and food-related *E. coli* to urinary tract infections (UTIs), which are among the most common bacterial infections globally [32]. Most of the 130–175 million cases per year worldwide are caused by *E. coli* [33]. In the United States, the economic burden of UTIs is approximately $1.5 billion annually [34]. Severe or repeated cases can cause complications including kidney damage (pyelonephritis) and blood infections (septicemia) [32].

Antimicrobial treatment, which can be of limited success in treating gastrointestinal forms of *E. coli*, is critical for treating UTIs and other diseases including meningitis, pneumonia, and sepsis. Over the past several decades, multiple classes of antibiotics used to treat



UTIs have become ineffective due to resistance. Further, contaminated food sources have been implicated in outbreaks of UTIs (Nordstrom 2013).

Concern has also been raised over the continued use of arsenic-based antimicrobial drugs in food animal production [35]. While evidence related to the environmental arsenic contribution was available at the time of the release of the previous Commission report [3], new research has shown that the administration of arsenic-based drugs contributes to concentrations of arsenic in chicken meat [36] and liver [37]. Residues of inorganic arsenic in edible chicken tissues increase the cancer risks of chicken consumers. While the most commonly used arsenic-based drug (roxarsone) was voluntarily suspended from sale by its manufacturer in 2011, the same sponsor continues to sell a chemically similar product (nitarsone) that is used in turkey production [38]. Beyond direct dietary exposures, new research has shown that feather meal, as a feed additive for poultry, swine, ruminants, and fish, is a mechanism for cycling arsenic through the animal production system [39].

Occupational Exposures

Since the publication of the Commission report, new research has demonstrated that the workplace is a site of antibiotic-resistant pathogen exposure for IFAP workers [3]. Much of this research has focused around characterization of *S. aureus* in swine production.

A study of nasal swabs taken from animals and workers at 45 swine operations (21 antibiotic-free and 24 conventional) in Illinois, Iowa, Minnesota, North Carolina, and Ohio used molecular characterization to examine rates of carriage of livestock associated MRSA (LA-MRSA).Carriage of LA-MRSA was documented in workers and pigs at conventional farms but was not found in any nasal swabs from antibiotic-free operations [14; 15].

A 2013 study examining workers at industrial livestock operations (with nontherapeutic antimicrobial use) and antibiotic-free livestock operations in North Carolina found similar carriage rates of *S. aureus* and MRSA among workers of both types of operations, but only found livestock-associated MRSA and MDRSA in the nasal passages of industrial livestock operation workers [15].

In addition to studies of IFAP workers, new research has shed light on the origins of LA-MRSA. An international team used whole genome sequence testing to trace the lineage of MRSA clonal complex 398 (CC398), widely recognized as an important strain of LA-MRSA, through the examination of the genomes of 89 CC398 isolates from a wide array of animal and human settings [40]. Using this specialized tool, the authors found that MRSA CC398 likely originated as a methicillin-susceptible form of *S. aureus* in humans, was transferred to swine populations where it acquired methicillin resistance due to antibiotic pressure from routine antibiotic use, and was returned to human populations as a drug-resistant strain.

Community and Environmental Exposures

Additional evidence has been generated regarding risks to rural communities posed by antibiotic-resistant bacteria originating at food animal production sites.A large fraction of the antimicrobials fed to farm animals is excreted unaltered (up to 75 percent) and may remain in soil following land application of manure. Antimicrobials and antimicrobial-resistant pathogens can also persist in water, as they are typically not removed completely in wastewater treatment and can be re-released to the environment [41]. Studies in China have identified antibiotic resistance genes in water, sediment samples, and fields next to swine feedlots [41; 42].

A recently published study used electronic health records and data from nutrient management plants to examine spatial relationships between animal production sites and crop field manure exposure and community associated MRSA (CA-MRSA) and skin and soft tissue infection (SSTI). The study found associations between geographic proximity to swine manure application (spray fields) and high-density livestock facilities to CA-MRSA and SSTI. This research suggests that the environmental presence of swine manure and IFAP facilities provides a pathway to antimicrobial-resistant human infections [43]. The study also concluded that more than 10 percent of CA-MRSA would be prevented if exposures to swine waste applied to cropland were eliminated.A different study of clinically diagnosed MRSA patients found that patients living in areas with higher livestock density were more likely to have LA-MRSA than other types of MRSA [44].

Summary of New Evidence

Since the Commission's 2008 recommendations to phase out and ban the nontherapeutic use of antimicrobials in farm animals, additional scientific evidence has strengthened the case that these uses pose unnecessary and unreasonable public health risks and have economic consequences. As discussed above, antimicrobial-resistant pathogens can transfer between animals and humans; food-related, environmental, and community exposures contribute to the burden of antimicrobial-resistant infections in humans. Gastrointestinal foodborne illness, MRSA, UTIs, and arsenic-related disease are several of the human health concerns associated with nontherapeutic antimicrobial use in IFAP. Further, from countries that have limited or banned antimicrobial use, we have learned that withdrawal of antimicrobials as growth promoters results in reduced rates of resistance in food animal isolates [29]. This change in policy is possible without reducing rates of production when combined with more frequent cleaning of animal housing and reduction in animal crowding, as has been seen in the Danish swine industry; since 1994, the Danish industry has seen antibiotic use fall from more than 25 mg to 10 mg of antibiotic per kg of meat produced, all while increasing overall production by about 10 million pigs annually [45].

Recent history related to the recommendation

Federal Legislative Efforts

Preservation of Antibiotics for Medical Treatment Act (1999 to present)

The Preservation of Antibiotics for Medical Treatment Act (PAMTA), currently sponsored by Rep. Louise Slaughter (D–NY), and its Senate companion bill, the Preventing Antibiotic Resistance Act, currently sponsored by Sen. Dianne Feinstein (D–CA), would require the FDA to withdraw approvals of nontherapeutic uses of medically important antimicrobials in food animals, except where a company holding an approval demonstrates with reasonable certainty that the nontherapeutic use of the drug will not harm human health by promoting the development of antimicrobial resistance [46;47]. These bills would also require a company seeking a new approval of a nontherapeutic use of a medically important antimicrobial to make the same demonstration; otherwise, approval would be denied.

Because most approvals of nontherapeutic uses are unlikely to meet this standard, enactment of PAMTA would probably result in the withdrawal of most such approvals, effectively implementing the Commission's recommendation with respect to nontherapeutic antimicrobial use. More than 450 public health, medical, and other organizations have endorsed the legislation [48]. Unfortunately, however, PAMTA has failed to pass either house of Congress in the 14 years since its initial introduction and is not expected to pass soon.

Notably, the definition of "nontherapeutic use" contained in PAMTA broadly aligns with the definition recommended by the Commission. In its 2008 report, the Commission defined "nontherapeutic" use as "any use of antimicrobials in food animals in the absence of microbial disease or known [documented] microbial disease exposure" (p. 63). This definition explicitly included use of an antimicrobial for growth promotion, feed efficiency, weight gain, or routine disease prevention, all of which the Commission considered to be nontherapeutic uses.

PAMTA defines "nontherapeutic use" as any use of an antimicrobial except "for the specific purpose of treating an animal with a documented disease or infection" (meaning that microbial disease is present) or in "an animal that is not sick but where it can be shown that a particular disease or infection is present, or is likely to occur" (implying that a microbial disease exposure has transpired) [46;47]. Importantly, the disease or infection in question cannot be present or likely to occur because of standard production practices or conditions. In accordance with the Commission's report, PAMTA explicitly designates growth promotion, feed efficiency, weight gain, and disease prevention as nontherapeutic uses.

Animal Drug User Fee Amendments of 2008

In sharp contrast to countries such as Denmark where antimicrobial use can be traced to individual producers [45], comprehensive data on antimicrobial use in U.S. food animals are not collected. The only comprehensive data that exist in the United States are antimicrobial sales data reported by drug companies to the FDA under Section 105 of the Animal Drug User Fee Amendments of 2008 (ADUFA) [49].

Because the 2008 legislation reauthorizing ADUFA was considered "must-pass" by both the FDA, which derives significant salary support from the user fees authorized under the law, and by the drug industry, which receives swifter review of new animal drugs as a result, the late Sen. Edward Kennedy and Sen. Sherrod Brown sought to implement the Commission's recommendation by including PAMTA in the bill. Following claims that more research was necessary to support restrictions on antibiotic use, the inclusion of PAMTA was scrapped in favor of the current reporting requirements. These requirements were intended to collect data in support of Congressional action, but such action has not been forthcoming.

ADUFA directs the agency to publish annual summaries of reported data. In some cases, sales data may be used as surrogates for antimicrobial use. Unfortunately, the FDA withholds the vast majority of data reported by companies. In the three years for which reports are available (2009–2011), the agency has included only domestic and export sales by antimicrobial class [50]. The sales of classes for which fewer than three companies actively market an antimicrobial are not reported separately; rather, they are aggregated into a "not independently reported" category. This format severely limits the utility of the summaries.

ADUFA must be reauthorized by Congress every five years [49]. The statute directs the FDA to negotiate recommendations for reauthorization with drug companies and to solicit public comments on these recommendations as well. During the 2013 reauthorization, a number of advocacy groups, professional associations, and academic researchers urged the agency to recommend enhancements to the antimicrobial sales reporting requirements [51;52]. As in 2008, ADUFA reauthorization was considered must-pass and therefore was seen as an opportunity to enact enhancements to reporting that the drug industry might oppose otherwise. These requests were to no avail, however; the FDA did not include any enhancements in its recommendations to Congress [53;54]. Rather, the agency separately solicited public comment on enhancements to the annual summaries as part of a public comment period on an "advance notice of proposed rulemaking" (see below).

ADUFA was reauthorized in June 2013 without any changes to the reporting requirements of Section 105; reauthorization is next required in 2018 [55].

Delivering Antibiotic Transparency in Animals Act (2013 to present)

The Delivering Antibiotic Transparency in Animals (DATA) Act, sponsored by Rep. Henry Waxman (D–CA), would amend the reporting requirements contained in ADUFA Section 105 to require drug companies to report additional sales data, and to require integrators to report data on antimicrobial use [56]. The bill would also direct the FDA to include additional information on reported data in the annual summaries, including breakdowns by route of administration and approved indication, animal species, and production class. The legislation, which was introduced in February 2013 prior to reauthorization of ADUFA, has not been enacted.

Antimicrobial Data Collection Act (2013 to present)

The Antimicrobial Data Collection Act, sponsored by Sen. Kirsten Gillibrand (D–NY), would, like the DATA Act, require the FDA to include additional information on antimicrobial sales data in the annual summaries required under ADUFA [57]. It would not, however, require any additional reporting of sales by drug companies or require reporting of antimicrobial use by integrators. It has not been enacted.

Federal Regulatory Efforts

To date, limited federal regulatory activity has occurred since the release of the Commission report. The majority of activity has focused on a series of voluntary FDA guidance documents focused on antibiotic use.

Guidance Documents

The FDA has pursued a voluntary and partial approach to restricting nontherapeutic antimicrobial use. In April 2012, the agency issued one guidance document and published a draft of a second guidance document that together urge drug companies to voluntarily withdraw approvals to market antimicrobials for certain nontherapeutic uses (i.e., growth promotion) while maintaining and likely adding approvals to market these drugs for other nontherapeutic uses (i.e., preventive or chemoprophylaxis use). (Notably, the FDA considers the latter nontherapeutic uses to be therapeutic, though its use of the term is inconsistent with the Commission's recommendation, as explained below.)

In April 2012, FDA issued *Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*, which presented two recommendations [58]. First, antimicrobial use "should be limited to those uses that are considered necessary for assuring animal health." This includes "uses that are associated with the treatment, control, or prevention of specific diseases" but does not include "production purposes (i.e., to promote growth or improve feed efficiency)" (p. 21). Second, antimicrobial use "should be limited to those uses that include veterinary oversight or consultation" (p. 22).

When the FDA issued Guidance 209 in April 2012, it simultaneously published a draft of *Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209* [59]. Guidance 213 is intended to implement the recommendations contained in Guidance 209 by requesting that drug companies voluntarily withdraw approvals to market antimicrobials for use in animal feed and drinking water for "production purposes" such as growth promotion and feed efficiency. It also requests that companies voluntarily amend approvals to market antimicrobials over the counter so that a veterinary prescription or veterinary feed directive (see next section) is required to purchase and use these drugs in feed and water. Guidance 213 requests that companies complete voluntary withdrawals and amendments within three years of the finalization of Guidance 213, which is expected soon.

The voluntary guidance documents are inconsistent with the Commission's recommendation that nontherapeutic use of antimicrobials in food animals be phased out and eventually banned. Most importantly, while the FDA has recommended that "production uses" be discontinued, it has endorsed the continued use of antimicrobials for routine disease prevention, which the Commission explicitly mentioned as an example of nontherapeutic use. Notably, Guidance 213 provides for the replacement of production approvals with disease prevention approvals, something that the drug industry has said it will pursue. In many cases, the doses and durations of antimicrobial use for disease prevention are similar or even identical to the doses and durations utilized for production purposes. This means that while antimicrobial approvals may change under Guidance 209 and Guidance 213, antimicrobial use may not.

The voluntary approach has come under withering criticism from the public health, medical, and other communities concerned about the increase in antibiotic-resistant bacterial pathogens. Many have highlighted the loophole that could allow disease prevention approvals to replace production approvals without altering actual use or selection for antimicrobial resistance [60; 61]. Some have also criticized the reliance on a voluntary approach in place of regulation (i.e., withdrawal proceedings) [62; 63]. These problems are interrelated: Voluntary action by drug companies depends on the companies' ability to replace withdrawn production approvals with new prevention approvals and thereby maintain current sales and use [64].

Veterinary Feed Directive Regulation

A veterinary feed directive (VFD) is essentially a veterinary prescription for a drug administered in feed. Guidance 213 requests that drug companies voluntarily amend current approvals to market in-feed antimicrobials over the counter so that a VFD is required for their use. Simultaneously, the agency is amending the requirements for issuing a VFD, ostensibly to "streamline" the process and encourage the transition from over-the-counter (OTC) to VFD status under the guidance document [65]. The FDA published a draft proposed rule in April 2012 and received comments on it. The agency will next publish a proposed rule and receive additional comments. Finally, the proposed rule will be finalized with any changes made by the FDA.

The Commission recommended increasing veterinary oversight of all antimicrobial use in food animal production. Unfortunately, while Guidance 213 may result in transitioning antimicrobials used in medicated feed from OTC to VFD status, thereby increasing veterinary oversight, changes to the VFD requirements could weaken significantly the meaning and value of such oversight. Most importantly, the draft proposed rule removes the requirement that a VFD only be issued in the context of a valid veterinarian-client-patient relationship (VCPR) [65]. A VCPR exists when the veterinarian, among other things, has recently seen and is personally acquainted with the keeping and care of animals. The removal of the VCPR requirement may allow veterinarians (such as those employed by large integrators) to issue a VFD to an operation without having visited the operation recently and without having examined the animals.

Cephalosporins

In April 2012, the FDA banned certain extra-label uses of cephalosporins [66]. (An extra-label use is an unapproved use of a drug approved for other conditions.) The ban followed the publication of studies finding that certain extra-label cephalosporin uses, especially the prophylactic injection of chicken eggs at hatcheries, promoted cephalosporin resistance in *Salmonella*. Cephalosporin resistance in these bacteria is concerning because cephalosporins are the drugs of choice for treating salmonellosis in pediatric settings; the drugs of choice in adult patients, fluoroquinolones, cause severe side effects in children. The 2012 extra-label use ban came after the FDA withdrew a more comprehensive ban proposed in 2008 following opposition from industry [67].

Advance Notice of Proposed Rulemaking

In August 2012, the FDA issued an advance notice of proposed rulemaking (ANPR) and solicited public comments on multiple issues related to data on antimicrobial sales and use. The agency stated that it intended to consider these comments as it identified approaches to collecting additional data [68]. During ADUFA reauthorization, when public health advocates urged the agency to recommend enhancements to the reporting requirements enacted under ADUFA in 2008, the agency claimed that it would pursue any such enhancements separately following consideration of comments on the ANPR. This engendered skepticism among public health stakeholders, as the ANPR appeared to be merely a means to deflect criticism of agency inaction on antimicrobial resistance during the reauthorization process.

State Legislative Efforts

Legislation that would ban the nontherapeutic use of antimicrobials in food animals or require the labeling of meat and poultry produced with these drugs has been introduced in multiple states, including California, Minnesota, Maryland, New York, and Pennsylvania. None of the bills has passed. In addition to opposition from the drug and food animal industries, opposition from state agencies has been reported. Ban and labeling bills, for example, that were introduced in Maryland in 2013 were opposed by the Maryland Department of Agriculture [69].

Maryland Arsenical Antimicrobial Drug Ban

On January 1, 2013, Maryland became the first state to prohibit the use of roxarsone and most other antimicrobial arsenical drugs in chicken feed [70]. Nitarsone, an arsenic-based drug approved for use in chicken and turkey production, was exempted from the ban.Several other states are now considering similar legislation, including New York [71] and Vermont [72].

State Regulatory Efforts

We could not find evidence of state regulatory measures to control antimicrobial use in food animal production.

Litigation

Natural Resources Defense Council v. Food and Drug Administration

In May 2011, the Natural Resources Defense Council (NRDC) and others sued the FDA, alleging that the agency was obligated to withdraw approvals to market penicillin and tetracyclines for nontherapeutic purposes following a 1977 finding that these approvals were not shown to be safe [73]. The plaintiffs further alleged that the FDA's failure to respond to two citizens' petitions for the withdrawal of nontherapeutic approvals that were submitted in 1999 and 2005 was unlawful. Although the 180-day deadline for agency responses to such petitions seldom is met, the 12 and six years that these petitioners had waited exceeded typical delays.

The FDA responded by attempting to avert both claims, first by denying (and thereby responding to) both petitions in November 2011 and then by withdrawing the 1977 findings during the following month [74-76]. In both cases, the agency claimed that withdrawal proceedings would be too costly and take too long while reiterating that it intended to address certain nontherapeutic approvals as described in the voluntary guidance documents (see above). The plaintiffs amended their complaint to challenge the denials of the petitions as "arbitrary and capricious" because they did not address either petition on its merits, focusing instead on agency resources.

In March 2012, a U.S. magistrate judge ruled that the FDA's failure to pursue withdrawals of penicillin and tetracycline approvals following the 1977 findings constituted an agency action unlawfully withheld and ordered the agency to reissue its findings and initiate withdrawal proceedings [63; 77]. In June 2012, the same judge ruled that the denials of the petitions were arbitrary and capricious and remanded them to the agency for review on their merits [62; 78]. The FDA has appealed both decisions; briefing and oral arguments in the appeal concluded in February 2013. A decision is expected soon.

Government Accountability Project v. Food and Drug Administration

As mentioned above, there have been a number of unsuccessful efforts to access additional antimicrobial sales data that the FDA collects under ADUFA but does not share with the public. Efforts to amend ADUFA during the 2013 congressional reauthorization were unsuccessful. Meanwhile, the agency has announced that it will reformat annual summaries of these data starting this year, but these remain subject to a number of constraints.

In early 2011, the Johns Hopkins Center for a Livable Future (CLF) approached the Government Accountability Project (GAP) for assistance in obtaining additional sales data. GAP submitted a Freedom of Information Act (FOIA) request to the FDA [79]. The agency denied the request, claiming that the requested data were "confidential commercial information" and therefore exempt from disclosure under FOIA (the statute contains a number of such exemptions). GAP appealed administratively to the Public Health Service (PHS), a division of the Department of Health and Human Services that includes the FDA. The PHS denied the appeal in September 2012, likewise holding that the data were confidential commercial information.

In December 2012, GAP filed a complaint in U.S. district court, alleging that the FDA had inappropriately denied the request for additional data [79]. In the FDA's motion for summary judgment, submitted in July 2013, the agency relied on affidavits from 13 drug companies that oppose the release of additional sales data. It is likely that companies' opposition to the release of sales data is based on a desire to avoid heightened scrutiny of their products. Briefing on summary judgment will conclude in September 2013, with a decision to follow.

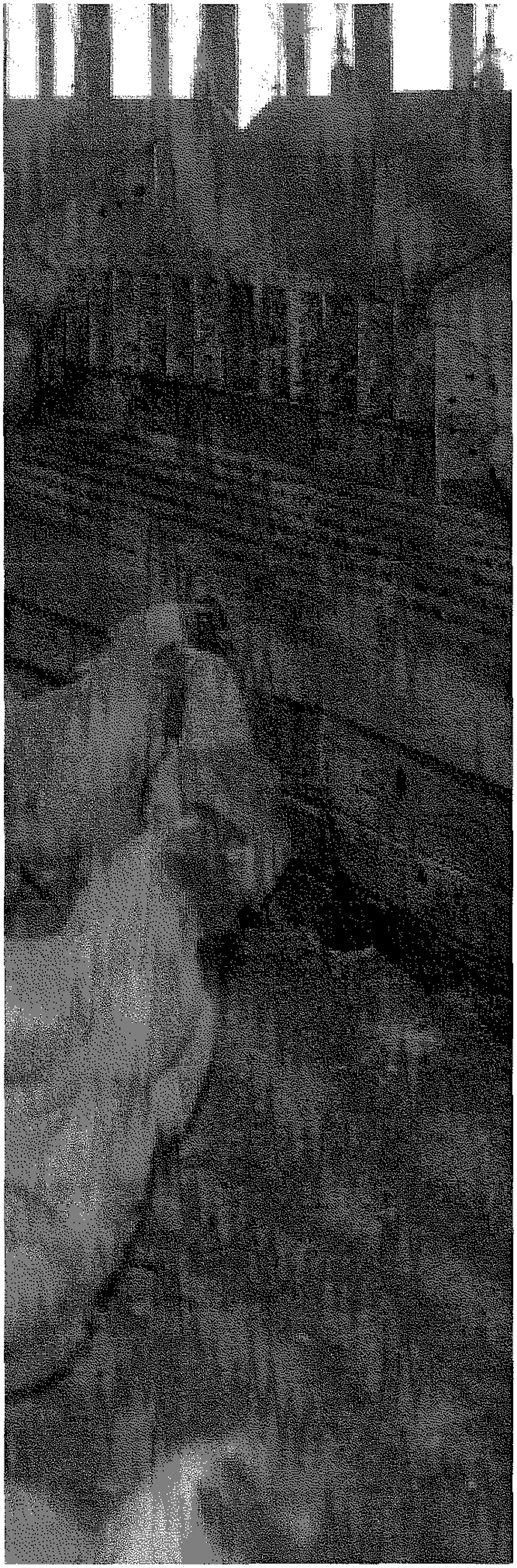
Lawsuits Relating to Arsenical Use

In 2013, two lawsuits were filed relating to the FDA's continued approval for the use of arsenic-based antimicrobial drugs in animal feed. After petitioning the FDA in 2009 to withdraw approvals for arsenic-based drugs in food animal production, the Center for Food Safety, the Institute for Agricultural and Trade Policy (IATP), and seven other groups filed suit in 2013 for not responding to their petition [80].In a separate suit, Food and Water Watch brought charges against the FDA for failing to respond to a Johns Hopkins Center for a Livable Future FOIA request for communications made between the agency and the Pfizer pharmaceutical company (which manufactures the arsenic-based drugs roxarsone and nitarsone) with regard to arsenical drugs [81]. As of September 2013, both lawsuits were pending.

Voluntary Industry Efforts

Suspension of Roxarsone by Pfizer

In June 2011, the FDA announced that Pfizer was voluntarily suspending domestic sales of the arsenic-based drug roxarsone. This action was taken after the FDA advised Pfizer of a new agency-conducted study that found that levels of inorganic arsenic in the livers of roxarsone-treated chickens compared to those in untreated chickens [82]. Despite the findings of its study, the FDA did not formally withdraw the approvals for roxarsone or other arsenic-based drugs.Consequently, Pfizer may reintroduce the drug into the market at will. Further, Zoetis (formerly Pfizer Animal Health) currently markets nitarsone domestically and continues to sell roxarsone outside the United States [36].



Conclusions

Evidence linking antibiotic misuse in IFAP to environmental transport of and human infection with antibiotic-resistant bacteria continues to accumulate. Despite the sizable body of literature supportive of a decision to eliminate antimicrobial use outside the context of veterinarian-diagnosed disease, little progress has been made to change patterns of use. While some meager success has been achieved (in the form of the ban of off-label uses of cephalosporins), the voluntary approach preferred by the FDA and the lack of willingness by the industry to alter its behavior suggest that meaningful change is unlikely in the near future. Similarly, in the case of arsenic-based drugs, the evidence linking use of these compounds to dietary and environmental arsenic exposures has become far stronger. Even with new evidence, the FDA has not taken action to remove these drugs from the domestic market.

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Gina Solomon's Blog

The Spread of Antibiotic Resistant Bacteria from Chickens to Farmers

Posted May 31, 2011 in Health and the Environment

During the past month, I have been privileged to have a talented young physician, Dr. Julia MacIsaac, working with me at NRDC. Dr. MacIsaac is a specialist in internal medicine who is pursuing subspecialty training at UCSF in occupational and environmental medicine. This month, she has been digging deep into the medical literature about antibiotic use in agriculture and the problem of antibiotic resistance. Here is a blog she wrote about this important topic:

I have been researching the human health implications of feeding antibiotics to healthy livestock – a common practice in U.S. agribusiness. As a physician, this issue is important to me because antibiotic-resistant bacteria make my patients sicker and make the drugs that I rely on less effective. In my research, I came across a particularly compelling study – simple, yet elegant – that captures the essence of the problem.

Dr. Stuart Levy, a physician at Tufts University, tested the bacteria that live in the intestines of farmers and farm communities. As background, it's important to know that each one of us have millions of bacteria that live in our intestines that are necessary for digestion – they are the healthy bacteria, or so-called bacteria 'flora'. But, just like bacteria that cause disease, these bacteria can become resistant to antibiotics. Then they can spread the genes that make them resistant to other bacteria that cause disease.

What Dr. Levy and his colleagues did was this: they studied a farm that had not yet incorporated antibiotics into the feed of their chickens – in fact, no feed with antibiotics had been used in the area for at least 7 years prior to the study. They took fecal (stool) samples and studied the bacteria in the stool. They recorded changes over time in intestinal bacteria from the chickens, farm dwellers, and their neighbors. They checked how many of these bacteria were antibiotic resistant, and found that very few were resistant at the beginning of the study.

Then the farm introduced a chicken feed that had an antibiotic in it. It was a tetracycline antibiotic, a drug commonly used in livestock for growth promotion and a drug also used commonly in medicine to treat a variety of common human ailments.

What the group found was this: Within one week of introducing the tetracycline supplemented feed, the chickens' intestinal bacteria contained almost entirely tetracycline-resistant organisms. The intestinal bacteria of the people who worked on the farm also started to become resistant, but more slowly – it took about 3-5 months to see the changes start to occur. Within 5-6 months however, 31.3% of weekly fecal samples from farm dwellers contained almost entirely (> 80%) tetracycline-resistant bacteria.

The research group also evaluated the effects of *removal* of the tetracycline-supplemented food from the farm. Astoundingly, within six months after removal of the antibiotic in the feed, no detectable tetracycline-resistant organisms were found (less than 1%) in the vast majority of the farm workers (8 of 10).

This study illustrated how the simple addition of tetracycline antibiotics into chicken feed can breed antibiotic resistant bacteria at first in the chicken, then the farmers, and how the removal of the antibiotic can significantly decrease the number of resistant bacteria.

There is another aspect of this study that is intriguing: After three to four months' exposure to tetracycline on the farm, the chickens and humans excreted bacteria that were resistant to multiple antibiotics including four OTHER types of antibiotics (streptomycin, ampicillin, carbenicillin and sulfonamides). Resistance to multiple antibiotics was found in more than 50% of the *E. coli* strains from chickens that ate the tetracycline feed for more than ten weeks. The study found that the genes that provided the resistance for the OTHER antibiotics were linked to the genes that provided resistance to the tetracycline antibiotics. So tetracycline selected for not only tetracycline resistance, but for resistance to other antibiotics.

The authors concluded, and rightfully so, that "The rise in frequency of resistant organisms in our environment is the obvious result of antibiotic usage", that "The only means to curtail this trend is to control the indiscriminate use of these drugs" and that these data speak "strongly against the unqualified and unlimited use of drug feeds in animal husbandry and speak for re-evaluation of this form of widespread treatment of animals."

Thirty-five years later, these statements are truer than ever.

You can access the study here (abstract free, full-text requires a subscription): S.B. Levy, G.B. FitzGErald, A. B. Macone. 1976. Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. New England Journal of Medicine. 295 (11): 583-588.

More information on this topic is available on the NRDC website and at Peter Lehner's blog.

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Comments

Kari O'Brien — May 31 2011 04:38 PM

This is an excellent blog! I will be coming back to find more great articles for our Twitter feed.

Thank you for your thorough and thoughtful writing.

Kari O'Brien
Community Manager
The Science Advisory Board

Michael M — Jun 1 2011 12:40 PM

Finally some focus on the real source of the problem! Too often antibiotic resistance is blamed on over-prescription to sick people. But the reality is that these industrial uses dwarf the use of antibiotics in human medicine. There is a good summary of all the factors involved in the development and spread of antibiotic resistance @ http://thescienceofacne.com/how-do-bacteria-become-resistant-to-antibiotics/

SusanK — Jun 3 2011 11:03 AM

So how did antibiotic resistance jump to the farmers? Were they eating the chickens that were fed the tetracycline feed? Thank you for explaining this as it is not clear in the article.

Courtney C — Jun 3 2011 12:18 PM

Is the population at risk of becoming resistant to antibiotics from the consumption of chickens from the store that have been treated with the antibiotics?

Gina Solomon — Jun 3 2011 02:53 PM

This study didn't evaluate exactly how the antibiotic resistance jumped to the farmers and to the local community members in this particular case -- the study just showed that it happened.

Other studies have found antibiotic-resistant bacteria in the animal feces, in the air downwind of confined animal facilities, in the nearby soil and water, and in the meat sold in stores, so there is no one pathway by which these 'super-bugs' escape from the facilities.

The population is most at risk of getting sick from an antibiotic-resistant form of bacteria if they eat chicken from the store that was treated with antibiotics. Studies have shown that antibiotic-treated chicken are far more likely to have contaminated meat compared to organically-raised chicken, and that the contamination is more likely to be drug-resistant.

Comments are closed for this post.

CHANGES IN INTESTINAL FLORA OF FARM PERSONNEL AFTER INTRODUCTION OF A TETRACYCLINE-SUPPLEMENTED FEED ON A FARM

STUART B. LEVY, M.D., GEORGE B. FITZGERALD, PH.D., AND ANN B. MACONE, B.S.

Abstract A prospective study was undertaken to determine whether feeding farm animals antibiotics in feed caused changes in the intestinal bacterial flora of farm dwellers and their neighbors. Chickens were fed tetracycline-supplemented feed (tet-feed), and, as expected, within one week their intestinal flora contained almost entirely tetracycline-resistant organisms. Increased numbers of resistant intestinal bacteria also appeared, but more slowly, in farm members, but not their neighbors. Within five and six months, 31.3 per cent of weekly fecal samples from farm dwellers contained >80 per cent tetracycline-resistant bacteria as compared to 6.8 per cent of the samples from the neighbors ($P<0.001$). Seven of the 11 farm members, but only three of the 24 neighbors, had two or more fecal samples containing >80 per cent tetracycline-resistant coliforms ($P<0.01$). These resistant bacteria contained transferable plasmids conferring multiple antibiotic resistances. Selective pressure by tet-feed for antibiotic-resistant bacteria in chickens extends to human beings in contact with chickens and the feed. (N Engl J Med 295:583-588, 1976)

THE prevalence of antibiotic-resistant bacteria in the environment has caused widespread concern.[1,2] Besides the difficult problem of treating clinical infection caused by antibiotic-resistant organisms, there is the threat posed by the potential transfer of resistances from nonpathogenic to pathogenic bacteria. The genetic information for antibiotic resistance resides primarily on extrachromosomal DNA elements, called R plasmids (R factors), many of which can be transferred from bacterium to bacterium even between different bacterial species.[3] Numerous reports in the literature have demonstrated the worldwide prevalence of resistance plasmids in bacteria in hospitalized and ambulatory persons,[1,4-6] in domestic and farm animals[1,7,8] and in food products.[9-12]

Antibiotics select for resistant bacteria in the animals and human beings taking the drug.[1,13,14] Many of these resistances are present on transferable plasmids. It has been suggested that one factor contributing to increased resistant bacteria in human beings is the selective pressure of antibiotics in animal feeds.[1,2,7,15,16] Anderson and Lewis linked an antibiotic-resistant *Salmonella typhimurium* to infection in cattle and human beings.[17] Evidence has suggested animal-to-human spread of resistant bacteria,[1,2,7,15] and this possibility has recently been documented with use of a biochemically marked plasmid and host bacterium.[18] However, a cause-and-effect relation between animal drug feeds and antibiotic-resistant strains in human beings is unclear, since antibiotics in different forms are used so frequently in animal and human groups.

To examine in a controlled manner what effect an antibiotic-supplemented feed given to animals had on the farm inhabitants, we designed the present study and recorded the changes in bacterial intestinal flora of chickens, farm dwellers and their neighbors before and after the introduction of a tetracycline-supplemented feed to the farm.

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Supported by a grant from the Animal Health Institute, Washington, DC, and a research career-development award to Dr. Levy.

Presented in part at a meeting of the American Society for Microbiology, New York, NY, May, 1975.

MATERIALS AND METHODS

Animals

Three hundred and twenty-five one-day-old Leghorn chickens purchased from SPAFAS (Connecticut) were received on a private farmstead in Sherborn, Massachusetts, on July 1, 1974. No antibiotic-containing feed products had been used in the area during at least the previous seven-year period. The chickens were raised to one month in a small brooder (1.4 m^2) heated with accessory lamps. They were maintained in the absence of antibiotics. Over 90 per cent of the chickens lived and were vaccinated twice against respiratory virus during this time. The vaccine was prepared without the antibiotics (penicillin and streptomycin) that are routinely added to commercial vaccines. Animals were fed commercial starter mash (Farm Bureau brand) for the first month. This feed contained the coccidiostat amprolium (0.005 per cent) and bacitracin. After the first month, the chickens were given a pullet developer (Purina) that contained no drugs. Each new lot of feed was tested for the absence of antibiotic activity by extraction of 1 g of feed with 5 ml of water and study of this extract for inhibition of growth of sensitive *Escherichia coli* on nutrient agar plates. From the age of three months, chicken feed with and without tetracycline (oxytetracycline) (100 g per 909 kg) (Pfizer) was given. Only extracts of the tet-feed showed antibacterial activity.

Human Subjects

The resident farm family consisted of two parents and nine children (4 to 20 years old). Five families (24 members, including 10 adults and 14 children) living within an 8-km radius of the farm, without direct contact with the chickens or with any antibiotic-supplemented feed, acted as a control group. Two people in the laboratory, and 10 volunteer Tufts University Medical School students also participated in the study; none of them were taking antibiotics.

Distribution of Chickens on the Farm

At two months of age the chickens were placed into six newly-constructed cages (9.4 m^2, approximately 50 chickens per cage). Four groups were raised inside a barn of 900 m^2, and two groups were housed outside. At each end of the 60-meter long barn two cages were constructed approximately 15 meters apart. Males and females were evenly distributed. Each chicken was identifiable by a number tagged to its foot. Chickens housed in two cages at one end of the barn and in one cage outside the barn were placed on tet-feed during the course of the study.

Stool Sampling and Plating

We obtained samples of chicken feces by introducing and rotating a sterile moistened swab (Handi Swab, Fisher Scientific) 6 to 8 cm into the cloacus of the chicken. The swab was placed in holding medium (Stuart's medium) for delivery to the laboratory for plating. These specimens were streaked onto MacConkey, phenyl ethyl alcohol and Hektoen plates and incubated at 30 to 37°C for 18 to 24 hours. Approximately one quarter to one half of the chickens in a cage were sampled each week. In general each chicken was sampled every other week. Human fecal specimens were also obtained with use of the sterile swab. Chicken fecal samples were plated within two to six hours after being obtained; human specimens were plated within two to 12 hours. Prior studies in the laboratory indicated that samples plated during this period did not differ from those plated immediately. Since most of the stool samples were taken from the anal canal, not directly from a stool sample, this method of sampling was compared with direct sampling of feces. No difference in numbers or kinds of bacteria was observed between two fecal samples taken from the same chicken and held in holding medium: one taken immediately after excretion and the other obtained by cloacal swab. Likewise, no difference was observed in the bacterial flora or the antibiotic-resistance pattern when three fecal specimens from the same human subject were compared: one plated immediately after excretion; one stored in holding medium for one hour at 25°C; and one taken from the rectum before the stool was passed and also stored in holding medium for one hour at 25°C. Within the limits of individual stool specimens, then, the method of obtaining the specimen appeared valid for that time and day.

To test the possibility that R plasmid-containing bacteria were unable to convert from anaerobic in vivo conditions to aerobic culture conditions for testing, animal fecal specimens were incubated in duplicate under aerobic or anaerobic conditions. The same numbers of colonies and the same resistance patterns were found aerobically and anaerobically on MacConkey agar plates. Aerobic and anaerobic analysis of fecal samples containing large numbers of R plasmid-containing *Esch. coli* showed no differences. R plasmids did not influence the ability of *Esch. coli* to convert to aerobic conditions.

Bacteriology

Routine bacteriologic analyses to identify organisms were performed on all fecal specimens from the chickens and human beings living on the farm.[19] In the initial bacterial studies two to four morphologically different colonies representing the predominant organisms were isolated from each of the three selective plates. These organisms were identified and classified by means of biochemical methods and were subsequently characterized for antibiotic sensitivity with use of antibiotic disks (Pfizer Diagnostics) on Mueller-Hinton plates.[20] Antibiotic sensitivity was tested to ampicillin (10 μg), carbenicillin (50 μg), chloramphenicol (5 μg and 30 μg), cephalothin (30 μg), streptomycin (10 μg), tetracycline (5 μg and 30 μg), sulfonamides (300 μg), trimethoprim-sulfamethoxazole (25 μg), gentamicin (10 μg) and neomycin (5 μg). When tet-feed was introduced on the farm, bacterial samples were replica-plated[21] onto MacConkey agar supplemented with tetracycline (25 μg per milliliter). By two-dimensional dilutional spreading of the initial stool specimen on the MacConkey plate, several hundred colonies could be observed and replica-plated, and the percentage of tetracycline-resistant organisms could be determined.

Characterization of Antibiotic Resistance

The patterns and types of antibiotic resistance were checked in coliforms. The transferability of drug resistances in *Esch. coli* was determined by overnight bacterial mating. The recipient was DO-11, a nalidixic acid-resistant derivative of *Esch. coli* CSH-2. Donor (final concentration 1.5×10^7 per milliliter) and recipient (final concentration 1.5×10^8 per milliliter) were incubated together overnight at 37°C in 10 ml of nutrient broth. The mixture was subsequently plated onto different selective plates to examine transfer of individual resistances. Recombinants were checked for coincident transfer of other resistance markers.

Results

Changes in Intestinal Flora after Introduction of Tet-Feed

Before tet-feed was given, *Esch. coli, Proteus mirabilis* and enterococci were the predominant organisms obtained from aerobic cultures of chicken and human feces. The relative quantities of each varied, but in both chicken and human specimens, *Esch. coli* was predominant (80 to 90 per cent) among the enterobacteria. Other enterobacteria in the chicken cultures included *Klebsiella pneumoniae, Enterobacter agglomerans,* pseudomonas and acinetobacter. No salmonella was detected. Other organisms obtained from human beings were *K. pneumoniae, Citrobacter freudi, Enterobacter cloacae* and *hafniae, Proteus rettgeri* and acinetobacter.

The feces of chickens contained low numbers of organisms resistant either to tetracycline, streptomycin or sulfonamides. Of the *Esch. coli* generally less than 10 per cent were resistant to tetracycline, and many fecal samples contained less than 0.1 per cent tetracycline-resistant organisms. Among farm personnel and neighbors the numbers of tetracycline-resistant organisms were relatively low from the beginning of the study. Over 90 per cent of the fecal samples contained less than 10 per cent tetracycline-resistant *Esch. coli,* and most of them had levels less than 0.1 per cent. All proteus and enterococci were resistant to tetracycline.

The tet-feed was received on the farm in September, 1974, and was given to the chickens during the second week of October. The amount of tetracycline in the feed was at a level used for therapy or prophylaxis. The intestinal flora of chickens changed rapidly within 36 to 48 hours from low numbers of resistant organisms to high numbers (>60 per cent) with tetracycline resistance. Within two weeks 90 per cent of the chickens were excreting essentially all tetracycline-resistant organisms. No change in the frequency of organisms was observed: *Esch. coli* remained predominant. Chickens not fed tet-feed maintained low numbers of resistant intestinal bacteria until four months after tet-feed was introduced into the barn, when the intestinal flora of over 30 per cent of the chickens inside the barn contained >50 per cent resistant bacteria. Bacteria were observed that were resistant to antibiotics other than tetracycline, including ampicillin, carbenicillin, streptomycin and sulfonamides. All chickens in the same cage had *Esch. coli* with similar antibiotic-resistance patterns, but patterns and frequencies differed among the cages.

During the first three months after introduction of tet-feed, monthly samples from the family and neighbors showed little difference in the number of individual samples containing high numbers (>80 per cent) of tetracycline-resistant organisms. However, the average number of tetracycline-resistant bacteria was higher in the farm group. In January the fecal samples from three of eight family members contained >80 per cent tetracycline-resistant bacteria with an average number of resistant organisms in fecal samples from the family members of 36 per cent. In contrast, only one of 15 neighbors sampled was excreting high numbers of resistant bacteria, and the average number of resistant organisms in this group was <10 per cent.

To control for seasonal variation and to assess at a period more regular than once a month, weekly samples were taken from the farm family and neighbors during the fifth and sixth months (March and April) after introduction of tet-feed to the chickens. Each subject was sampled at least six times, and in most cases for nine weeks. Ten members of the first-year Tufts medical-school class and two members of the Tufts laboratory in Boston were similarly tested and served as controls outside the community. The results showed increased tetracycline resistance in the intestinal bacteria from farm personnel (Fig. 1). Of the 83 fecal samples received from the 11 members of the farm family, 31.3 per cent contained >80 per cent tetracycline-resistant organisms, primarily *Esch. coli*. In contrast, 0 to 12.1 per cent of the samples from any neighboring family showed high numbers (>80 per cent) of resistant organisms, and the average from all the neighboring families was 6.8 per cent. Furthermore, the overall number of tetracycline-resistant organisms in the samples from the neighbors was lower than that in those from the farm. Samples from the Boston group closely resembled those of the Sherborn neighbors in that only 3.8 per cent of the samples showed >80 per cent organisms resistant to tetracycline. Assuming that each sample is independent, the probability of getting a result this extreme is <0.001.

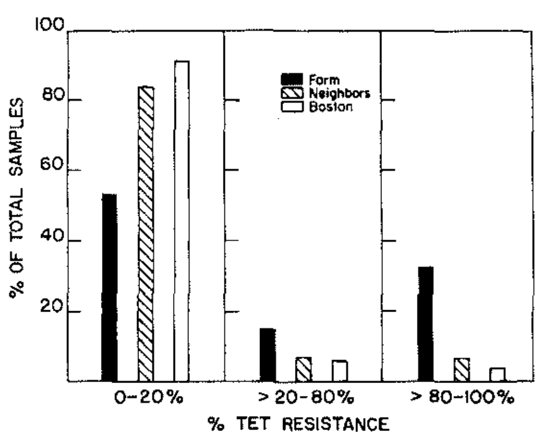

Figure 1. Proportion of Tetracycline-Resistant Bacteria in Fecal Samples from Farm Family (83), Neighbors (189) and Boston Group (79) during a Nine-Week Period, Five and Six Months after Tetracycline Was Introduced onto the Farm.

Resistance of 0 to 20 per cent is regarded as within the normal range.

Seven of the farm personnel and family members produced two or more fecal samples with >80 per cent tetracycline-resistant organisms as compared to only three of 24 neighbors (P<0.01). Moreover, four of the subjects on the farm, but only one of the neighbors, had consecutive weekly elevated numbers (>80 per cent) of tetracycline-resistant bacteria.

Emergence of Multiply Resistant Bacteria in Chickens and Human Beings after Exposure to Tet-Feed

With lengthened time of exposure of chickens to tet-feed, there was an increased frequency of *Esch. coli* carrying resistance to unselected antibiotics, including streptomycin, ampicillin, carbenicillin and sulfonamides (Fig. 2). Resistance to ampicillin and carbenicillin was not detected in chickens before their ingestion of tet-feed and was found only in chickens housed inside the barn. Multiple resistance was found in more than 50 per cent of the *Esch. coli* strains from chickens eating tet-feed for more than 10 weeks. After two months on tet-feed, over 20 per cent of the *Esch.*

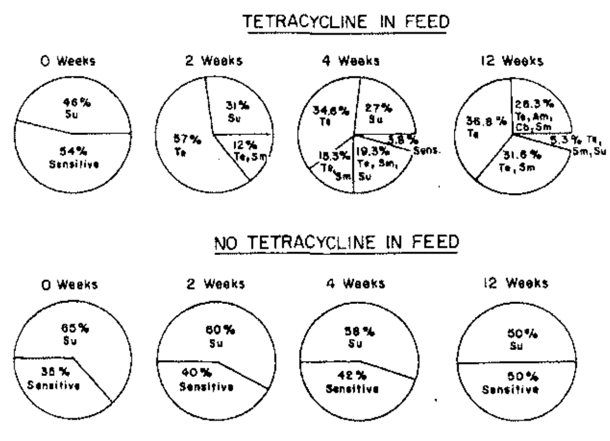

Figure 2. Effect of Time of Exposure to Tet-Feed on Predominant *Esch. coli* in Intestinal Flora of Chickens Housed inside the Barn.

From weekly samples from 10 to 20 chickens, predominant coliforms were isolated on MacConkey plates and were tested for antibiotic sensitivity. Resistances were noted to sulfonamides (Su), tetracycline (Te), streptomycin (Sm), ampicillin (Am) and carbenicillin (Cb).

coli organisms from chickens inside the barn carried the pattern of resistance to tetracycline, ampicillin, carbenicillin and streptomycin. In the outside cage, over 25 per cent of bacteria cultured from tetracycline-fed chickens showed resistance to tetracycline in association with streptomycin and sulfonamides.

Similarly, increased multiply resistant *Esch. coli* were noted in the farm dwellers, but not in neighbors, during the later months of tet-feed administration on the farm (Table 1). Over the period examined, 36 per cent of bacteria from the farm family showed resistance to three or more antibiotics, as compared to 6

Table 1. Antibiotic-Resistance Pattern of *Esch. coli* Strains Cultured from Feces.*

Mo	No. of People Sampled	Total Samples	Sensitive Strains	No. of Resistant Strains: Te	N	Sm	Te Sm	Te Su	Sm Su	Am Cb	Te Sm Su	Te Sm N	Sm Cm Su	Te Sm Su N	Te Am Cb Sm	Am Cb Sm Su	Te Am Cb Sm Su	Te Am Cb N Sm Su	Te Am Cb Sm SXT Su
Farm family:																			
Oct	6	6	2	2		1	1												
Nov	8	13	6	1	1	2										1	1	1	
Dec	9	17	5		1		2									3	2	2	2
Jan	10	20	9		2	1	1					1			1	2	3		
Feb	8	14	4	3		1							1			4	1		
Totals		70	26	6	4	5	4	0	0	0	0	1	1	0	1	10	7	3	2
Neighbors:																			
Oct	12	14	10				2		1					1					
Nov	3	4	2							2									
Dec	7	13	8					1		4									
Jan	15	26	22				1		1	1	1								
Feb	5	9	6							1	2								
Totals		66	48	0	0	0	3	1	2	8	3	0	0	1	0	0	0	0	0

*Te denotes tetracycline, N neomycin, Sm streptomycin, Su sulfonamides, Am ampicillin, Cb carbenicillin, Cm chloramphenicol, & SXT trimethoprim + sulfamethoxazole.

per cent from the neighbors. Resistance to more than four drugs was found only in farm dwellers. During October to February only 18 of 41 (44 per cent) of predominant *Esch. coli* strains isolated from the farm family were sensitive to antibiotics in contrast to 34 of 42 (81 per cent) from neighbors.

Transferability of Antibiotic Resistance in Chickens and Human Beings

Bacterial matings were performed to determine whether the genes mediating resistance were transferable to other *Esch. coli.* Tetracycline resistance when found alone in *Esch. coli* in chickens or human beings was rarely transferable. Only four of the 41 isolates from chickens tested showed transfer, and none of 17 isolates from human subjects. As this resistance gene became associated with other resistances, its transfer became more easily detected. When associated with streptomycin resistance in *Esch. coli* from chickens, tetracycline resistance transferred from about 70 per cent of the donors, approximately half the time with streptomycin resistance (Table 2). Transfer of the tetracycline resistance gene was not detected when in combination with sulfonamide resistance, but transfer was detected from about 30 per cent of the donor bacteria when in combination with resistance to streptomycin and sulfonamides. When associated with resistance to streptomycin, ampicillin and carbenicillin, tetracycline resistance was transferred from every donor tested. All resistant organisms were transferred from the donor en bloc, indicating their presence on a single R plasmid.

A more varied pattern of antibiotic resistance was seen in the human samples (Table 1); however, *Esch. coli* strains were found with resistance patterns similar to those observed in chickens. In general, one or more of the resistances were transferable; in many, resistances were transferred separately. Tetracycline and streptomycin resistances were transferred together, as was seen in the *Esch. coli* from chickens. Ampicillin resistance, found in combination with resistance to many other antibiotics, was transferred over 90 per cent of the time, always in association with carbenicillin resistance.

Table 2. Transfer of Antibiotic Resistance from *Esch. coli* Isolated from Chickens.*

Resistance Pattern	No. of Strains Tested	Resistance Transferred
Te	41	Te(4)† 9.7%
Sm	4	Sm(2) 50%
Te, Sm	14	Te(2) 14.3%; TeSm(8) 57%
Te, Su	12	(0) <8%
Te, Sm, Su	10	TeSm(3) 30%
Te, Sm, Am, Cb	15	TeSmAmCb(15) 100%

*Te denotes tetracycline, Sm streptomycin, Su sulfonamides, Am ampicillin, & Cb carbenicillin.

†Figures in parentheses represent no. of strains.

Effect of Eating Eggs from Tet-Fed Chickens on Consumers' Intestinal Flora

Over a two-month period beginning four months after introduction of the tet-feed, three neighbor families (18 family members) consumed eggs daily only from tet-fed chickens whereas two neighbor families (six members) received eggs from non-tet-fed chickens. Boston consumers ate commercial eggs. No effect on intestinal flora was noted from ingestion of eggs from tet-fed chickens: no change or difference in flora was found between the two groups. Eggs carefully washed before distribution were also tested for presence of resistant organisms on the shells; none were found.

Effect of Removal of Tet-Feed from the Farm on the Intestinal Flora of Farm Dwellers

To evaluate the reversibility of the increased number of tetracycline-resistant organisms found in farm dwellers, we recultured stools of 10 of the farm residents twice during the third week of January, 1976, six months after removal of all tet-feed from the farm. Duplicate samples were the same. No detectable tetracycline-resistant organisms (<1 per cent) were found in the intestinal flora of eight out of 10 subjects; one had 5 per cent resistant organisms, and 1 had >80 per cent. These frequencies were much lower than those found before removal of the tet-feed and lower than that found in January of the previous year. They resembled those found in the neighbor population.

Discussion

An increase in resistant intestinal bacteria was found in farm dwellers in contact with tetracycline-fed chickens and the tet-feed. Although this change was seen in the chickens within a week of tetracycline ingestion, it was not obvious in the farm personnel until three to five months after tet-feed was introduced on the farm. Similarly, chickens maintained on tet-free feed inside the barn did not show a change in flora until four to five months after introduction of tet-feed on the farm. The gradual increase in resistance in this non-tet-fed group presumably indicated exposure with time to the antibiotic on the farm. Since the most notable change in human flora was an increase in the number of fecal samples containing almost entirely (>80 per cent) tetracycline-resistant organisms, and since the resistant organisms cultured from the human subjects did not all show the same resistance patterns as those from chickens, we assume that this conversion to resistance resulted from contact with tetracycline in the feed and environment. Transfer of resistant organisms between chickens and man, aided by the selective influence of tetracycline in the environment, could also have contributed.[18]

During the same test period, low numbers of resistant organisms were found in two control groups: neighbors living in the same area and attending the same schools, but with little contact with the animals or feed; and an urban (Boston) group not directly exposed to antibiotics. The fact that an occasional weekly sample in some control persons showed large numbers of tetracycline-resistant organisms suggests unrecognized ingestion of a tetracycline, possibly in food, at some time before the sampling.

Previous studies have reported more frequent drug resistance in bacteria isolated from human beings on farms with livestock given antibiotic feed than from those on farms without animals.[22-24] One report matched antibiotic-resistant patterns of *Esch. coli* from farm families with those from their animals.[25] These studies have recorded such differences many years after multiple drug usage on these farms. Our study now records prospectively a change with time in the intestinal flora of farm dwellers as compared with neighbors in the presence of one antibiotic feed and in the known absence of any other antibiotic usage. The change occurred within four to six months after introduction of the feed to the farm and did not occur in the neighbors. This apparent selection for resistant organisms was reversible after nine months' usage of tet-feed on the farm since it was not present six months after removal of the tet-feed from the farm.

The rapid conversion of animal intestinal flora to drug resistance after animal ingestion of antibiotic-supplemented feed has been described.[13,26,27] Such a finding was seen in our studies with tet-feed. The predominant organism, however, remained *Esch. coli* despite the presence originally of 10 to 20 per cent tetracycline-resistant strains of *P. mirabilis*. This observation suggests that *Esch. coli* have a selective advantage in the intestinal tract over *P. mirabilis*. The different antibiotic-resistance patterns of bacteria from the same chickens fed tetracycline inside and outside the barn suggest an environmental influence, as well, on the intestinal flora. All chickens in a cage showed similar intestinal flora, illustrating a communal reservoir of organisms.

Patients being treated with tetracycline were found to excrete fecal coliforms with multiple resistance patterns.[14] In previous farm studies, multiple resistance patterns were found in bacteria isolated from animals, but the use of many drugs could have led to this finding. We have been able to observe prospectively in this natural farm setting the rapid selection by one drug, tetracycline, for resistance to other unrelated antibiotics. After three to four months' exposure to tetracycline on the farm, chickens and human subjects excreted bacteria that were resistant to other antibiotics, but linked with tetracycline on a plasmid. In the chicken, we had detected low numbers of organisms resistant to sulfonamides, tetracycline and streptomycin before introduction of tet-feed. We assume that these organisms were then selected by tet-feed, but we do not know why the multiply resistant organisms should increase in frequency over those with single tetracycline resistance. The origin of resistance to ampicillin-carbenicillin is also unclear. Furthermore, in the chickens, where alimentation could be controlled, we noted more frequent transfer of the tetracycline-resistant gene as the number of resistance patterns in *Esch. coli* increased.

No change in intestinal flora was seen in persons eating eggs from tet-fed chickens. During the time of this study, no sickness occurred that was associated with resistant organisms. However, the resistant intestinal bacteria represent a reservoir of transferable resistance genes. The tetracycline gene is associated with transfer genes on many plasmids, and, in fact, many resistances were transferred linked with resistance to tetracycline. The possible transfer of these plasmids from nonpathogenic to pathogenic bacteria or from animal to man must be considered a potential consequence of increased resistant bacteria in the farm environment.

The rise in frequency of resistant organisms in our environment is the obvious result of antibiotic usage. The only means to curtail this trend is to control the indiscriminate use of these drugs. All areas of antibiotic usage deserve critical evaluation. Contrasting views have been expressed regarding the real as opposed to the potential human health hazard of resistant bacteria in animals and the impact of antibiotic-supplemented feeds on this problem.[1,2,7,27,28] The present findings clearly demonstrate, however, that antibiotic-supplemented feed is a factor contributing to the selection of human resistant strains of bacteria. These data speak strongly against the unqualified and unlimited use of drug feeds in animal husbandry and speak for re-evaluation of this form of widespread treatment of animals.

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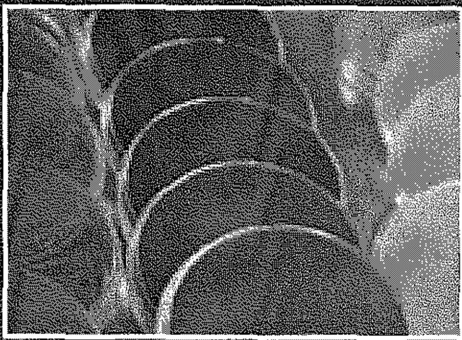
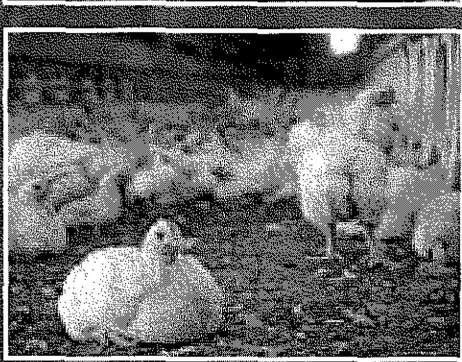
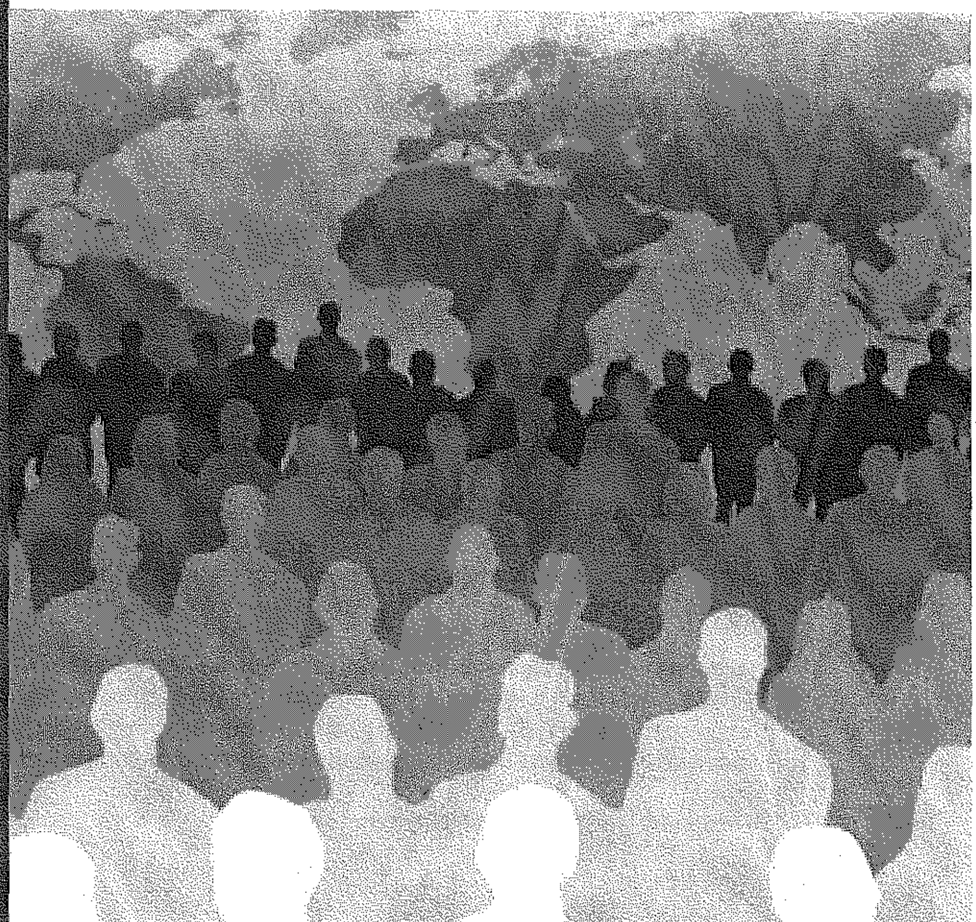




The evolving threat of antimicrobial resistance

Options for action



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Chapter 4.

Reducing the use of antibiotics in animal husbandry

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Reducing the use of antibiotics in animal husbandry

Antibiotics are used widely and in vast quantities to ensure the health and promote the growth of livestock, poultry and fish reared for food production. The fact that greater quantities are used in healthy animals than in unhealthy humans is a cause for serious concern, particularly as some of the same antibiotics are involved and food animals have been shown to carry resistant human pathogens. Some countries have banned the use of antibiotics as growth promoters but the practice remains widespread. Legislation and regulation with enforcement are needed to control the use of antibiotics for these purposes in many countries.

Summary

Antibiotics are used in greater quantities in healthy food-producing animals than in the treatment of disease in human patients. In animal husbandry, antibiotics are used extensively for disease prevention and as growth promoters, involving mass administration to many animals at the same time. This practice constitutes the main difference between the use of antibiotics in animals and in humans. Some of the same antibiotics or classes are in use in food animals and in human medicine, carrying the risk of emergence and spread of resistant bacteria, including those capable of causing infections in both animals and people. The importance of food animals as reservoirs of resistant human pathogens is well documented. The spread of resistance genes from animal bacteria to human bacteria is another potential danger. The problems associated with the use of antibiotics in animal husbandry, including in livestock, poultry, and fish farming, are growing worldwide without clear evidence of the need for or benefit from it, leading to increasing recognition that urgent action is needed.[109]

There appear to be major differences in the amounts of antimicrobials used per kilogram of meat produced in high-income countries, which together account for 70% of global meat production. Working groups hosted by WHO, the Food and Agriculture Organization (FAO), and the World Animal Health Organisation (OIE) have proposed options for actions to be taken by national and international authorities. Large-scale interventions are already being instituted in a number of countries, mainly aimed at reducing the use of specific classes of antimicrobial agents, especially those used in human clinical practice. The steps to be taken include the introduction and enforcement of regulations, methods to promote the prudent use of antibiotics, and measures to improve animal health so that less antibiotic treatment is needed. Several such interventions have led to a demonstrable reduction in AMR, though this is not always the case.

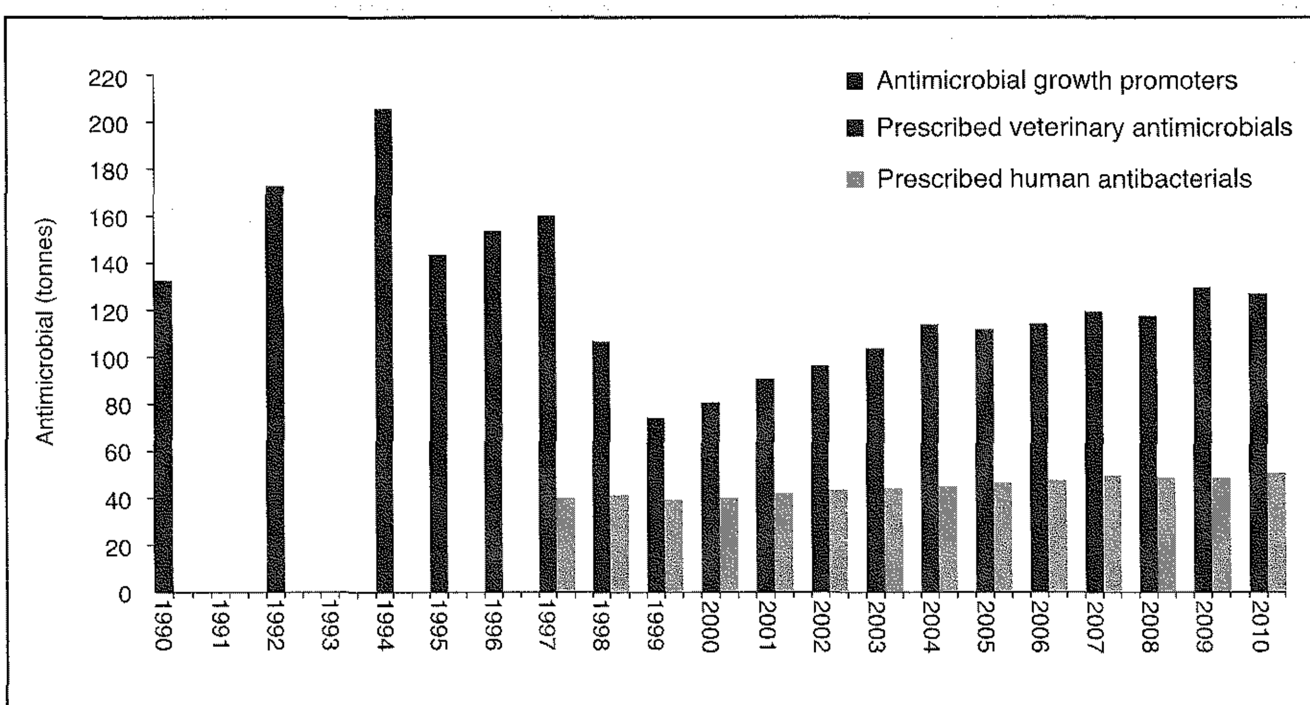
Important gaps and challenges remain. More information is needed on the prevalence of AMR in bacteria of animal origin and its impact on human health, on the quantity of antibiotics used for different indications and on the classes of antibiotics used. Risk assessments and risk management are impeded by a lack of data and/or inability to access available data. Legislations and regulatory frameworks for the approval of veterinary medicines and for controlling their use need strengthening in many countries. Capacity to implement interventions varies and the potential impact of specific interventions in different settings is largely unknown. This chapter considers the present situation and the range of options for action, citing examples of experiences with different interventions.

1. Reducing antimicrobial use in animal husbandry to reduce AMR

As in medical care for people, the introduction of antimicrobials was a significant milestone in veterinary practice. As in humans, these medicines are used for the treatment of infectious diseases in individual domestic pets and in farm and food-producing animals to ensure animal welfare and global food production. The development and spread of AMR is therefore also of concern in veterinary medicine. Furthermore, resistant bacteria carried by food-producing animals can spread to people, mainly via the consumption of inadequately cooked food, handling of raw food or by cross-contamination with other foods, but also through the environment (e.g. contaminated water) and through direct animal contact.

Use is the main driver for resistance in all of these situations. For companion animals such as cats, dogs and horses, the use is similar to that in general human medical practice, with individual animal treatment being the norm. The main difference between antibiotic use in humans and animals is seen in the context of food production, where there is mass administration of antimicrobials to many animals at the same time for the purposes of disease prevention and growth promotion. Such practices provide favourable conditions for the emergence, spread and persistence of AMR bacteria capable of causing infections not only in animals, but also in people. The antimicrobial agents used for food-producing animals are frequently the same, or belong to the same classes, as those used in human medicine. The total amount used in animals accounts for well over 50% of total antibiotic use, according to the available evidence (Figure 4.1).[21]

Figure 4.1 Annual antibiotic use for human and veterinary practice in Denmark



Source: Reproduced from [21] with permission.

The importance of food animals as reservoirs of AMR bacteria which are pathogenic for humans is well documented for zoonotic bacteria such as non-typhoidal *Salmonella enterica* serovars[110] and *Campylobacter* spp.[111] It has been frequently demonstrated that the use of antimicrobial agents in food animals favours the development of resistance among bacteria which can then be transmitted to people, and may cause infections and illness. Bacteria and resistance to critically important antimicrobial agents associated with food animals include: *Escherichia coli* and *Salmonella* spp resistant to 3rd and 4th generation cephalosporins and to fluoroquinolones; *Campylobacter* spp resistant to macrolides and fluoroquinolones; *Staphylococcus aureus* resistant to all beta-lactam-type drugs (i.e. MRSA); enterococci resistant to vancomycin (VRE) and *C. difficile*.

There are significant direct and indirect effects of antimicrobial use in animals on AMR in human pathogens, as several lines of evidence have indicated. Data are as yet insufficient to allow this relationship to be fully evaluated, but it is clear that action is needed to reduce the use of antibiotics in food animals, and to obtain further information on the impact on AMR. This chapter describes experiences with the implementation of some of the most important interventions worldwide, recognizing the differences in situations between countries and regions.

2. WHO guidance on reducing antimicrobial use in animal husbandry

The 2001 WHO Global Strategy for Containment of AMR includes specific recommendations on the use of antimicrobials in animal husbandry which are based on *WHO global principles for the containment of antimicrobial resistance in animals intended for food, 2000* (Box 4.1).[109] The recommendations include phasing out the use in food animals of antimicrobials which are used in human medicine, improving their use through regulation, education and guidelines, and monitoring use and resistance in this sector (Appendix1).[1]

Box 4.1 WHO principles for the containment of AMR in animals intended for food

- Introduce pre-licensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs.
- Monitor resistance to identify emerging health problems and take timely corrective action to protect human health.
- Develop guidelines for veterinarians to reduce the overuse and misuse of antimicrobials in food animals.
- Require obligatory prescriptions for all antimicrobials used for disease control in food animals.
- In the absence of a public health safety evaluation, terminate or rapidly phase out the use of antimicrobials for growth promotion if they are also used for the treatment of humans.
- Create national systems to monitor antimicrobial use in food animals.

The importance of the problem and the urgent need to take action were again stressed during the 2011 World Health Day. The core actions called for in the WHD policy briefs include the creation and enforcement of an enabling regulatory framework, strengthening surveillance and monitoring, promoting education and training on antimicrobial use in food-producing animals, and reducing the need for antimicrobials through better animal husbandry. The needs for national leadership and intersectoral collaboration are also emphasized (Appendix 2).[2]

3. The present position regarding these recommendations

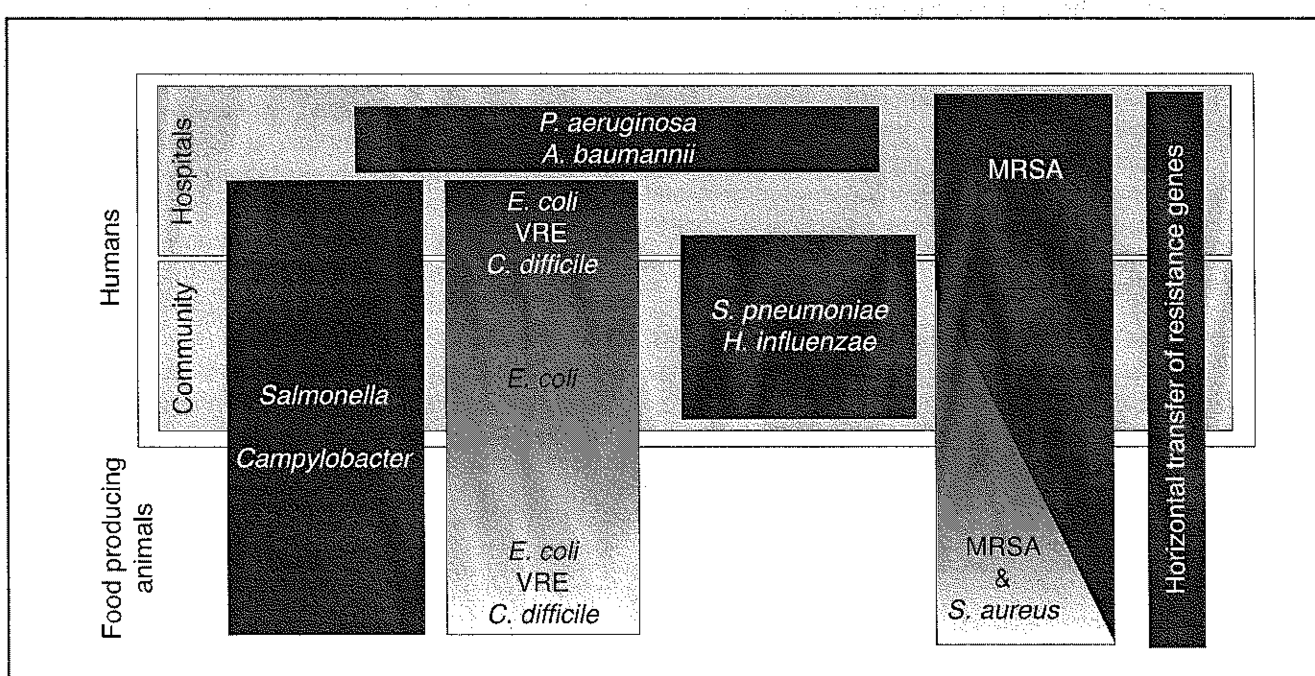
The following sections examine key factors in the role of antimicrobial use in food animals which contribute to the growing threat of AMR, and national and international actions taken to tackle the problem, illustrated by experiences from different parts of the world.

3.1 Increasing recognition of the problem of AMR through food of animal origin

Extensive and effective monitoring of AMR in animals is carried out in only a very limited number of countries, and frequently these monitoring systems are not comparable due to differences in methodology. However, AMR among bacteria of animal origin is certainly prevalent throughout the world, at varying rates in individual countries and regions. With increasing global trade in food products of animal origin, the numbers of reports documenting resistant bacteria spreading from one country to another through food, and thereby causing infections, are also increasing. The international spread of resistant pathogens calls for urgent global initiatives to minimize the risk of AMR bacteria developing and spreading from food animals to people, and further within communities and hospitals. Working groups hosted by WHO, FAO and OIE have reviewed these issues extensively and proposed options for action to be taken by national and international authorities.[109,112-114]

Figure 4.2 is a schematic overview depicting the overlap between different reservoirs for some AMR pathogens. While some are strictly confined to the human reservoir, others have a mainly or partially animal reservoir.[66]

Figure 4.2 Reservoirs of AMR bacteria causing human infections



Schematic overview of some of the most important antimicrobial resistant pathogens and the overlap between the different reservoirs. As indicated some pathogens are strictly confined within the human reservoir, whereas others have a mainly or partly animal reservoir.
Source: Reproduced from[66] with permission

The use of fluoroquinolones (e.g. enrofloxacin) in food animals resulted in the development of ciprofloxacin-resistant *Salmonella*, *Campylobacter* and *E. coli*, which have caused human infections and spread worldwide through travel and food trade. An increasing number of studies indicate that a major proportion of resistant *E. coli* that cause extra-bowel infections in humans may have originated in food animals, especially poultry.[115,116]

Since 2003, a new variant of MRSA has emerged and spread among food animals, primarily in pigs, in many countries. The importance of this new farm-associated MRSA for human health has not yet been fully assessed, but it is already a problem for the control of MRSA in some countries and the prevalence appears to be increasing.[117]

C. difficile colonizes many food animals and also causes disease in food animals such as piglets, with an associated high mortality rate[118] and has been found in 4.6%–45% of retail meat samples.[119] Since 2005, in the Netherlands and other countries, there has been an increase in community-acquired human infections caused by *C. difficile* strain types similar to those found in food animals.[120] Community human carriage of *C. difficile* is likely to increase the risk of *C. difficile* disease, especially among patients who enter health-care facilities and are treated with antibiotics. It may also increase the likelihood of *C. difficile* spores contaminating the hospital environment and spreading from person to person. However, the overall contribution of animal *C. difficile* to human disease is not well documented.

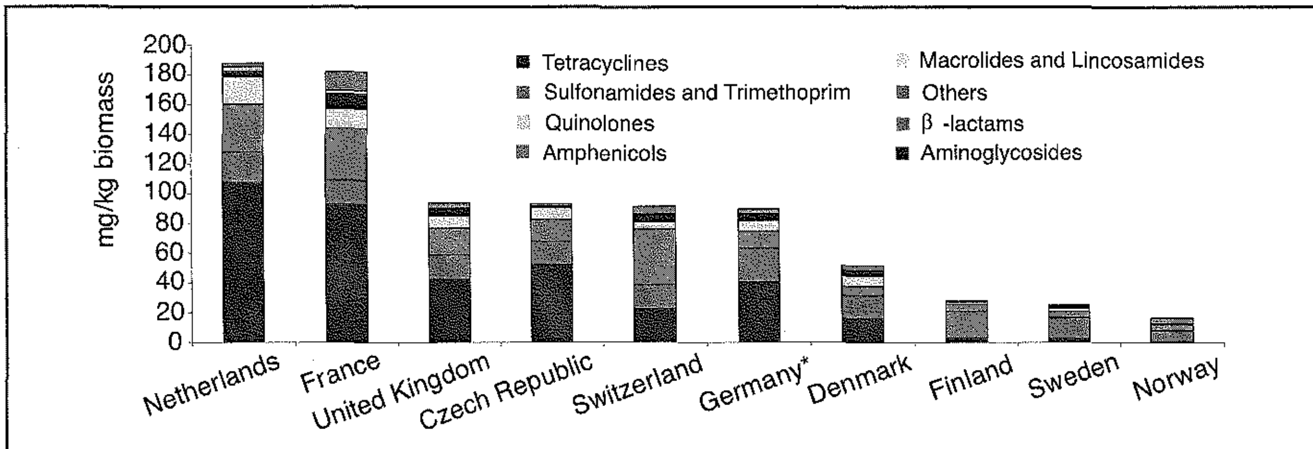
As well as selecting for resistant bacteria, the use of antimicrobial agents in food animals also selects for transferable resistance genes. This phenomenon raises the possibility that resistance genes could be transferred from animals to humans via non-pathogenic bacteria in food products, and that they could then be transferred to bacterial pathogens in the human gastro-intestinal tract. Consistent with this hypothesis is the presence of similar vancomycin and cephalosporin resistance genes in both human and animal bacteria.[121]

3.2 Antimicrobial use in food production

In modern food production systems, there is widespread and intensive use of antimicrobial agents. The impact of this practice may vary considerably between countries and regions, influenced by the interaction between human populations (social structure), land use, contaminated water sources, animal demography (species, distribution, and density), national policies (production, trade, food security, animal health, etc), and national and international trade. The production systems also vary between countries according to technological, social, and economic circumstances. More than 50% of the world's pork production and over 70% of poultry meat currently originate from industrialized countries.

In general, the quantities and classes of antimicrobials used in food animals today are insufficiently documented or controlled worldwide. Monitoring of antimicrobial consumption is carried out in only a limited number of countries and, with very few exceptions, this is restricted to total amounts used, and not categorized by animal species and antimicrobial classes. Initial crude estimates from different countries which do measure antimicrobial use show major differences in the amounts used per kilogram of meat produced (Figure 4.3). This implies that there is considerable scope for reduction in countries where the higher amounts of antimicrobials are in use.[122]

Figure 4.3 Estimated antimicrobial use to produce one kilogram of meat in different countries



Amounts in mg of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data
Source: Reproduced from [122] with permission from Oxford University Press.

Data on antimicrobial use are necessary for risk analysis, interpreting resistance surveillance data, and to assess the impact of interventions to promote prudent use. Sales data are the usual source of information on antimicrobial use. Data which can have an impact on policies and practice are very often lacking from developing countries, but Kenya is a notable exception where both the total amounts and the classes of antibiotics are monitored: from 1995–1999, Kenya used on average 14 594 kg of antibiotics distributed as 7975 kg of tetracyclines, 3104 kg of sulfonamides, 955 kg of aminoglycosides, 905 kg of betalactams, 94 kg of quinolones, 35 kg of macrolides and 24 kg of others, including tiamulin.[123]

Depending on the species of animals, periods of higher risk for infection can be identified. For example, when animals from different origins are assembled and first placed together, physiological stress is at its highest level and there is increased potential for inter-animal transmission of infections. Antimicrobial prophylaxis of all animals is often carried out to prevent clinical disease in such situations. In some countries, mass treatment is timed to an epidemic (either started or expected), a practice termed "metaphylaxis". The regulatory status of such use often resides on the fringe of labelled use for the 'control' of disease. To facilitate administration to a large number of animals, oral routes (water and/or feed) are used in addition to parenteral injections. Prophylaxis and metaphylaxis practices need to be carefully assessed to find an appropriate balance between the need to prevent diseases during high-risk periods and the potential to contribute to AMR.

3.3 Actions being taken worldwide

Awareness of the risks for human health which can result from the use of antibiotics in animal husbandry appears to be on the increase, as evidenced by the many media reports and scientific publications on this topic in recent years, and the large-scale interventions which are being instituted in different parts of the world.

There are several international networks which coordinate AMR surveillance in human and animal populations (see Chapter 2). The WHO-Global Foodborne Infections Network (GFN) and the international molecular subtyping network for foodborne disease surveillance (PulseNet International[a]) are examples. The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) has developed guidance documents for global standardization of methods for monitoring AMR and antimicrobial use in food animals[b].

[a] http://www.pulsenetinternational.org/Pages/default.aspx
[b] http://www.who.int/foodborne_disease/resistance/agisar/en/index.html

Most interventions are aimed at reducing the use of specific classes of antimicrobial agents in food animals, especially those classes which are used in human clinical practice. The measures which have been implemented include the introduction and enforcement of regulations governing the use of antimicrobials, methods to promote the prudent use of antibiotics by end-users, and measures to improve animal health so that less antibiotic treatment is needed.

Regulations to restrict the use of antibiotics in animals

National and international efforts to control AMR require a firm legal and regulatory foundation on which measures can be introduced and enforced. Regulations can contribute at many levels, from licensing to end use of antimicrobials. While regulatory frameworks exist in most countries, there are differences in the extent to which regulations are implemented. In most countries, veterinary pharmaceutical products undergo a licensing process that assesses the risk/benefit balance of the proposed products, similar to the process followed for human use products. For antimicrobials, an evaluation of the potential impact on human health is also included in many countries. Initially this evaluation focused on avoiding antimicrobial residues in food products, but more recently it has been extended to include effects on AMR in bacterial populations in slaughter-ready animals. The approval process may also include consideration as to whether specific antimicrobials are of critical importance for human health,[124] often with measurable impact on AMR (Box 4.2). WHO has categorized antimicrobials which are critically important for human use.[125] However, current national legislations do not always restrict the use of such critical antibiotics in animals.

In many countries, it can be difficult to withdraw approval for an already licensed pharmaceutical product. However, it is often possible within the existing legislation to implement restrictions on the approved usages of licensed antimicrobials (Box 4.2). For example, it is possible to limit off-label / extra-label use or to restrict use to individual animals.

Box 4.2 **Approval and regulations on use of antimicrobials of critical importance**

The U.S. Food and Drug Administration successfully withdrew the approval of fluoroquinolones for use in poultry on 12 September, 2005.[126] To achieve the withdrawal, the agency had to demonstrate that the use of enrofloxacin in poultry causes the development of fluoroquinolone-resistant Campylobacter in poultry, that these fluoroquinolone-resistant organisms are transferred to humans, that they may cause the development of fluoroquinolone-resistant Campylobacter in humans, and that fluoroquinolone-resistant Campylobacter infections in humans are a health hazard. The process began in 2000, involved the collection and evaluation of thousands of studies, expert testimony, an oral hearing, and a complex risk assessment.

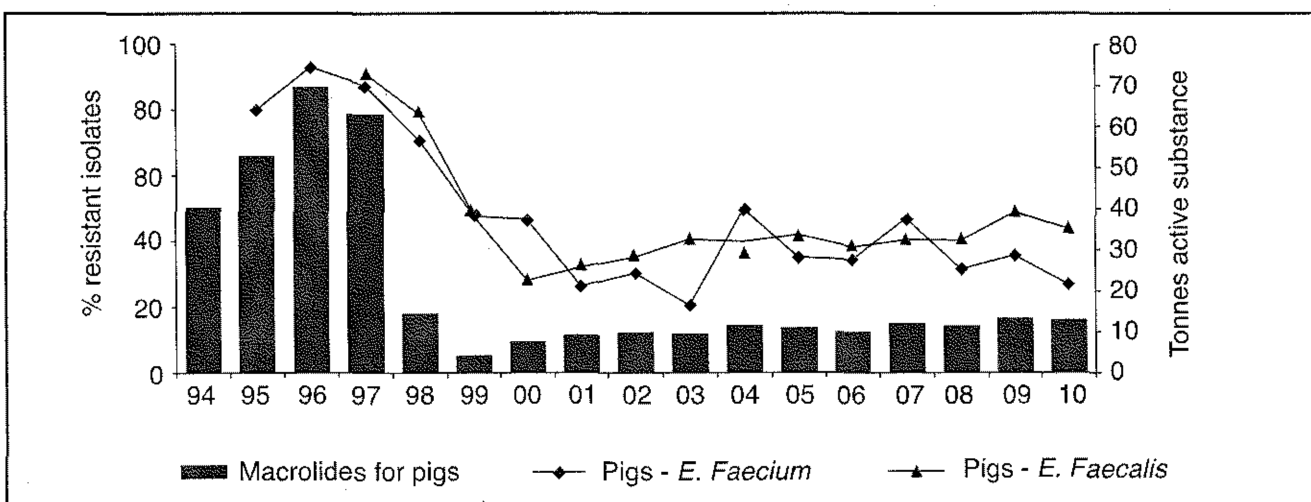
In Australia, fluoroquinolones (e.g. ciprofloxacin), which are antimicrobials of 'critical importance' in human use, have never been approved for use in food production animals. Fluoroquinolone-resistant bacteria are either at very low levels or else non-existent in food animals and resistance is very low in Australian human bacterial isolates in comparison with other countries. Data from the Australian Group on Antimicrobial Resistance 2006 surveillance report show fluoroquinolone resistance in 2006 to be less than 5% in clinical isolates of Gram-negative bacilli.[127]

The approval of fluoroquinolones for use in food animals in 1993 in Denmark saw the rapid emergence of resistance to this class, with 23% of C. coli isolates from pigs found to be resistant during 1995 to 1996. Consequently, in 2002 restrictions were imposed on the veterinary use and prescription of fluoroquinolones for food-producing animals: fluoroquinolones could only be used in food-producing animals for the treatment of infections proven by laboratory tests to be resistant to all other antimicrobials, and administered only by injection by a veterinarian, with the use reported to the regional veterinary officer. This reduced fluoroquinolone use in animals in Denmark from 183 kg in 2001 to 49 kg in 2006 and it has remained low since then. Resistance was detected in just 12% of C. coli isolates from pigs tested in 2009.[21]

Restrictions on the mode of administration could be another useful means of limiting use in animals, particularly for antimicrobials that are critically important for human use, for example, by limiting them to injection-only. However, this type of restriction is applicable in individual animal treatment, but may not always be feasible for large numbers, for example in poultry flocks.

Increasing numbers of countries are banning the use of antibiotics as growth promoters, a very positive development which has been highlighted in recent media reports. Experiences following cessation of use of antimicrobial agents are encouraging. By January 2000, the use of all antimicrobials as growth promoters had been prohibited in Denmark. This has resulted in an overall reduction in resistance among bacteria in animals. The temporal association between the reduction of macrolide use and the prevalence of AMR among enterococci isolated from pigs in Denmark is shown in Figure 4.4. Resistance will probably never return to pre-antibiotic use levels, and so consumption of antimicrobials needs to be kept at low levels as excessive use could again rapidly drive AMR upwards.

Figure 4.4 Macrolide use and resistance among *enterococci* in pigs, Denmark

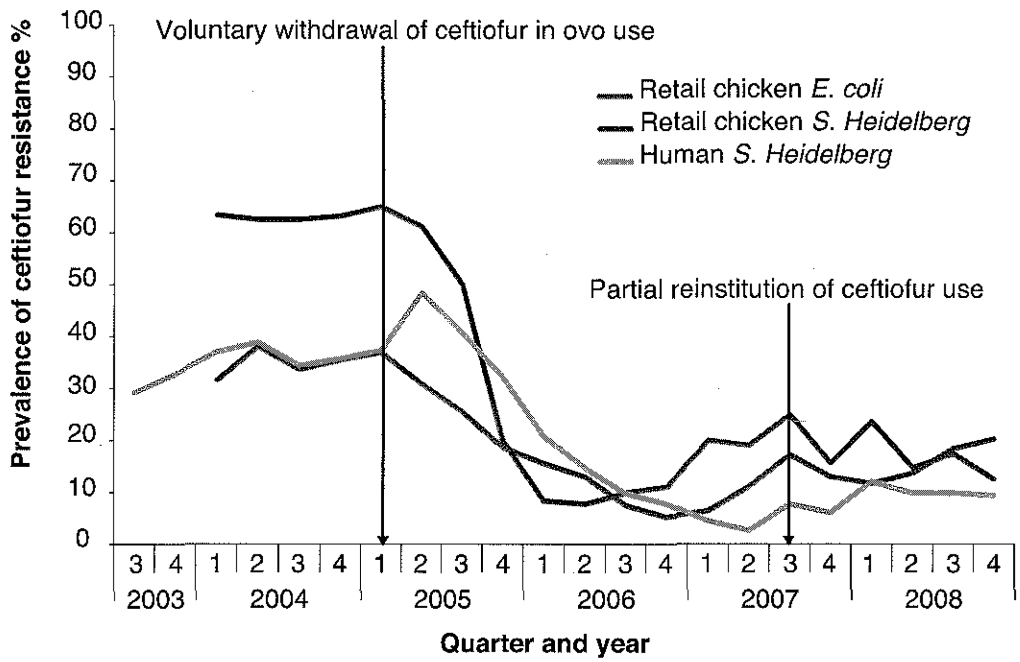


Source: Reproduced from [21] with permission.

In 1995 a ban of the growth promoter avoparcin (a glycopeptide) which selects for vancomycin-resistant enterococci (VRE) in Denmark led to a reduction in the prevalence of VRE among animals and in the general human population. However, VRE has persisted for up to 12 years in poultry farms after the ban and is likely to persist for many more years. The complex relationship between reducing use and the levels of resistance is being explored.[128-130]

Experience has shown that any negative effects due to the prohibition of growth promoters are minimal in the long term, once industry adapts to the changes.[131] Apart from prohibitions on the use of antibiotics in food animals, there have also been a number of voluntary withdrawals. In Canada and the USA, ceftiofur, a 3rd generation cephalosporin, may legally be used in an extra-label manner for routine administration into eggs or one day-old chicks in hatcheries, to prevent infections. Surveillance in the province of Quebec, Canada, demonstrated a marked increase in the prevalence of resistance to 3rd generation cephalosporins and penicillins among *S. enterica* serotype Heidelberg isolates from humans and chickens in early 2005. A survey of antimicrobial use in hatcheries in Quebec confirmed that in 2004 all chicken hatcheries switched to exclusive use of ceftiofur. In early 2005, Quebec hatcheries stopped this use voluntarily, after which there was a dramatic decline in the prevalence of ceftiofur resistance (Figure 4.5). Anecdotal reports indicate that the industry has subsequently re-introduced alternating use of ceftiofur with other antimicrobials, and that this has been followed by a resurgence of resistance.[132]

Figure 4.5 Cephalosporin resistance after stopping its use in poultry in Quebec, Canada



Source: Reproduced from [132] with permission.

Unfortunately, there are few incentives to encourage voluntary withdrawal of growth promoters and no barriers or sanctions for re-introducing them.

Easy access to antimicrobials through sources such as online pharmacies, animal feed outlets and pet shops contributes to their overall excessive use and makes it increasingly difficult to enforce regulations on the use of these products.

Financial incentives

Ideally, sales of an antimicrobial should never involve financial benefit for the prescriber. Limitations on the sales profits obtained by veterinarians in Denmark from 1994 to 1995 led to major reductions in the therapeutic use of antimicrobials, especially tetracyclines, without any obvious overall harm to animal health.

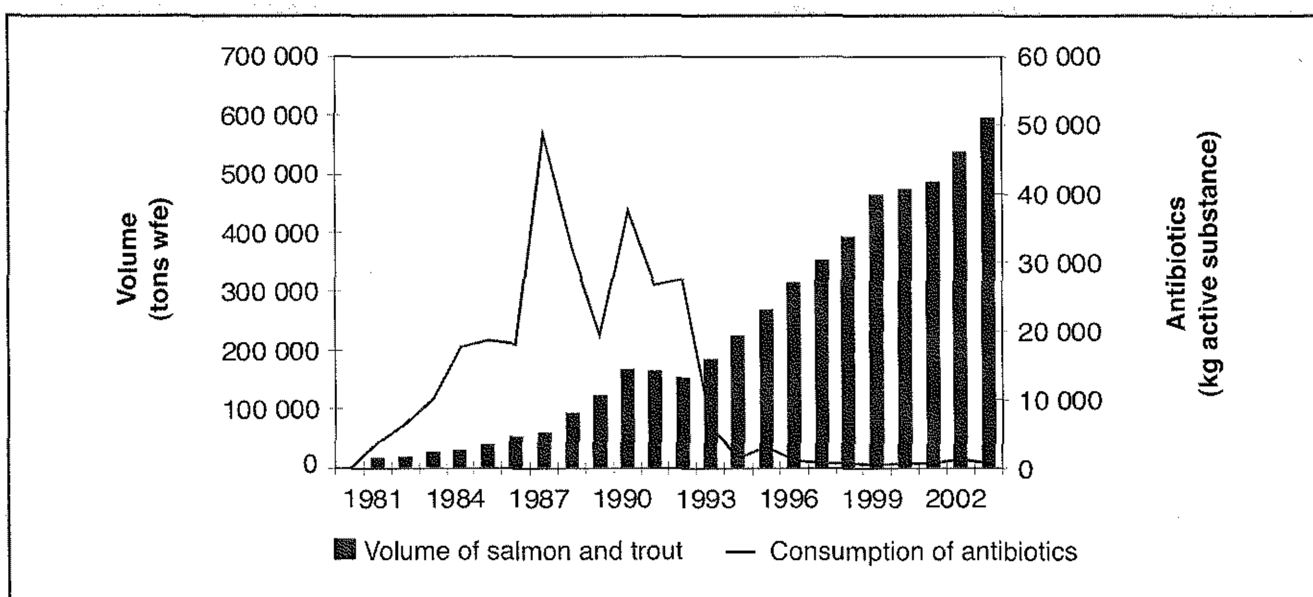
Prudent use guidelines and education

To reduce inappropriate use and promote prudent use, developing treatment guidelines and popularising them among veterinarians and farmers is likely to be helpful. Prudent use guidelines have been issued in the Netherlands (1986), Denmark (1998), USA (1999/2000), Germany (2000), and in many other countries more recently. However, the influence of these guidelines has not been monitored adequately, for example the Netherlands is still among the highest users of antimicrobials in food animals in Europe.

Improving animal health to reduce the need for antibiotics

The most effective means to reduce the use of antimicrobials and thus prevent AMR is to reduce the need for antimicrobial treatment. This could be achieved by improving animal health through measures such as immunization against prevalent infections. In Norway, the introduction of effective vaccines in farmed salmon and trout in 1987 and improved health management reduced the annual use of antimicrobials in farmed fish by 98% between 1987 and 2004 (Figure 4.6).[133] Many countries and the EU already have regulations in place to enforce and promote vaccination as a method of reducing infections in food animals. However, even if health improves, it is not certain that established practices and consumption will change, since most antimicrobial agents for growth promotion and prophylaxis are used without any evidence of the need for, or benefit from, their use.

Figure 4.6 Reduction in antimicrobial use after the introduction of vaccination in aquaculture



Wfe: whole fish equivalent.
Source: Reproduced from [133] with permission.

Improving hygiene in food production

The FAO/WHO Codex Alimentarius[c] provides recommendations for many aspects of food production including hygiene, from primary production through to final consumption, highlighting the key controls at each stage. It recommends a *Hazard Analysis and Critical Control Point (HACCP)* approach. Good agriculture practices particularly at the farm level have also been defined. The Codex Task Force on Antimicrobial Resistance recently developed a risk analysis and management tool to assess the risks to human health associated with foodborne antimicrobial resistance.

In 2006, the EU put in place a programme with specific targets for reduction in salmonella contamination. Based on data from 27 EU Member States in 2009, 18 have reached the EU reduction targets in breeding flocks of fowl and the decreasing trend in human salmonellosis cases is continuing.[134] Microbiological criteria for a maximum acceptance level for certain types of AMR *Salmonella enterica* in food animals have been implemented in Denmark. The impact of these interventions has not yet been fully evaluated but Denmark has a low rate of domestically-acquired salmonella infections.

Applying advances in data management technology

Herd Health and Production Management (HHPM) programmes have been used to improve productivity

[c] http://www.codexalimentarius.org/

incrementally, mainly in intensive production systems. HHPM monitors the interaction between farm management, herd health and production, and integrates these components in order to obtain optimal results. These programmes use computer-based Management Information Systems (MIS) and the databases thus developed could direct attention to AMR and allow recognition of the contributions of local management, and of environmental and biological factors, to the development of AMR (Box 4.3).

Box 4.3 Computer-based monitoring of antimicrobial use and resistance to improve production

The MIS database used in Costa Rica records both prophylactic use (uterine infusion after artificial insemination, dry-off treatment etc), and therapeutic use (disease treatment, mastitis treatment, uterine infusions, etc) of antimicrobial agents in cattle. It includes a module for drugs, which allows the personnel responsible for use to register the drug used. This module enables data gathering for surveillance of antimicrobial use, AMR, and monitors the actions of veterinarians and/or producers. Similar HHPM programmes could be used more widely to monitor AMR at farm level, and correlate the data with environmental and managerial aspects to identify risk factors for AMR.

4. Gaps and challenges

Data on AMR associated with animal husbandry: The extent of AMR in foodborne bacteria, and the global burden of human infections due to such bacteria, are unknown. Continuous and updated information on foodborne pathogens, their spread and the status of AMR is necessary to guide risk profiling, risk assessment and risk management and to measure the impact of interventions. However, very few countries appear to have these monitoring systems in place, and where data are collected, they are often not comparable because of methodological differences (Chapter 2). Regional and national laboratory networks using standard methods would alleviate this situation.[135] There is scope for widening participation in existing networks and for strengthening the capacity of the participating laboratories. Databases could also be usefully improved to include phenotypic and genotypic features of the bacteria being monitored.

Data on quantities used: Data on total volumes of antimicrobials used and the indications for which they are used are also limited. The use of antimicrobials in animal husbandry is generally not based on sound scientific principles. Although use for growth promotion is being reduced in many countries, the practice is still widespread in many parts of the world. Correct use for prophylaxis and metaphylaxis is the subject of ongoing debate, and more could be done to limit antimicrobial use in these areas. The agents used and the modality of use differs widely between countries and within countries. OIE has published a list of critical antimicrobial agents needed for animal health[136] with an overview of the agents used and considered important in different countries.

Regulatory provisions: In many countries, the legal and regulatory framework to control the use of antimicrobials in animals could be strengthened. Regulations governing the approval of veterinary medicines and restrictions on their use are often lacking, or not adequately enforced. Restricting the use in food production animals of antibiotics that are "critically important" for human health is recommended by many experts and authorities. Currently, WHO gives priority to restricting the use of 3rd generation cephalosporins and fluoroquinolones.[125] Regulations could also include provisions for prohibiting for animal use any new drug class developed for human medicine, and of those that are used only in human medicine (e.g. linezolid, daptomycin, carbapenems, glycopeptides). Regulations also have a potentially valuable role in supporting compliance with the international standards for food safety practices in the production of food of animal origin, developed by the FAO/WHO Codex Alimentarius and OIE.

Data for registration of antimicrobials: It is standard practice for regulatory agencies to require data on the efficacy of a new medicine prior to registration, but these data are rarely available in the public domain.

This particularly applies to older products that have not been subjected to recently-introduced rigorous approval processes. Pharmacovigilance systems in place in many countries include the obligation to declare lack of efficacy, which could be a problem with drugs that have been in use for a longer period of time.

Routine, usually qualitative, assessments of risks for developing AMR are now incorporated into the pre-market authorization process for veterinary antimicrobials in some countries. However, these assessments are made difficult by the complexities of the producer-to-consumer continuum and lack of data in several important areas. Positive, albeit modest, developments include quantitative risk assessment for specific antimicrobial/organism combinations (e.g. fluoroquinolone resistance in *C. jejuni*). Improvements in methodologies for risk assessment, risk management and risk communication could be beneficial and additional guidance in this area from Codex Alimentarius would be helpful. The application of such guidance at national/regional and international levels could be improved.

Evaluation of impact: The potential impact of different interventions in different settings is still largely unknown. Measuring impact on food safety, enteric and other zoonotic diseases in people, animal health, animal productivity, national economy and other indicators at the regional/national level requires standardized indicators and sustainable capacity for monitoring AMR and antimicrobial use. At a local level, the impact could probably be determined by targeted research studies, and meta-analyses of such available global data could prove useful.

Capacity to respond to AMR: National capacity to respond to problems due to AMR is not uniform at either country or local level. Capacity at farm level is lacking in many countries, for reasons such as a lack of effective organizational structure, trained personnel, and sufficient knowledge about the risks involved. To improve this situation, instruments to guide the characterization and evaluation of institutional and operational capabilities, measure advancement, and propose strategic actions for technical cooperation have been developed by the Pan American Health Organization (PAHO)[d].

Application of modern technologies: Available technologies could be better harnessed to analyse local situations and risk factors, and for effective communication including the improvement of existing communication networks to disseminate already available information. The possibility of developing new vaccines, particularly against the infections for which most antibiotics are being used, such as gastro-intestinal infections in pigs and calves, mastitis in cattle and *E. coli* infections in poultry, could be explored. Another possible option is the development and evaluation of probiotics, which are probably valuable alternatives to antibiotics in the control of gastro-intestinal infections in food animals.

Selection of appropriate interventions: Different commodity groups in different settings may require different interventions. For example an intervention to reduce resistance in 180-day swine system may not be directly applicable to a 42-day broiler chicken system, and interventions suited to extensive agriculture are unlikely to be of equivalent efficacy in intensive settings. Thus, the choice of interventions could be based on a process of identification, analysis and prioritization of needs and options which could include the introduction and/or enforcement of regulations on the use of antimicrobials in animals; measures to improve animal health; promotion of prudent antimicrobial use; strengthening hygiene in the food chain; and specific targeted measures in areas with a higher risk of AMR development or serious consequences.

Capacity building activities including staff training are still needed in many places. Public education on issues related to the use of antibiotics in food-producing animals may be needed to raise awareness of the potential harm and unclear benefit from their use in agriculture and aquaculture.

[d] http://www.paho.org/English/AD/DPC/VP/fos-program-page.htm

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Antibiotic Resistance and Food Animal Production: a Bibliography of Scientific Studies (1969-2013)

This bibliography lists the latest published scientific and economic literature concerning the contribution of routine antibiotic use in food animals to the growing public health crisis of human antibiotic resistance. Research on how antibiotic use in food animal production contributes to the growing health crisis of antibiotic resistance dates back more than 30 years. As Dr. Frederick J. Angulo, then acting associate director of science in the Centers for Disease Control and Prevention's National Center for Environmental Health and the Agency for Toxic Substances and Disease, said in a August 1, 2009, news article in the *Journal of the American Veterinary Medical Association*:

> "There is scientific consensus that antibiotic use in food animals contributes to resistance in humans. And there's increasing evidence that such resistance results in adverse human health consequences at the population level. Antibiotics are a finite and precious resource, and we need to promote prudent and judicious antibiotic use."

Table of Contents:

ANTIBIOTIC RESISTANCE IN ANIMAL AGRICULTURE

The impacts of antibiotic resistance in animal agriculture on livestock, the environment and the spreading of infectious diseases.

Joint Committee on the use of antibiotics in animal husbandry and veterinary medicine ("Swann Report"). M.M. Swann, K.L. Blaxter, H.I. Field, J.W. Howie, I.A.M. Lucas, E.L.M. Millar, J.C. Murdoch, J.H. Parsons and E.G. White. Cmnd. 4190. London: Her Majesty's Stationery Office, 1969.

Summary: Reports on the status of antibiotic use in man and animals. Outlines the uses and amounts consumed for both. Reviews the reasons for which antibiotics are administered to food animals, including disease prevention, use in growth promotion, stress reduction and therapy. States that there are possible dangers to the human population stemming from the administration of antibiotics to animals, such as the rise of antibiotic-resistant strains of bacteria in animals that could cause disease in humans. The resulting infection could then be difficult to treat due to the null effect of antibiotics. Other dangers include the transmission of resistance determinants from animal strains to human strains of bacteria. It is known that such transfers take place and the fear is that resistance may be transferred to normal bacteria that inhabit the human bowel and/or to pathogens that may then cause disease. Discusses the prevalence of multiple antibiotic-resistant strains of bacteria and how they may arise. States that even though there are multiple antibiotics available for treatment of certain diseases, those reserved as a drug of choice may have a number of advantages over alternative treatment. Strains with multidrug resistance pose a greater threat in that the only effective drugs left for treatment in humans may be unsuitable because of toxicity or allergy. These infections are likely to arise where humans and animals share a pathogen such as *Salmonella* and the administration of antimicrobials to animals no doubt encourages the prevalence of resistance in these strains. Concludes that the use of antimicrobials in food animal production, especially when used in growth promotion, is of great concern and that limiting factors should be put in place to secure the use of antibiotics of greatest importance in human administration for therapeutic uses only and in some cases excluded from animal use altogether.

Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. S.B. Levy, G.B. Fitzgerald and A.B. Macone. *New England Journal of Medicine,* 1976. 295(11): 583-588.

Summary: Reports a study to determine if giving animals antibiotics in feed caused changes in intestinal bacterial flora and if workers and neighbors of the farm were affected. Chickens were screened for bacteria before and after a diet that included tetracycline-supplemented feed. Resistance to tetracycline changed dramatically within 36 to 48 hours of changing the diet of the animals. Within two weeks, 90 percent of the chickens were found to excrete essentially all tetracycline-resistant organisms. Within five to six months, there was a large increase in tetracycline-resistant bacteria in farm dwellers while the neighbors showed no change in bacterial count.

An epidemic of resistant *Salmonella* in a nursery: Animal-to-human spread. R.W. Lyons, C.L Samples, H.N. DeSilva, K.A. Ross, E.M. Julian and P.J. Checko. *Journal of the American Medical Association*, 1980. 243(6): 546-547.

Summary: Studies the case of a pregnant woman, infected with *Salmonella heidelberg*, who worked on her father's farm until four days before delivery. Her baby subsequently developed mild diarrhea, as did two others sharing the hospital nursery. *Salmonella heidelberg* was isolated from each and in all cases was resistant to chloramphenicol, sulfamethoxazole and tetracycline. The strain was presumed to originate from a herd of infected dairy cows at the woman's father's farm as those bacteria showed the same resistance pattern as did those collected from the father.

Emergence of multidrug-resistant *Salmonella enterica* serotype Typhimurium DT104 infections in the United States. M.K. Glynn, C. Bopp, W. Dewitt, P. Dabney, M. Mokhtar and F.J. Angulo. *New England Journal of Medicine,* 1998. 338(19): 1333-1338.

Summary: Reviews *Salmonella* data collected by local and state health departments and public health laboratories between 1979 and 1996. Finds that a rapid increase of multidrug-resistant *Salmonella enterica* serotype typhimurium (DT104), a strain widely distributed in food animals and known to cause disease in humans, occurred in this period. The percentage rose from 0.6 percent in 1979–1980 to 34 percent in 1996. Concludes that more prudent use of antibiotics on farms is necessary to reduce the dissemination of multidrug-resistant *Salmonella* and emergence of further resistant strains.

Epidemiologic aspects, control, and importance of multiple-drug resistant *Salmonella* typhimurium DT104 in the United States. J.E. Akkina, A.T. Hogue, F.J. Angulo, R. Johnson, K.E. Petersen, P.K. Saini, P.J. Fedorka-Cray and W.D. Schlosser. *Journal of the American Veterinary Medical Association,* 1999. 214(6): 790-798.

Summary: Studies an animal strain of *Salmonella* and its prevalence of infection in humans. States that multidrug-resistant *Salmonella* DT104 is the second-most-prevalent *Salmonella* organism isolated from humans in England and Wales in the time frame of this study. Gives numerous examples of outbreaks in the U.S., most of which are traced to milk. Cattle, along with pigs, sheep, chickens, turkeys and several other animals, are known carriers of this strain.

Transfer of antibiotic resistant bacteria from animals to man. H.C. Wegener, F.M. Aarestrup, P. Gerner-Smidt and F. Bager. *Acta Veterinaria Scandinavica Supplementum*, 1999. 92: 51-57.

Summary: Describes zoonotic bacterial infections and their treatment. States that most *Salmonella, campylobacter, yersinia* and entero-haemorrhagic *E. coli* (EHEC) infections do not require antibiotic therapy, but in some cases these tools provide life-saving cures. Increasing levels of resistance in these bacteria, especially fluoroquinolone resistance, give rise for concern when it comes to human infections. Calls for infection control at the herd level and the need for prudent use of antibiotics in food animals.

The use of drugs in food animals: Benefits and risks. Committee on Drug Use in Food Animals, Panel on Animal Health, Food Safety, and Public Health, National Research Council. 1999.

Summary: This review focuses on the following topics associated with antibiotic use in animal agriculture: background and perspectives; production practices and drug use; benefits and risks to human health; drug development, government approval and the regulatory process; drug residues and microbial contamination in food costs of eliminating sub-therapeutic use; and approaches to minimize antibiotic use in food animal production. Primary findings include 60 to 80 percent of livestock and poultry receive antibiotics. This use of antibiotics increases the potential for resistant zoonotic bacteria to impact humans and for resistant genes to be shared by species of bacteria. The review finds an increase cost of $4.84 to $9.72 per consumer per year should sub-therapeutic use be banned.

Ceftriaxone-resistant *Salmonella* infection acquired by a child from cattle. P. Fey, T.J. Safranek, M.E. Rupp, E.F. Dunne, E. Ribot, P.C. Iwen, P.A. Bradford, F.J. Angulo and S.H. Hinrichs. *New England Journal of Medicine,* 2000. 342: 1242-1249.

Summary: Reports the case of a 12-year-old boy who lived on a farm in Nebraska and was infected with a ceftriaxone-resistant strain of *Salmonella enterica* serotype typhimurium that was traced to his father's herd of cattle using molecular techniques. States that this finding adds to the growing body of evidence suggesting that the use of antibiotics in livestock is the prominent source of resistance to these agents in *Salmonella* infection.

Appropriate regulation of antibiotics in livestock feed. R.L. Goforth and C.R. Goforth. *Boston College Environmental Affairs Law Review*, 2000. 28(1): 39-77.

Summary: Reviews nontherapeutic uses of antimicrobials in food animals and their impact on human health. States that this practice is creating possibly irreversible effects on the viability of antibiotics used to treat human disease. Concludes that despite short-term economic benefits associated with the widespread use of antibiotics in agriculture, the risk to human health justifies a change in policy.

Antibiotic resistance in *Campylobacter* strains isolated from animals, foods and humans in Spain in 1997–1998. Y. Saenz, M. Zarazaga, M. Lantero, M.J. Gastaneres, F. Baquero and C. Torres. *Antimicrobial Agents and Chemotherapy,* 2000. 44(2): 267-271.

Summary: Studies *Campylobacter* isolated from foods, animals and humans. Finds that a high percentage of *Campylobacter jejuni* contaminates food (54.4 percent), broilers (81 percent) and pigs (88.9 percent). Isolates collected from broilers and pigs showed a 99 percent resistance rate to ciprofloxacin, with only a slightly lower number of human isolates (72 percent) also resistant. High resistance percentages to ampicillin, erythromycin, gentamicin and amikacin also were detected for *C. coli* isolated from these sources. Concludes that "more restrictive policies on the use of antibiotics in animals may result in an improvement of the current situation in the medium term."

The effect of banning avoparcin on VRE carriage in The Netherlands. A.E. van den Bogaard, N. Bruinsma and E.E. Stobberingh. *Journal of Antimicrobial Chemotherapy,* 2000. 46: 146-148.

Summary: Discusses the removal of avoparcin, an antimicrobial similar to vancomycin, from commercial food animal production in several settings. Sweden, which banned the use of antibiotics as growth promoters in 1986, has not reported any vancomycin-resistant *Enterococci* (VRE). This example strongly suggests that the removal of selective pressure will remove VRE from the human population over time. Denmark also banned the use of avoparcin in 1995 and saw the prevalence of poultry-isolated cases of VRE drop from greater than 80 percent in 1995 to less than 5 percent in 1998.

Epidemiology of resistance to antibiotics: Links between animals and humans. A. Van der Bogaard and E.E. Stobberingh. *International Journal of Antimicrobial Agents*, 2000. 14: 327-335.

Summary: Discusses the ban on avoparcin in food animals in the European Union and resulting significant decreases in resistance to vancomycin (a related drug) in intestinal *Enterococci* bacteria in animals and humans. States that resistant bacteria from animals can infect or reach the human population by direct contact and via food products of animal origin. Shows evidence for transfer of resistant genes between bacteria in humans and animals and recommends reducing the amount of antibiotics used in food animals in order to protect public health and safeguard the efficacy of antibiotics in veterinary medicine.

Selective pressure by antibiotic use in livestock. W. Witte. *International Journal of Antimicrobial Agents,* 2000. 16: S19-S24

Summary: Describes the selective pressures seen in the use of antibiotics as growth promoters. States that discovery of glycopeptide resistance outside of hospitals in *Enterococcus faecium* is linked to avoparcin use in animals. The review concludes that the spread of resistance is worrisome as mobile genetic elements are seen transferring between bacterial species that could lead to non-resistant pathogens picking up resistance from non-pathogenic strains. It concludes in support of the ban on growth promoters introduced in Europe as this might interfere with treatment in humans.

Quinolone and macrolide resistance in *Campylobacter jejuni* and *C. coli*: Resistance mechanisms and trends in human isolates. J. Engberg, F.M. Aarestrup, D.E. Taylor, P.Gerner-Smidt and I. Nachamkin. *Emerging Infectious Diseases,* 2001. 7(1):24-34.

Summary: Reviews the increasing resistance of *Campylobacter* strains to macrolide and quinolone antibiotics in human clinical isolates with respect to the use of these agents in food animals. Data suggest that while erythromycin and other macrolides should continue to be the antibiotics of choice in most regions, fluoroquinolones may be of limited use in many areas as the overuse of enrofloxacin and other drugs in food animals has caused a sharp upswing in the resistance of *Campylobacter* to these antibiotics.

The need to improve antimicrobial use in agriculture: Ecological and human health consequences. Alliance for the Prudent Use of Antibiotics. *Clinical Infectious Diseases*, 2002 supplement. 34 (S3): S71-144.

Summary: Reviews more than 500 studies relating to agricultural uses of antibiotics and concludes that "elimination of nontherapeutic use of antimicrobials in food animals and agriculture will lower the burden of antimicrobial resistance."

Potential mechanisms of increased disease in humans from antimicrobial resistance in food animals. M. Barza. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S123-125.

Summary: Summarizes five potential mechanisms by which antimicrobial resistance may adversely affect human health. Two of the five relate to antimicrobial use in animals: (1) that resistant pathogens acquired by animals as the result of treatment with antibiotics transmit these pathogens through the food chain; and (2) that commensal flora of animals may acquire resistance traits from the previous pool of resistant pathogens, which then may be passed to human commensals and/or pathogens through the food chain.

Antimicrobial residues in animal waste and water resources proximal to large-scale swine and poultry feeding operations. E.R. Campagnolo, K.R. Johnson, A. Karpati, C.S. Rubin, D.W. Kolpin, M.T. Meyer, J.E. Estaban, R.W. Currier, K. Smith, K.M. Thu and M. McGeehin. *The Science of the Total Environment,* 2002. 299: 89-95.

Summary: Reports on data from numerous antimicrobial residues collected from animal wastes, surface water and groundwater proximal to large-scale swine and poultry operations. Data indicate that animal waste applied as fertilizer to the land may serve as a contaminating source of antimicrobial residues for the environment as a detectable level of antimicrobial compounds was found in waste-storage lagoons and surface and groundwater proximal to these operations.

Antimicrobial use and resistance in animals. S.A. McEwen, and P.J. Fedorka-Cray. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S93-106.

Summary: Describes antibiotic use in each animal class. Discusses a 1999 report on the economic effects of banning subtherapeutic antibiotic use in the U.S. Concludes that meat producers following good management practices would not be adversely affected by such a ban. Reviews antimicrobial-resistance-monitoring programs in bacteria of animal origin and the techniques involved. States alternatives to using antibiotics in food animals, such as providing good sanitation, air temperature and clean water, as well as vaccine use and development and use of probiotics that consist of live, beneficial bacteria.

Emergence, spread and environmental effect of antimicrobial resistance: How use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else. T.F. O'Brien. *Clinical Infectious Diseases*, 2002. 34(Suppl 3): S78-84.

Summary: Discusses how a bacterial community responds to antimicrobial use by obtaining resistance genes as well as how these genes are spread around the globe and between different bacterial populations. States that in Europe a ban of avoparcin, an antibiotic similar to vancomycin, was implemented in 1997 because of rising concerns that strains of vancomycin-resistant *Enterococci* were being used for growth promotion.

Generally overlooked fundamentals of bacterial genetics and ecology. A.O. Summers. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S85-92.

Summary: Reviews how treatment with any given antibiotic may result in resistance to several antibiotics because of the ability of bacteria to obtain genetic elements that code for multidrug resistance. States that the exchange of bacteria between a host and its environment is a continual process and that selective pressure applied to any part of the ecosystem will result in a highly resistant bacterial population. Also states that once resistance is acquired it will be hard to reverse because of molecular mechanisms inherent in bacteria that ensure future generations hold on to resistance characteristics.

Human diseases caused by foodborne pathogens of animal origin. M.N. Swartz. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S111-122.

Summary: 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.

Antimicrobial resistance of *Escherichia coli* 0157 isolated from humans, cattle, swine, and food. C.M. Schroeder, C. Zhao, C. DebRoy, J. Torcolini, S. Zhao, D.G. White, D.D. Wagner, P.F. McDermott, R.D. Walker, and J. Meng. *Applied and Environmental Microbiology*. 2002. 68(2): 576-581.

Summary: Examines the prevalence and antimicrobial resistance of Shiga toxin-producing *E. coli* (STEC) 0157 in a collection of samples collected for diagnostic purposes from humans, swine, cattle, and food between 1985 and 2000. Of 361 isolates available to analyze, 210 (58 percent) were STEC 0157. The greatest prevalence of STEC was found in isolates from cattle, followed by humans, food, and swine. Though swine had the smallest prevalence of STEC, isolates from swine demonstrated the highest prevalence of resistance. Prevalence of resistance to ampicillin, sulfamethazole, gentamicin, tetracycline, and trimethoprim-sulfamethoxazole was greater in non-STEC isolates than STEC isolates, however, all isolates were susceptible to ceftriaxone and ceftiofur. Of 191 isolates identified as *E. coli* O157:H7, cattle remained the most frequent source, followed by humans, and food. No O157:H7 was found in swine samples. All isolates from food were susceptible to all antimicrobials tested. Isolates from humans and cattle demonstrated similar resistance prevalence to ampicillin (5 vs. 1 percent), cephalothin (4 vs. 1 percent), chloramphenicol (0 vs. 1 percent), sulfamethoxazole (9 vs. 12 percent), tetracycline (7 vs. 11 percent), and amoxicillin-clavulanic acid (0 vs. 1 percent). Antimicrobial treatment of *E. coli* O157:H7 infection in humans may lead to release of Shiga toxin leading to hemolytic uremic syndrome (HUS). However, clinical trials are underway in which a chemically synthesized analog of Shiga toxin receptor Gb3 is given to patients to absorb the toxin and prevent HUS. If these trials prove successful, antimicrobials may become more important in the treatment of infection from *E. coli* 0157:H7. The findings from this study that most STEC isolates were susceptible to all antimicrobials tested is encouraging. However, presence of resistance in isolates from swine and cattle to drugs used in these food-animals suggests that antimicrobial use in these animals contributes to the emergence of resistance in *E. coli* O157:H7.

Antimicrobial resistance in livestock. B. Catry, H. Laevens, L.A. Devriese, G. Opsomer and A. Kruif. *Journal of Veterinary Pharmacology and Therapeutics,* 2003. 26: 81-93.

Summary: Reviews 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." States that commensal bacteria in healthy animals fed or administered antibiotics contain resistance genes that if ingested by humans could colonize the gut and transfer these genes to pathogenic bacteria. This transfer would result in treatment difficulty because of antibiotic resistance.

Emergence of multidrug-resistant *Salmonella enterica* Serotype Newport infections resistant to expanded-spectrum cephalosporins in the United States. A. Gupta, J. Fontana, C. Crowe, B. Bolstorff, A. Stout, S. Van Duyne, M.P. Hoekstra, J.M. Whichard, T.J. Barrett and F.J. Angulo. *Journal of Infectious Diseases,* 2003. 188: 1707-1716.

Summary: Discusses the emergence of new strains of multidrug-resistant *Salmonella* in New England. Reports that isolates of Newport-MDRAmpC among *Salmonella* serotype Newport from humans rose from 0 percent in 1998 to 53 percent in 2001. This strain shows resistance to amoxicillin/clavulanic acid, cephalothin, cefoxitin and ceftiofur. Concludes that the use of antimicrobial agents in livestock is linked to the emergence of antimicrobial-resistant nontyphoidal *Salmonella* and that the emergence of Newport-MDRAmpC strains in humans has coincided with the same infections in cattle.

Evidence of an association between use of anti-microbial agents in food animals and antimicrobial resistance among bacteria isolated from humans and the human health consequences of such resistance. F.J. Angulo, V.N. Nargund and T.C. Chiller. *Journal of Veterinary Medicine,* 2004. 51: 374-379.

Summary: Reviews antimicrobial-resistant infections occurring in humans as a result of antibiotic use in food animal production. States that "a review of outbreaks of *Salmonella* infections indicated that outbreaks were more likely to have a food animal source than outbreaks caused by anti-microbial-susceptible *Salmonella*." Reports that the human health consequences resulting from bacterial resistance include infections caused by resistant pathogens, an increase in treatment failures and increased severity of disease.

Nontherapeutic use of antimicrobial agents in animal agriculture: Implications for pediatrics. K.M. Shea. *Pediatrics,* 2004. 114(3): 862-868.

Summary: Examines how antimicrobials are used in food animal production and how this practice could contribute to resistance in humans. Notes that children are at greater risk from resistant infections than the general population.

Antibiotic use in agriculture and its impact on the terrestrial environment. K. Kumar, S.C. Gupta, Y. Chander and A.K. Singh. *Advances in Agronomy,* 2005. 87: 1-54.

Summary: Discusses the impact of antibiotic use on disease treatment and growth promotion in animals. States that overuse of antibiotics results in the excretion of drugs that are not absorbed in the animal and that the resulting manure stock may be spread on fields, altering the soil bacteria and contaminating water sources. Notes that the continued prevalent use of antibiotics in agriculture is increasing the emergence of antibiotic-resistant bacteria both in both clinically relevant strains of pathogens and in normal commensal microorganisms. Concludes that "prudent use of antibiotics to a bare minimum along with alternative methods that minimize development and proliferation of resistant bacteria need investigation."

Agricultural antibiotics and human health: Does antibiotic use in agriculture have a greater impact than hospital use? D.L. Smith, J. Dushoff and J.G. Morris, Jr. *PLoS Medicine,* 2005. 2(8): 731-735.

Summary: Reviews the emergence and spread of antibiotic-resistant bacteria and notes that mathematical models can help with understanding underlying mechanisms and guiding policy responses. Agricultural antibiotic use may generate novel types of antibiotic-resistant bacteria that spread to humans; models can help estimate how much additional disease has been caused by agricultural antibiotic use. Depending on the assumptions used, the model suggests that transmission from agriculture can have a greater impact than hospital transmission on human populations.

Resistant bugs and antibiotic drugs – State and county estimates of antibiotics in agricultural feed and animal waste. K. Florini, R. Denison, T. Stiffler, T. Fitzgerald, and R. Goldburg. *Environmental Defense,* 2005.

Summary: A report on the use of antibiotics in food animal production. States that an estimated 70 percent of the antibiotics used in the U.S. each year are used as feed additives for chickens, hogs and beef cattle. These are used mainly to promote growth and to compensate for poor health conditions. The National Academy of Sciences estimates that a cost estimate of $4 to $5 billion is associated with antibiotic-resistant bacteria. The report presents state and county specific estimates of antibiotic use and estimates of the amount of antibiotics excreted as animal waste. Farm families and the surrounding communities where there is greater on-farm antibiotic use may be at a greater risk of exposure to resistant bacteria. Estimates were derived from the U.S. Department of Agriculture's 2002 Census of Agriculture in conjunction with the Union of

Concerned Scientists per-animal estimates of antibiotic feed-additive use for certain animal groups. North Carolina and Iowa both use an estimated three million pounds of antibiotics annually, which is equal to the estimated amount used for human treatment nationwide. The highest amounts of medically important antibiotics are used in hogs. An estimated 13.5 million pounds of antibiotics are excreted in the form of animal wastes, which is nearly half of the estimated total amount added to animal feeds. Also highlights that food is a pathway for resistance gene spread and that disease such as urinary tract infections may originate from food sources.

The potential role of concentrated animal feeding operations in infectious disease epidemics and antibiotic resistance. M.J. Gilchrist, C. Greko, D.B. Wallinga, G.W. Beran, D.R. Riley and P.S. Thorne. *Environmental Health Perspectives*, 2007. 115(2): 313-316.

Summary: Reports the recommendations of a working group that was part of the 2005 *"Conference on Environmental Health Impacts of Concentrated Animal Feeding Operations: Anticipating Hazards – Searching for Solutions."* Recommendations include the following: discontinue nontherapeutic use of antibiotics as growth promoters; establish nationwide surveillance programs to fully assess the contribution of antibiotic use in livestock production to the creation of ecological reservoirs of resistance or the transmission of that resistance to humans; identify resistant strains; and establish minimum separation distances for swine and poultry facilities to reduce the risk of influenza outbreaks and municipal-style waste treatment to limit microbial and nutrient contamination of surface and groundwater.

Fluoroquinolone-resistant *Campylobacter* species and the withdrawal of fluoroquinolones from use in poultry: A public health success story. J.M. Nelson, T.M. Chiller, J.H. Powers and F.J. Angulo. *Clinical Infectious Diseases,* 2007. 44: 977-980.

Summary: Reviews fluoroquinolone use and the resulting effect of resistance occurring in the *Campylobacter* that followed the withdrawal of enrofloxacin from use in treating poultry. States that 13 percent of all resistant infections occur from travel abroad, showing that resistance is a global threat and that U.S. regulatory actions are not effective internationally. Concludes that "judicious use of antimicrobial agents should be stressed to preserve the efficacy of these important chemotherapeutic agents."

Environmental health impacts of concentrated animal feeding operations: Anticipating hazards—searching for solutions. P.S. Thorne. *Environmental Health Perspective,* 2007. 115: 296-297.

Summary: Outlines potential risks to human health from concentrated animal feeding operations (CAFOs) and the research needed to better understand the impact of these operations on public health. Examples of policy change include establishment of a requirement for minimum separation distances, use of solid-waste storage tanks to eliminate the possibility of microbial contamination spreading to water sources and provision of clean water sources for drinking. Expresses concerns over air quality and the need for better surveillance in this area. Expresses a need to phase out the use of antimicrobial agents as growth promotants.

Response of antibiotics and resistance genes to high-intensity and low-intensity manure management. H.N. Storteboom, S-C Kim, K.C. Doesken, K.H. Carlson, J.G. Davis, and A. Pruden. *Journal of Environmental Quality,* 2007. 36: 1695-1703.

Summary: The goal of the study was to understand how antibiotics and antibiotic resistance genes respond to different levels of manure management. Management practices studied were high intensity management and low intensity management. High intensity was defined as amending with alfalfa and dried leaves with regular watering and turning the manure to enhance degradation. Low intensity was defined as piling or windrowing manure, which then received no treatment. A small scale pilot study and a large scale study were performed in which the large scale study focused on feedlot cattle manure and dairy cattle manure. The authors found that high intensity was more successful increasing the rate at which antibiotics degrade but was not a significant factor in reducing levels of resistant genes. Feedlot manure had a significantly higher level of resistant genes than did dairy manure, likely due to the feedlot cattle receiving routine subtherapeutic concentrations of antibiotics. The persistence of resistant genes is speculated to be due to the presence of degraded antibiotics as these products are often still effective and may allow selection pressure to remain. The authors suggest that longer treatment times may be necessary to further reduce levels of antibiotic resistant genes.

Association of antimicrobial resistance in *Campylobacter* isolated from food-producing animals with antimicrobial use on farms. T. Asai, K. Harada, K. Ishihara, A. Kojima, T. Sameshima, Y. Tamura, and T. Takahashi. *Japanese Journal of Infectious Diseases*. 2007. 60: 290-294.

Summary: This study describes the use of antimicrobials in food-animals in Japan and examines the association between the use of antimicrobials and fluoroquinolone-resistant *Campylobacter*. Fluoroquinolone resistance was of interest because it was approved for therapeutic use in food-production animals in 1991. The most widely used antimicrobials were tetracyclines (7.8 percent), penicillin (6.5 percent), aminoglycosides (4.6 percent), and macrolides and lincosamides (4.3 percent). Fluoroquinolones were used for therapeutic purposes on 1.5 percent of 1,374 operations surveyed. Of operations positive for *C. jejuni*, oxytetracycline (OTC) resistance was present in 57.1 percent of operations using tetracycline antibiotics and on 43.2 percent of operations not using tetracyclines. For *C. coli* positive operations, 92.5 percent using tetracylcines and 74.3 percent not using tetracyclines were resistant to OTC. Enrofloxacin (ERFX) resistance was found in 66.7 percent and 16.7 percent farms reporting fluoroquinolone use for *C. jejuni* and *C. coli*. Farms not reporting use of fluoroquinolones had 15.5 percent and 28.8 percent prevalence of ERFX-resistant *C. jejuni* and *C. coli* respectively. Authors conclude that although fluoroquinolone-resistance in *Campylobacter* arose after approval for use in the treatment of sick animals, ERFX-resistance in *Campylobacter* is able to persist on food-animals operations regardless of use of fluoroquinolones.

Antibiotic resistance in bacteria associated with food animals: A United States perspective of livestock production. A.G. Mathew, R. Cissell, and S. Liamthong. *Foodborne Pathogens and Disease*. 2007. 4(2): 115-133.

Summary: Reviews the debate concerning use of antibiotics in animal production in the U.S. by presenting benefits of use but focusing on the problem of development of antibiotic resistant bacteria. Presents the types of antibiotics used in food-animal production and the main reasons for use including therapeutic, metaphylaxis (short-term treatment of infection), prophylactic, and for growth promotion. The origin of antibiotic resistance and the mechanisms of development and transfer of resistance among bacteria are discussed in detail. Surveillance programs are now present in the U.S. to track resistant bacteria and three are discussed. Based on surveillance and prior research, *Salmonella, Campylobacter, Listeria, Yersinia, Enterococcus,* and *Escherichia coli* are presented as bacteria of concern related to food animal production and human health. Use of antibiotics in the beef cattle, dairy cattle, swine, and poultry industry is discussed. Challenges regulators, the animal production industry, and consumers to take steps in limiting risks based on science-based information.

Associations between antimicrobial resistance genes in fecal generic *Escherichia coli* isolates from cow-calf herds in western Canada. S.P. Gow, C.L. Waldner, J. Harel and P. Boerlin. *Applied and Environmental Microbiology,* 2008. 74(12): 3658-3666.

Summary: Studies antimicrobial-resistance gene distribution among cow-calf herds in western Canada. Finds that 65 percent of the 207 examined isolates of *E. coli* were resistant to at least one antimicrobial. Several patterns emerged from this research, suggesting that when a bacterium acquires resistance to one antimicrobial it is likely to become resistant to others because of the transfer of mobile genetic elements that harbor regions of multiple drug resistance. This suggests that even with careful restriction of antimicrobial use on farms, bacteria may still pick up resistance unrelated to the antimicrobials being used.

Industrial food animal production, antimicrobial resistance, and human health. E.K. Silbergeld, J. Graham and L.B. Price. *Annual Review of Public Health,* 2008. 29: 151-169.

Summary: Reviews the use of antimicrobials in agriculture and presents evidence for resistance stemming from their use in food animals. States that agricultural use of antibiotics can significantly shorten the useful life of these drugs, which are also used to treat disease in humans and animals. Suggests that estimates of nontherapeutic antibiotic use in agriculture fall between 60 percent and 80 percent of total antimicrobial production in the U.S. Concludes that "the use of antimicrobials for nontherapeutic purposes in agriculture is a major factor driving the emergence of antimicrobial resistance globally," and that "prudent public health policy thus indicates that nontherapeutic uses of antimicrobials in food animal production should stop."

Effect of subtherapeutic administration of antibiotics on the prevalence of antibiotic-resistant *Escherichia coli* bacteria in feedlot cattle. T.W. Alexander, L.J. Yanke, E. Topp, M.E. Olson, R.R. Read, D.W. Morck, and T.A. McAllister. *Applied and Environmental Microbiology,* 2008. 74(14): 4405-4416.

Summary: A study of *E. coli* resistance in feedlot cattle when they were administered a sub-therapeutic level of antibiotics. Cattle previously not treated with antibiotics were brought to a research feedlot where they were divided into groups each receiving a different regimen of sub-therapeutic antibiotics along with one group as a control not being treated. Cattle were fed two different diets during their treatments, one silage based diet and another grain based. Cattle tested before entering the feedlot (before starting sub-therapeutic treatment) were colonized with *E. coli* resistant to tetracycline (TET) at a rate greater than 40 percent, suggesting a colonization of TET resistant *E. coli* from birth (i.e. there is a high population of *E. coli* in circulation with TET resistance). Additionally the group fed chlortetracycline plus sulfamethazine (TET-SUL) showed an increased rate of TET resistance. A grain-based diet also appeared to increase not only the finding of *E. coli* but also increased the rate of finding TET resistant *E. coli.* Noted is that when antibiotic treatment was stopped for a period of about one to two months during each diet there was not a significant decline in the shedding of resistant *E. coli* except in the TET-SUL group where a slight decline was observed. However, upon starting treatment again the decline was reversed and prevalence of resistance continued to climb. The authors do note that in previous studies a decline in resistance has been shown when antibiotics (selective pressures) were removed from diets of animals, but this may sometimes take years to see a marked decrease. In summary feeding of certain diets and addition of certain sub-therapeutic levels of antibiotics in feed will increase the rate of resistance in *E. coli.*

The effects of transport and lairage on counts of *Escherichia coli* O157 in the feces and on the hides of individual cattle. N. Fegan, G. Higgs, L. Duffy and R.S. Barlow. *Foodborne Pathogens and Disease,* 2009. 6(9):1113-1120.

Summary: Reports on a study in which *E. coli* O157 rates from feces and from hides of cattle were monitored to determine whether a change occurred during transport from the feedlot to slaughter. Concludes that "transport and lairage did not lead to an increase in the number or isolation rate of *E. coli* O157 from cattle."

Comparison of the prevalence of bacterial enteropathogens, potentially zoonotic bacteria and bacterial resistance to antimicrobials in organic and conventional poultry, swine and beef production: a systematic review and meta-analysis. I. Young, A. Rajic, B.J. Wilhelm, L. Waddell, S. Parker, and S.A. McEwen. *Epidemiol. Infect.,* 2009. 137: 1217-1232.

Summary: A systematic review of the literature in comparing organic and conventional meats. Finds that the prevalence of *Campylobacter* was higher in organic broiler chickens at slaughter, but a difference was not seen in retail chicken. *Campylobacter* from conventional retail chicken was more likely to be ciprofloxacin resistant. Furthermore, bacteria isolated from conventional food animal production were found to exhibit higher levels of antibiotic resistance. The authors conclude that further research is necessary in this area as this type of data from other food-animal species was limited or inconsistent.

The transformation of U.S. livestock agriculture: Scale, efficiency, and risks. J.M. MacDonald and W.D. McBride. *Economic Information Bulletin Number 43,* United States Department of Agriculture, 2009.

Summary: Report from the United States Department of Agriculture detailing the nature, causes and effects of structural changes in livestock production. States that due to the increase seen in farm size, livestock wastes are becoming geographically concentrated in the US and the application of these wastes to land poses risks to air and water resources. Large-scale operations are more likely to see a rapid spread of disease due to the concentration of animals and tend to administer sub therapeutic doses of antibiotics routinely in feed and water to animals to promote health and prevent disease. These antibiotics may enter the environment though manure application and overuse may contribute to increased resistance in animal and human pathogens. Other technologies, including better sanitation and testing procedures, can be substituted for these practices in some production stages especially in poultry production. These practices, used in most operations not providing their animals sub therapeutic antibiotics, include: the testing of feed for specific pathogens; testing of flocks routinely for disease; cleaning out and sanitizing houses after each flock; and typically were required to have a hazard analysis and critical control point plan in place to direct food safety measures. The farms that do not rely on sub therapeutic antibiotics for disease prevention were nearly twice as likely to follow these procedures as those farms that used sub therapeutic antibiotics.

Fate and transport of antibiotic residues and antibiotic resistance genes following land application of manure waste. J.C. Chee-Sanford, R.I. Mackie, S. Koike, I.G. Krapac, Y.F. Lin, A.C. Yannarell, S. Maxwell and R.I. Aminov. *Journal of Environmental Quality,* 2009. 38: 1086-1108.

Summary: This review article can be broken down into three parts:

1) Dissemination of antimicrobial residues into the environment: Antibiotics fed to food animals are not always fully absorbed and will be excreted in waste. This waste is often applied to the environment as a disposal and fertilization technique. During this process excreted antibiotics that have not broken down during storage of waste are applied to the environment. Numerous studies are cited where antibiotic residues were found in soil and water near or on concentrated animal feeding operations (CAFO).

2) Resistance characteristics and presence of bacteria in CAFO and their transport into the environment: Antibiotic resistance in animals is likely to arise among commensal bacteria as there is a large pool in the gut (often $>10^{14}$) and antibiotic resistance may be selected for each time an antibiotic is administered regardless of the animals health. This is the most likely pathway for the development of pathogen resistance as commensal bacteria may transfer mechanisms of resistance to bacterial pathogens. It is well documented that these bacteria may survive waste treatment methods and are applied to the soil that may have harmful environmental implications.

3) Antibiotic resistance gene transfer in the environment: By applying animal waste to the environment a pool is created that holds a potentially significant amount of resistance genes; however, the transfer of these mechanisms into commensal bacteria of the environment is relatively unknown. Studies are listed showing that the transfer of resistance genes does occur between bacteria of different genera in such areas as soil and groundwater. The authors conclude that although the impacts from antibiotic use in food animal production and the effects on the environment are not completely clear, there are established studies pointing to an increase of incidences in antibiotic resistance.

Sublethal antibiotic treatment leads to multidrug resistance via radical-induced mutagenesis. M.A. Kohanski, M. A. DePristo and J.J. Collins. *Molecular Cell,* 2010. 37:311-320

Summary: Looks at mutation rates of *E. coli* exposed to sublethal doses of different antibiotics. Finds that when sublethal doses of antibiotics were given, cell production of radical oxygen species (ROS) occurred, leading to mutations. ROS can damage DNA, causing a mutation in such a way that the cells may acquire resistance to classes of antibiotics different from those with which they are being treated. Gives a clinical example of incomplete treatment with antibiotics (e.g., a missed pill), but one could postulate that in food animal production, where subtherapeutic levels of antibiotics are given for the purpose of growth promotion, this event may also occur.

Use and environmental occurrence of antibiotics in freestall dairy farms with manured forage fields. N. Watanabe, B.A. Bergamaschi, K.A. Loftin, M.T. Meyer, and T. Harter. *Environmental Science and Technology,* 2010. 44:17 6591-6600.

Summary: Investigates the use and occurrence of antibiotics in concentrated dairy feeding operations to assess their potential transport into first-encountered groundwater. The study finds that wide arrays of antibiotics are used in the farms leading to several hundred grams of antibiotics being excreted per farm per day. Samples containing sulfonamides, tetracyclines and lincomycin were most frequent; however, it appeared that the occurrence of antibiotics in collected samples was limited to farm boundaries and were usually associated with lagoons, hospital pens and calf hutches. There was detection of antibiotics in shallow groundwater 10 meters from lagoons. The authors conclude that these occurrences of antibiotics at the farm surface need closer study as they may affect the ecosystem and microbial community including the development of antibiotic resistance.

The interface between veterinary and human antibiotic use. T.R. Shryock and A. Richwine. *Annals of the New York Academy of Sciences,* 2010. 1-14.

Summary: This review looks at the overlaps between human and veterinary medicine and how current views are redirecting company pipelines in regards to new veterinary antimicrobial drug discovery. The authors state that the listing of "critically important" antibiotics by the World Health Organization has led to a prejudice against the food animal use of specific antimicrobial classes. The authors state several possible remedies to use in parallel or in replacement of these antibiotic classes including novel antibiotic development, vaccines, immunomodulators, bacteriophages and probiotics. A resounding theme is the ever-increasing demand of animal-derived protein and that the current and future availability of novel antimicrobial agents for use in food animal production be considered from this perspective. Other key points addressed include appropriate risk assessment before regulation, as uninformed decisions may discourage innovation of new antibiotics and that industry should apply the use of risk management interventions such as appropriate antibiotic use guidelines.

The effects of moral obligations to others and others' influence on veterinarians' attitudes toward and recommendations to utilize antibiotics in feedlot cattle. J-S. Jan, Wm. A. Mcintosh, H. M. Scott, and W. Dean. *Journal of Rural Social Sciences.* 2010. 25 (2): 122-148.

Summary: A questionnaire was sent to feedlot veterinarians querying about areas of social pressure that may affect behavior in treatment of animals. Outcomes suggest that pressure from pharmaceutical companies led to a less likely scenario that veterinarians would have a positive attitude toward using antibiotics in acutely sick cattle. The opposite was seen when rule and norm-making organizations such as veterinary professional organizations, the FDA or state licensing boards applied pressure in that veterinarians' attitudes were positively affected toward the use of antibiotics. Favorability toward using antibiotics was also seen when pressure from feedlot managers and retained owners of cattle was applied but only when moral obligations to these clients were taken into consideration. Otherwise these pressures had little influence on attitudes or recommendations.

Tetracycline and sulfonamide antibiotic resistance genes in livestock lagoons of various operation type, configuration, and antibiotic occurrence. C.W. McKinney, K.A. Loftin, M.T. Meyer, J.G. Davis, and A. Pruden. *Environmental Science & Technology.* 2010. 44: 6102-6109.

Summary: The purpose of this study was to look at waste lagoons among various livestock facilities and examine the behavior of *tet* (tetracyclines) and *sul* (sulfonamide) antibiotic resistance genes (ARGs) over the course of one year. ARG concentrations were significantly higher in lagoon samples from conventional dairy farms compared to organic. Chicken layer operation lagoons had the lowest detectable levels of *tet* and *sul* ARGs, while the highest were in swine lagoons. In general *sul* ARGs were more recalcitrant than *tet* ARGs. The study demonstrated that liquid manure lagoons may show some promise in reducing *tet* ARGs as passing waste though several lagoons decreased *tet* ARGs; however, when compared to sediment samples taken upstream from the facilities, the lagoon water samples still contained three to five times higher *tet* ARGs.

CTX-M-type extended-spectrum ß-lactamases present in *Escherichia coli* from the feces of cattle in Ohio, United States. T.E. Wittum, D.F. Mollenkopf, J.B. Daniels, A.E. Parkinson, J.L. Mathews, P.R. Fry, M.J. Abley and W.A. Gebreyes. *Foodborne Pathogens and Disease.* 2010.

Summary: CTX-M extended-spectrum ß-lactamases are enzymes produced by bacteria that allow them to inhibit the antimicrobial effects of penicillins and cephalosporin drugs. This is of public health concern as expanded-spectrum cephalosporins are the treatment of choice for infections such as salmonellosis in children. In this study, samples from bovine fecal samples were screened for CTX-M producing strains of *E. coli*. Results show that 6 percent (3/50) of fecal samples collected harbored CTX-M genes. It has been hypothesized that ceftiofur use in livestock populations may provide the necessary selection pressure for such resistance genes as CTX-M to disseminate. Results from this study support the hypothesis as *E. coli* harboring CTX-M was isolated from a calf that was recently treated with ceftiofur therapy.

Producer attitudes and practices related to antimicrobial use in beef cattle in Tennessee. A.L. Green, L.R. Carpenter, DE. Edmisson, C.D. Lane, M.G. Welborn, F.M. Hopkins, D.A. Bemis and J.R. Dunn. *JAVMA.* 237 (11): 1292-1298.

Summary: This study involved a sampling by mail of 3,000 beef producers across the state of Tennessee, with 1,042 returned. The results showed 56.3 percent of beef cattle operations reported having used antimicrobials within the past year. Producers with multiple operation types (MOT) were more likely than producers with only cow-calf operations to have administered antibiotics either by mouth or by injection within the past year. The MOT producers were also slightly more likely to agree that antibiotics are not working as effectively than in the past. Herd size also had a positive correlation with antimicrobial use. The authors suggest that beef quality assurance programs should be employed and an effort to reach producers not involved in these programs should be explored. Additionally, efforts to reduce antibiotic use among producers may be found through educational efforts focused on practical, cost and labor effective alternatives such as a focus on bio-security, vaccination and low-stress handling of livestock and decreased stocking density to minimize disease transmission.

Effects of restricted antimicrobial exposure on antimicrobial resistance in fecal Escherichia coli from feedlot cattle. P.S. Morley, D.A. Dargatz, D.R. Hyatt, G.A. Dewell, J.G. Patterson, B.A. Burgess and T.E. Wittum. *Foodborne Pathogens and Disease,* 2011. 8-1: 1-12.

Summary: A study on two types of feedlot cattle. Conventional was raised and fed a diet with antibiotics while natural was raised and fed a diet of no antibiotics and were only exposed to antibiotics if disease occurred. The authors conclude that there was no difference in resistance to collected *E. coli* from either group in the study and suggest that conventional feedlot production methods do not predictably increase the prevalence of antimicrobial resistance in *E. coli* when compared to animals raised with restricted exposure to antibiotics.

The study design assigned pens to the natural cattle that may have previously housed cattle fed a conventional diet and no documentation is made on if pens were cleaned before study groups were placed. Cattle from the conventional group were also sometimes clustered in pens adjacent to the natural group to facilitate feeding. Also, after antibiotics were administered to sick cattle they were returned to their previous pens, which may have exposed other cattle in the group to the treated animal's microbial flora. While antibiotic susceptibility testing showed little to no difference (higher resistance to tetracycline and chloramphenicol was observed in conventional

cattle) in resistance patterns of collected *E. coli*, the conventional cattle were fed Tylosin, a macrolide antibiotic and there were no macrolides in the susceptibility panel of testing. The authors do not address if the naturally raised cattle could have been exposed to bacteria from previous cattle fed antibiotics that were housed in the same pens.
Also of note is that this study was designed around "natural" raised and "conventional" raised cattle. These definitions are synonymous with the only differences being that "natural" products are minimally processed and do not contain artificial or synthetic ingredients or coloring additives; however, in this study they did attempt to keep the "natural" beef antibiotic free.

Dose imprecision and resistance: Free-choice medicated feeds in industrial food animal production in the United States. D.C. Love, M.F. Davis, A. Bassett, A. Gunther, and K.E. Nachman. *Environmental Health Perspectives*, 2011. 119(3):279-283.

Summary: Food animals in the US are often provided food that includes antibiotics and antiparasitic drugs on a "free choice" basis meaning the animals decide when to eat food and how much of it to consume. This practice is referred to as using free-choice medicated feeds (FCMF) and is shown to result in imprecision of drug intake leading to under and over-medication of animals. Imprecision in dosing of animals can lead to the development of antibiotic-resistant microorganisms or the presence of drug residues in food products. Various factors including labeling, veterinary oversight, feed characteristics, animal and herd behavior, behavior of workers, and drug pharmacokinetics may affect the dose ingested and received by the animal. Little oversight or control of FCMF exists in the US and no federal requirements exist for reporting use of antimicrobial drugs in animal production. This is despite the proposal of the Preservation of Antibiotics for Medical Treatment Act (PAMTA) introduced to Congress in 2009 and a statement from the US Food and Drug Administration (FDA) that "the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health." The authors conclude that use of FCMF poses an unnecessary risk to public health and that a more appropriate system of medicating animals should be used only when necessary to treat clinically diagnosed disease.

Food animals and antimicrobials: Impacts on human health. B.M. Marshall and S.B. Levy. *Clinical Microbiology Reviews*. 2011, 24(4): 718-733.

Summary: Reviews literature on the link between nontherapeutic antimicrobial (NTA) use in food-animal production, including aquaculture, and the emergence of antibiotic-resistant bacteria in humans and concludes that a wealth of evidence exists to support this link. Use of antibiotics is a powerful force in the selection of resistant bacteria and use anywhere can lead to resistance at point of use and in other areas. Identifies gaps in knowledge related to NTA use highlighting the lack of research regarding genetic infrastructure and spread between commensal and environmental bacteria.

Antibiotic resistance, gene transfer, and water quality patterns observed in waterways near CAFO farms and wastewater treatment facilities. B.M. West, P. Liggit, D.L. Clemans, and S.N.Francoeur. *Water, Air & Soil Pollution*. 2011. 217(1-4): 473-489.

Summary: Reports findings from a water quality assessment study that sampled up and downstream of waste water treatment plants (WWTP) and locations affected by confined animal feeding operations (CAFO) and reference locations unaffected by CAFOs. Chemical and biological water quality indicators were evaluated. Sites up and downstream of WWTPs met current chemical and biological water quality standards and were considered environmentally healthy. Fecal coliform density ranged from 70-2,300 CFU/100 ml in these locations. High, but similar, levels of drug-resistant fecal coliforms were found up and downstream of WWTPs. In contrast, sites near CAFOs had reduced water quality compliance and fecal coliform levels ranged from 700 CFU/100 ml to too numerous to count. CAFO affected sites had much higher levels of multi-drug resistant bacteria (42 percent) as compared with agricultural sampling sites not affected by CAFOs (17 percent). In laboratory experiment, antibiotic-resistant bacteria collected at all locations demonstrated the ability to transfer resistance genes. Concludes that surface waters may be an important source of human exposure to antibiotic-resistant bacteria and monitoring of antibiotic-resistance should become part of the standard monitoring of waterways.

In-feed antibiotic effects on the swine intestinal microbiome. T. Looft, T.A. Johnson. H.K. Allen, D.O. Bayles, D.P. Alt, R.D. Stedtfeld, W.J. Sul, T.M. Stedtfeld, B. Chai, J.R. Cole, S.A. Hashsham, J.M. Tiedje, T.B. Stanton. *Proceedings of the National Academy of Sciences*. 2012. 109(5): 1691-1696.

Summary: Supplementation of livestock feed with antibiotics may lead to changes in the commensal bacteria present in the gastrointestinal tract of animals receiving such supplemented feed, which in turn could lead to increases in antibiotic resistance genes and transfer to pathogens. This study examined the gut microbiota of piglets given feed supplemented with ASP250 (a mix containing chlortetracycline, sulfamethazine, and penicillin) and a group of piglets given the same feed without ASP250. A fecal sample was taken before piglets received any ASP250 and three more times over a 21days. By day 14, the microbial make up found in samples from the two groups of pigs were found to be different. A greater abundance of 6 resistance-gene types were found at day 14 in the medicated animals as compared to the non-medicated animals even though no difference in these gene types was seen at day 0. Authors conclude that dosing with antibiotic supplemented feed increases the abundance and diversity of antibiotic resistance genes, and promotes changes in the make-up of the microbiome.

Feather meal: A previously unrecognized route for reentry into the food supply of multiple pharmaceuticals and personal care products (PPCPs). D.C. Love, R.U. Halden, M.F. Davis, K.E. Nachman. *Environmental Science & Technology*, 2012. 46: 3795-3802.

Summary: Feather meal is created by rendering poultry feathers and included as an animal feed ingredient in addition to other uses. Authors examined commercially available feather meal products for the presence of pharmaceuticals and personal care products (PPCP). Researchers found that residues of 17 of 46 antimicrobials, representing 6 different drug classes, were detectable in 100% (12/12) of commercial feather meal samples tested. Most of the antimicrobials detected in these samples are from drug classes approved for use in industrial poultry production. PPCP were identified in 83 percent (10/12) of samples. PPCP identified included an antidepressant, an antihistamine, fungicide, analgesic, sex hormone, and stimulant. In order to show the importance of the presence of antimicrobials in commercial feather meal products, researchers performed other experiments that showed that when a susceptible strain of *Escherichia coli* was exposed to autoclaved feather meal, a process that approximates rendering, growth of the bacteria was inhibited. When a resistant strain of *E. coli* was grown with feather meal, growth of the bacteria was not inhibited. The results presented in this study indicate the presence of active antimicrobials and other products in commercial feather meal after rendering.

A review of antibiotic use in food animals: Perspective, policy, and potential. T.F. Landers, B. Cohen, T.E. Wittum, and E.L. Larson. *Public Health Reports*. 2012. 127(1): 4-22.

Summary: Reviews the published information on the use of antibiotics in food animals as well as policies related to their use, and summarizes the potential impact on human health. Although there is widespread use of antibiotics, it appears that a lack of reliable information to indicate the quantity and patterns of antibiotic use in food animals is available. Estimates for the proportion of antibiotics used in food animals range from 17.8 million to 31.9 million pounds annually with varying proportions estimated to be used sub-therapeutically. Although benefits of antibiotic use are often put forward and deserve consideration, most of the claims have not been substantiated and a body of literature exists that lends support to an association between antibiotic use in food animals and antibiotic resistance bacteria in humans. As few benefits have been realized and a large concern based on scientific research has grown, a large body of policies and recommendations has been put forward and are presented in detail. Based on the literature available, authors 1) recommend that the scientific community develop a plan to generate the scientific data that is missing to date; 2) urge the U.S. government and other funding agencies to place more of an emphasis on funding scientific work to address the use of antibiotics in food animal production; and, 3) confront and deal with obstacles to collecting data and conducting scientific research. The review concludes that it is imperative that the use of antibiotics in food animals be recognized as an important contributor to antibiotic resistant infections in humans and be addressed directly.

Antimicrobial drug resistance in *Escherichia coli* from humans and food animals, United States, 1950-2002. D.A. Tadesse, S. Zhao, E. Tong, S. Ayers, A. Singh, M.J. Bartholomew, P.F. McDermott. *Emerging Infectious Diseases*. 2012, 18(5): 741-749.

Summary: Explores and describes the emergence of antimicrobial resistance among 1,729 *Escherichia coli* isolates obtained from animals and humans (983) between 1950 and 2002. Overall, 934/1729 (54 percent) of animal isolates were resistant to at least one antimicrobial drug with resistance to older drugs including tetracycline (41 percent), sulfonamide (36 percent), streptomycin (34 percent), and ampicillin (24 percent) most common. Of isolates from humans, 65 percent were not resistant to any of the 15 antimicrobials tested as compared to 20 percent of animal isolates. However, the proportion of pan-susceptible isolates decreased over time from 74 percent in 1950-1959 to 19 percent in 2000-2002, while the proportion of multidrug-resistant isolates increased during the same period (7 to 64 percent). When resistance trends were examined over time, animal isolates demonstrated an increasing trend for resistance to 11/15 antimicrobial drugs. Isolates from humans showed an increasing trend for resistance to three of the same drug classes (ampicillin, streptomycin, and tetracyclines) for which animal isolates showed an increasing trend, but no additional classes of drugs. Authors conclude these findings provide information to support the development of resistance over time and that antimicrobial resistance in *E. coli* can be temporally linked with use of antimicrobials.

Selective pressure of antibiotic pollution on bacteria of importance to public health. A. Tello, B. Austin, T.C. Telfer. *Environmental Health Perspectives*. 2012, April 16 Epub.

Summary: Antibiotics used in agriculture are commonly released into the environment where many bacteria can survive and grow. The exposure of these bacteria to antibiotics at high enough concentrations is thought to produce a selective pressure that would select for antibiotic-resistant bacteria and inhibit growth of wild-type bacteria that is not resistant to the antibiotic. This study gathered information regarding concentrations of ciprofloxacin, erythromycin, and tetracycline in different environments from literature and examined the selective pressure that may be present on clinically important bacteria found in the respective environments at the concentrations identified and at concentrations considered to be action limits in environmental risk assessment. Antibiotics at the concentrations measured in river sediments are estimated to inhibit growth of wild-type bacteria in up to 60 percent of bacterial genera. High proportions of bacterial genera were also found to be inhibited at concentrations of antibiotics found in swine feces lagoons (92 percent), liquid manure (100 percent) and farmed soil (30 percent). When authors compared measured concentrations of ciprofloxacin and tetracycline in environments with levels thought to inhibit 100 percent growth of wild-type populations among bacterial genera, wild-type populations of several species would be completely inhibited. At concentrations of ciprofloxacin and erythromycin used as soil action limits in environmental risk assessment, wild-type populations were inhibited for 76 and 25 percent of bacterial genera. Authors conclude the concentrations of antibiotics may be sufficient to apply a selective pressure to bacterial populations found in the same environments, many of which are clinically important. Further, environments including river sediments, liquid manure, and farmed soil may be important areas of concern based on reported concentrations of antibiotics. Moving forward, antibiotic resistance should be considered as part of environmental risk assessments and efforts to reduce antibiotics in the environment should be strongly considered to curb the increase of antibiotic resistance.

Antimicrobial susceptibilities and resistant genes in *Campylobacter* strains isolated from poultry and pigs in Australia. A. Serwaah Obeng, H. Rickard, M. Sexton, Y. Pang, H. Peng, M. Barton. *Journal of Applied Microbiology*, 2012. 78(8):2698-705. [June 2 E-pub ahead of print]

Summary: Describes the presence of and antibiotic resistance profiles of *Campylobacter* species isolated from free range meat chickens, free range egg layers, and commercial meat chickens in Australia. Results concerning antimicrobial resistance genes found among *Campylobacter* isolated from pigs from the same area are also presented. Resistance to lincomycin, ampicillin, and tetracycline was observed in all three types of chickens. No differences in the presence of antibiotic resistance or the presence of resistance genes among the three types of chickens sampled were found. *Campylobacter* isolated from pigs demonstrated resistance to ampicillin, ciprofloxacin, clindamycin, erythromycin, streptomycin, and tetracycline. Although differences in resistance and resistance genes were present, authors report that isolates from poultry and pigs were of related clonal groups. Differences may be due to differences antimicrobial use among these animal types.

The shared antibiotic resistome of soil bacteria and human pathogens. K.J. Forsberg, A. Reyes, B. Wang, E.M. Selleck, M.O.A. Sommer, G. Dantas. *Science*. 2012, 337: 1107-1111.

Summary: Antibiotic-resistance genes identified among non-disease causing bacteria commonly found in soil display were identical to the antibiotic-resistance genes among human pathogens. The genes represent a variety of known mechanisms of resistance. The findings support evidence indicating the potential for exchange of antibiotic-resistance genes between non-pathogenic environmental bacteria, such as those in soil, and human pathogens, either directly or indirectly. This indication of the potential for exchange raises concerns about environmental use of antibiotics, including within livestock production, which may consequently contribute to selective pressure and increased presence of antibacterial resistance among harmless and disease causing bacteria.

Livestock density as risk factor for livestock-associated methicillin-resistant *Staphylococcus aureus*, the Netherlands. B.J. Feingold, E.K. Silbergeld, F.C. Curriero, B.A.G.L. van Cleef, M.E.O.C. Heck, J.A.J.W. Kluytmans. *Emerging Infectious Diseases*. 2012. E-pub.

Summary: Reports results from a study conducted to affirm previously reported individual-level risk factors and identify other factors for livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) as compared to other types of MRSA. The study examines 27 cases of LA-MRSA carriage (clonal complex 398) and 60 cases of non-LA-MRSA in the Netherlands. Based on spatial and statistical analyses, contact with pigs, contact with cows, and living in a rural area were important individual-level factors associated with increased odds of LA-MRSA. Additionally, increasing density of pigs, cows, or veal calves in the municipality of residence was also associated with increased odds of LA-MRSA. These results carry important policy implications for the Netherlands and other areas with high densities of livestock including the United States, but should be interpreted with caution as they are based on small numbers.

Multidrug-resistant coagulase-negative Staphylococci in food animals. K. Bhargava, Y. Zhang. *Journal of Applied Microbiology*. 2012. 113(5): 1027-1036.

Summary: Although coagulase-negative Staphylococci (CoNS) are not the most pathogenic species of staphylococci, CoNS are common commensal bacteria carried by animals and often carry genes conferring antimicrobial-resistance that are easily transferable to other, more pathogenic bacteria. Among 87 CoNS isolates resistant to oxacillin and obtained from a range of food animals, 79 percent were resistant to ampicillin, 92 percent to penicillin, 68 percent to tetracycline, 37 percent to erythromycin, 28 percent to clindamycin, and 15 percent to quinupristin-dalfopristin. Approximately 54 percent of isolates were resistant to at least three antimicrobial classes and were labeled multidrug resistant (MDR). MDR isolates were found among most animal types with 80 percent of isolates from chicken and turkey classified as MDR as well as 67 percent from duck, 62 percent from goats, 60 percent from sheep, 57 percent from pigs, and 37 percent from cattle. Prevalence information regarding the presence of specific antimicrobial resistance genes was also reported at varying levels. Researchers demonstrated transfer of the gene that confers resistance to tetracycline, between CoNS and a strain of *Enterococcus*. CoNS may function as a reservoir of antimicrobial resistance genes.

Correlation between upstream human activities and riverine antibiotic resistance genes. A. Pruden, M. Arabi, H.N. Storteboom. *Environmental Science and Technology*. 2012. E-publication.

Summary: Sediment samples collected at a range of sites encompassing pristine areas and those tainted by human activity within the South Platte River Basin were analyzed for the presence of antibiotic resistance genes (ARGs) to examine correlations between ARGS and upstream sources of ARGs in a watershed. Researchers examined the presence mobile genetic elements conferring resistance to sulfonamide and tetracycline antimicrobials. Information about the proximity of sampling sites to animal feeding operations, wastewater treatment plants, and fish hatchery and rearing units was determined for each sampling site. Increased presence of the gene for sulfonamide resistance was associated with upstream animal feeding operations and wastewater treatment plants. Prevalence of the tetracycline resistant gene was not associated with upstream sites. The findings indicate the contribution of animal feeding operations and wastewater treatment plants to the dissemination of ARGs into the environment through water ways. These findings suggest the importance of water to transport ARGs which may contribute to the disease burden of antibiotic-resistant infections in humans.

Urine from treated cattle drives selection for cephalosporin resistant Escherichia coli in soil. M. Subbiah, D.H. Shah, T.E. Besser, J.L. Ullman, D.R. Call. PLoS One. 2012. 7(11): e48919.

Summary: The study looked at giving the results of giving cattle ceftiofur, a commonly used cephalosporin antibiotic. They monitored the drug and its breakdown products in urine. Ceftiofur-resistant E. coli from the animals was found in the environment and the drug could remain in the soil for days to weeks, depending on the temperature. To demonstrate transmission, bedding was sprayed with a suspension of ceftiofur-resistant E. coli and allowed to dry. Then calves were introduced to the environment and by the second day, the calves were also shedding ceftiofur-resistant E. coli in their feces. These results show that when ceftiofur is administered to animals its breakdown products are excreted through urine and may persist in the soil or environment for a prolonged period allowing for selection of ceftiofur-resistant bacteria and exposure of the animals to these bacteria through their environment.

Extended-spectrum cephalosporin-resistant gram-negative organisms in livestock: An emerging problem for human health? S.N. Seiffert , M. Hilty, V. Perreten, A. Endimiani. 2013. *Drug Resistance Updates*. Epub.

Summary: There is an increase in the prevalence of gram-negative organisms that produce extended-spectrum-β-lactamases (ESBL), which confers resistance to extended-spectrum cephalosporins (main antibiotics to treat infections caused by gram-negative bacteria). The contribution of use of antibiotics in food-animal production as a major contributing factor to the increase in extended-spectrum cephalosporin-resistant gram-negative bacteria found among food animals and humans is modeled. Detailed information regarding the prevalence of resistant *E. coli*, *Salmonella*, and *Acinetobacter* among food-animals and humans as well as antibiotic use is presented by country. A summary of the evidence linking resistant bacteria found among food animals to that found in humans is provided and transmission routes between food-animals and humans are reviewed. Strategies for controlling the increase and spread of resistant bacteria include: 1) banning the use of antimicrobials as growth promoters in food-animal production; 2) require veterinarian prescription and oversight for administration of antibiotics to food-animals; and, 3) drastically limit the use of antibiotics that critically important for human health.

Stored swine manure and swine faeces as reservoirs of antibiotic resistance genes. T.R. Whitehead and M.A. Cotta. *Letters in Applied Microbiology*. 56: 264-267.

Summary: Presents a short report of a small study of the presence of antibiotic resistance (AR) genes identified in bacteria from one swine fecal sample and two swine manure samples taken from a swine production facility in Illinois. A range of bacteria including *Enterococcus, Lactobacillus, Streptococcus,* and *Clostridium* were isolated. These bacteria were found to harbor a variety of antibiotic-resistance genes which have the ability to be exchanged between different micro-organisms. Authors conclude that although the present study was small, it indicates that stored swine manure could serve as a reservoir for AR genes. Further research is needed to determine the levels of AR genes present in stored manure and the consequences of practices such as use of antibiotics in feed on the levels of AR genes in stored waste.

SWINE

Ways in which swine production affects air, water and farm workers.

An outbreak of multidrug-resistant, quinolone-resistant *Salmonella enterica* serotype typhimurium DT104. K. Molbak, D.L. Baggesen, F.M. Aarestrup, J.M. Ebbesen, J. Engberg, K. Frydendahl, P. Gerner-Smidt, A.M. Petersen, and H.C. Wegener. *New England Journal of Medicine,* 1999. 341: 1420-1425.

Summary: Reviews a 1998 *Salmonella enterica* serotype typhimurium DT104 outbreak in Denmark. The outbreak had 25 confirmed cases, with 11 patients hospitalized and two deaths. Previous cases were resistant to five antibiotics; however, cases in this outbreak also were resistant to nalidixic acid and had reduced susceptibility to fluoroquinolones. Analysis traced the infection to a swine herd delivered to a slaughterhouse and the resulting retail pork was found to be the common food source.

Concentrated swine-feeding operations and public health: A review of occupational and community health effects. D. Cole, L. Todd, and S. Wing. *Environmental Health Perspectives,* 2000. 108: 685-699.

Summary: Reviews the effects of industrial farms on community health. States that there are many potential routes of community exposure to industrial farming hazards and that people residing near swine farms may be exposed to these agents through pathways such as airborne contaminants produced by building ventilation fans, soil transport of microbes from land-applied wastes and leaking lagoons that contaminate groundwater. States that more research is needed to determine the far-reaching effects of industrial farms on community health.

Occurrence and diversity of tetracycline-resistance genes in lagoons and groundwater underlying two swine production facilities. J.C. Chee-Sanford, R.I. Aminov, I.J. Krapac, N. Garrigues-Jeanjean, and R.I. Mackie. *Applied and Environmental Microbiology,* 2001. 67(4): 1494-1502.

Summary: States that 25 percent to 75 percent of antimicrobials administered to food animals are poorly absorbed in the gut and are excreted in feces. These unaltered substances are then applied to land by spreading of manure. Finds that a broad range of tetracycline-resistance genes occurred in two swine-waste lagoons and that upon release into the environment these genes can potentially mobilize and persist. Data suggest that the presence of the resistance genes is due to seepage and movement of groundwater underlying the lagoons and that it may be substantial, as resistance genes were found in a well 250 meters downstream of the lagoon sampled.

Effects of administration of antimicrobials in feed on growth rate and feed efficiency of pigs in multisite production systems. S.S. Dritz, M.D. Tokach, R.D. Goodband, and J.L. Nelssen. JAVMA 2002. 220:11 1690-95.

Summary: A study consisting of 10 trials involving a total of 24,099 finishing and nursery pigs. Trials involving pigs feed antimicrobials were selected based on commonly used production system regimens. A control group was also included that was not administered antibiotics unless necessary due to disease and then at a therapeutic dose. When all data were compiled, only nursery pigs showed an increase in average daily gain when given antibiotics in feed. Feed efficiency was lower in all nursery groups given antibiotics in feed compared to the control and feed efficiency was not significantly different in either finishing or nursery groups between control and treated animals. It was concluded that giving antibiotics in feed to finishing pigs had no effect on average daily gain. The authors note that this study differs from other similar studies, as their noted average daily gains were less than previous reports. Listed explanations include: previous data being biased toward publication of data with positive results; the excellent performance of the control group in the present study; and the fact that current hygienic conditions used exceeded that in previous trials allowing for the control group to perform at a higher level. The authors state that results of the present study indicate that the use of multisite pig production methods greatly reduce pathogen burden on pigs and in turn allows for reduction in use of non-therapeutic antimicrobials.

Productivity and economic effects of antibiotics used for growth promotion in U.S. pork production. G. Y. Miller, K. A. Algozin, P. E. McNamara, and E. J. Bush. *Journal of Agricultural and Applied Economics*, 2003. 35(3): 469-482.

Summary: Studies the use of growth promoting antibiotics (GPA) in pork production. Finds that when GPA are removed from production operations that use less than four different rations (feed) there is a net decrease in return at sale of nine percent. However, when farms use greater than four different rations there is an increase in feed conversion without the use of antibiotics. Furthermore, when farms used greater than four different rations and applied GPA, feed conversion decreased. The authors state "our results imply that antibiotics used for growth promotion are of value mainly when four or fewer different rations are used in finishing."

Antimicrobial resistance in commensal flora of pig farmers. H. Aubrey-Damon, K. Grenet, P. Sall-Ndiaye, D. Che, E. Cordeiro, M.E. Bougnoux, E. Rigaud, Y. Le Strat, V. Lemanissier, L. Armand-Lefèvre, D. Delzescaux, J.C. Desenclos, M. Liénard, and A. Andremont. *Emerging Infectious Diseases,* 2004. 10(5): 873-879.

Summary: Compares the carriage rates of antibiotic-resistant bacteria isolated from pig farmers and non-farmers matched for sex, age and county of residence in France. Finds that farmers carry a higher percentage of resistant commensal bacteria than non-farmers. States that the rate of VRE colonization did not differ between farmers and non-farmers and that this finding suggests that the 1997 ban of avoparcin was effective.

Airborne multidrug-resistant bacteria isolated from a concentrated swine feeding operation. A. Chapin, A. Rule, K. Gibson, T. Buckley, and K. Schwab. *Environmental Health Perspectives*, 2005. 113: 137–142.

Summary: Reports the results of studies air samples taken within confined hog operations for antibiotic-resistant bacteria. Ninety-eight percent of bacteria sampled 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. Notes that "these data are especially relevant to the health of swine CAFO [concentrated animal feeding operations] workers, their direct contacts in the community, and possibly nearby neighbors of swine CAFOs."

Detection and occurrence of antimicrobially resistant *E. coli* in groundwater on or near swine farms in eastern North Carolina. M.E. Anderson and M.D. Sobsey. *Water Science and Technology*, 2006. 54(3): 211-218.

Summary: Compares the extent of groundwater contamination from antibiotic-resistant *E. coli* from industrial swine farms and reference sites. Sixty-eight percent of the *E. coli* from the swine farm sites were resistant to at least one antibiotic, while only one isolate from each of the reference sites showed resistance. Concludes that groundwater on or near swine farms may pose as an environmental pool for antibiotic-resistant *E. coli* and resistance genes.

The effect of subtherapeutic chlortetracycline on antimicrobial resistance in the fecal flora of swine. J.A. Funk, J.T. Lejeune, T.E. Wittum, and P.J. Rajala-Schultz. *Microbial Drug Resistance*, 2006. 12(3): 210-218.

Summary: Studies the occurrence of antimicrobial-resistant *Salmonella* due to the subtherapeutic use of chlortetracycline in the diets of swine. Concludes that "there was a positive association between inclusion of subtherapeutic chlortetracycline in the diet and resistance to multiple antimicrobials."

Isolation of antibiotic-resistant bacteria from the air plume downwind of a swine confined or concentrated animal feeding operation. S.G. Gibbs, C.F. Green, P.M. Tarwater, L.C. Mota, K.D. Mena, and P.V. Scarpino. *Environmental Health Perspectives*, 2006. 114: 1032–1037.

Summary: Studies air samples from upwind, downwind and inside of a confined hog operation. Bacterial samples were tested for antibiotic resistance and *Staphylococcus aureus was* the dominant species recovered. Samples taken within the barn displayed the highest rate of resistance; samples taken up to 150 meters downwind of the barn showed a higher level of resistance than samples taken upwind. Multiple antibiotic-resistant organisms were also found within and around the barn. Concludes that this increase in antimicrobial resistance could have a negative on the health of people who live around these facilities.

Community-acquired MRSA and pig-farming. X.W. Huijsdens, B.J. van Dijke, E. Spalburg, M.G. van Santen-Verheuvel, M.E. Heck, G.N. Pluister, A. Voss, W.J.B. Wannet, and A.J. de Neeling. *Annals of Clinical Microbiology and Antimicrobials*, 2006. 5(26).

Summary: 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.

Risk factors for antimicrobial resistance among fecal *Escherichia coli* from residents on forty-three swine farms. T.H. Akwar, C. Poppe, J. Wilson, R.J. Reid-Smith, M. Dyck, J. Waddington, D. Shang, N. Dassie, and S.A. McEwen. *Microbial Drug Resistance*, 2007. 13(1): 69-76.

Summary: Focuses on residents and workers of hog operations that fed antibiotics and those that did not. *E. coli* was obtained from 115 residents and tested for resistance; 25.8 percent of *E. coli* sampled was resistant to at least one antibiotic. Prevalence of resistant bacteria was higher among workers or residents of the farms where antibiotics were fed to hogs. Results indicate that farmers have an increased occupational hazard of exposure to antibiotic-resistant bacteria when antibiotics are fed to animals.

Monitoring and source tracking of tetracycline resistance genes in lagoons and groundwater adjacent to swine-production facilities over a 3-year period. S. Koike, I.G. Krapac, H.D. Oliver, A.C.

Yannarell, J.C. Chee-Sanford, R.I. Aminov, and R.I. Mackie. *Applied and Environmental Microbiology,* 2007. 73(15): 4813-4823.

Summary: Studies the dissemination of tetracycline-resistance genes from lagoons into the surrounding environment. DNA was extracted and analyzed by real-time quantitative PCR showing a similarity of 99.8 percent for a selected resistance gene between collected groundwater sample DNA and that of the lagoons. States that this is clear evidence that animal waste seeping from lagoons can affect the environment by spreading resistance genes though groundwater contamination.

Antibiotic-resistant *Enterococci* and fecal indicators in surface water and groundwater impacted by a concentrated swine feeding operation. A.R. Sapkota, F.R. Curriero, K.E. Gibson, and K.J. Schwab. *Environmental Health Perspectives*, 2007. 115(7): 104-1045.

Summary: Reviews the risks associated with exposure to manure-contaminated water sources by industrial farms. The authors could not obtain specific data on levels of antibiotics in swine feed because it was premixed and delivered by a contracted integrator, which had deemed antibiotic-usage data proprietary information. Reports that elevated levels of fecal indicators and antibiotic-resistant *Enterococci* were detected in water sources situated down-gradient from a swine facility compared with up-gradient surface water and groundwater. Concludes that "the presence of resistant bacteria in both drinking water and surface water sources contaminated by swine farms could contribute to the spread and persistence of both resistant bacteria and antibiotic resistance determinants in humans and the environment."

Antibiotic resistant bacterial profiles of anaerobic swine-lagoon effluent. J.P. Brooks and M.R. McLaughlin. *Journal of Environmental Quality,* 2009. 38: 2431-2437.

Summary: Focuses on three types of swine farms—farrowing, nursery and finisher. Antibiotic-resistant bacteria were screened for and isolated from all three types of farm lagoons. States that selective pressures appear to have an effect on the amount of resistant isolates recovered from swine-waste lagoons. Nursery lagoons appeared to be most contaminated, with antibiotic-resistant bacteria most likely due to the elevated use of antibiotics in these operations. Finisher farm lagoons contained the lowest concentration, signaling a lower use of antimicrobials in this environment.

Prevalence, numbers and characteristics of *Salmonella* spp. on Irish retail pork. D.M. Prendergast, S.J. Duggan, U. Gonzales-Barron, S. Fanning, F. Butler, M. Cormican, and G. Duffy. *International Journal of Food Microbiology,* 2009. 131: 233-239.

Summary: Explores results of a survey of *Salmonella* in samples of pork from butcher shops and retail markets in Ireland and reports that it was found to contaminate 2.6 percent of samples assayed. *S. Typhimurium* was the dominant serotype found, at a rate of 85 percent; it is also one of the most frequently isolated serotypes from humans in the Irish population. Evidence of cross-contamination was found between samples, pointing to the need for good hygiene practices at the retail level.

Occurrence and persistence of erythromycin resistance genes (*erm*) and tetracycline resistance genes (*tet*) in waste treatment systems on swine farms. J. Chen, F. C. Michel Jr. S. Sreevatsan, M. Morrison, and Z. Yu. *Microbial Ecology,* 2010.

Summary: This study focuses on how to control antibiotic resistance (AR) that is generated by use of antibiotics in confined animal feeding operations (CAFOs). The authors suggest there are two ways to control AR: reduce the use of antimicrobials on farms or find an effective way to minimize AR dissemination off farms by destroying or containing AR on farms. This study focuses on the latter of those two ways and looks to gain perspective on how well swine farms are containing antibiotic resistance by treating animal manure that is produced in CAFOs before it is being disseminated into the environment. Three swine farms were sampled with different types of waste treatment systems. Upon testing in various stages of waste clean up the authors find that "AR arising from swine-feeding operations can survive typical swine waste treatment processes" and call for treatments that are more functional in destroying AR on farms.

Abundance and diversity of tetracycline resistance genes in soils adjacent to representative swine feedlots in China. N. Wu, M Qiao, B. Zhang, W-D Cheng, and Y-G. Zhu. *Environmental Science and Technology,* 2010.

Summary: Studies the prevalence of tetracycline genes in soil samples from farmlands in the vicinity of nine swine farms located in three cities in China. Finds that 15 tetracycline-resistance genes were commonly detected in soil samples. A strong correlation was found between the concentrations of tetracycline residues, bacterial load and organic matter. Suggests that soils containing bacteria near swine farms may play an important role in the spread of antibiotic resistance and are a large environmental reservoir.

Changes in the use of antimicrobials and the effects on productivity of swine farms in Denmark. F.M. Aarestrup, V.E. Jensen, H-Dorthe Emborg, E. Jacobsen, and H.C. Wegener. *American Journal of Veterinary Research,* 2010. 71:7 726-33.

Summary: Evaluates the changes in antimicrobial use and swine productivity in Denmark between the years 1992 - 2008. In an effort to control the use of antimicrobials in food animal production, Denmark placed a ban on the use of growth promoting antibiotics in January of 2000. In the previous years leading up to the ban, other laws were passed limiting the veterinary profits that could be made on the prescription sale of antibiotics and also included treatment advice for veterinarians to guide the use of antibiotics. The study found there was a greater than 50 percent decrease in the use of antimicrobials per kg of pig produced during the time period from 1992 - 2008 which was associated with the policy to discontinue the use of growth promoting antibiotics. During this time the mortality rate was steady and production increased suggesting that this policy did not have a negative impact on swine production in Denmark.

Ceftiofur use in finishing swine barns and the recovery of fecal *Escherichia coli* or *Salmonella* spp. resistant to ceftriaxone. E.A. Lutz, M.J. McCarty, D.F. Mollenkopf, J.A. Funk, W.A.Gebreyes, and T.E. Wittum. *Foodborne Pathogens and Disease.* 2011. 8(11): 1229-1234.

Summary: Ceftiofur is the only third-generation cephalosporin labeled for veterinary use. It can be used to treat infections from Gram-negative bacteria and is used widely in the swine industry. The drug of choice to treat human infections from Gram-negative bacteria is another third-generation cephalosporin, ceftriaxone. This study examines the association between antibiotic-resistance in *Salmonella* spp. and *Escherichia coli* swine and ceftiofur use in swine operations in North Carolina. Barns were classified based on ceftiofur use rates as rare, moderate, or common with 579, 648, and 672 fecal samples taken from each category respectively. *E. coli* resistant to ceftriaxone was recovered from 45 percent of samples from rare use barns, 73 percent from moderate use barns, and 68 percent from common use barns. *Salmonella* spp. with resistance to ceftriaxone were found in 4.1 percent of samples from rare use barns, 0.15 percent of samples from moderate use barns, and 6 percent of samples from common use barns. Authors suggest that barns with increased ceftiofur use have greater proportions of *E. coli* and *Salmonella* spp. that are resistance to ceftriaxone.

Detection of the staphylococcal multiresistance gene *cfr* in *Proteus vulgaris* of food animal origin. Y. Wang, Y. Wang, C. Wu, S. Schwarz, Z. Shen, W. Zhang, Q. Zhang, and J. Shen. *Journal of Antimicrobial Chemotherapy*. 2011. 66: 2521-2526.

Summary: Details the presence of a plasmid-borne resistance gene commonly found in gram-positive bacteria in the chromosomal DNA of a gram-negative bacterium taken from a pig. The *cfr* gene has the ability to mediate transfer of resistance to linezolid, an antibiotic used in clinical practice to treat human infections caused by gram-positive bacteria resistant to other antibiotics. In this case *cfr* was found in a *Proteus vulgaris* isolate from the nares of a pig raised on a conventional pig operation in China. This finding supports the claim that selective pressure from the use of antibiotics in pig production may allow for the maintenance and transfer of antibiotic resistance among bacteria.

Prevalence and antimicrobial resistance profile of *Campylobacter* spp. isolated from conventional and antimicrobial-free swine production systems from different US regions. D.A. Tadesse, P.B. Bahnson, J.A. Funk, S. Thakur, W.E. Morgan Morrow, T. Wittum, F. DeGraves, P. Rajala-Schultz, and W.A. Gebreyes. *Foodborne Pathogens and Disease*. 2011. 8(3): 367-74.

Summary: Investigates the prevalence and antimicrobial resistance patterns of *Campylobacter* among pigs raised in a conventional environment and in antibiotic-free (ABF) environments at various stages of processing from pre-evisceration to post-chill through the collection of fecal and carcass swab samples. Approximately 95 percent (1034/1087) of isolates available for speciation were found to be *C. coli*, and the remainder was not *C. coli* or *C. jejuni*. 58.9 percent of conventional pigs (252/428) and 53.8 percent (220/411) ABF pigs were positive for *Campylobacter*. Prevalence of *Campylobacter* varied at different stages of production with the chill stage demonstrating the highest prevalence for both types of operations in both regions examined. The most common resistance pattern for *Campylobacter* isolated from ABF operations was resistance to tetracycline only (25.2 percent), erythromycin-tetracycline (10.3 percent), and erythromycin-nalidixic acid-tetracycline (10.3 percent). From conventional operations the dominant resistance patterns were erythromycin-tetracycline (33.4 percent), tetracycline (16 percent) and erythromycin (12.6 percent). Conventional and ABF production systems demonstrated 1.2 and 3.7 percent ciprofloxacin resistance. Of all isolates 2.9 percent (37/1257) were resistant to erythromycin and ciprofloxacin, the drugs of choice for treating human *Campylobacter* infection.

A longitudinal study on persistence of antimicrobial resistant *Campylobacter* in distinct swine production systems at farm, slaughter, and environment. M.P. Quintana-Hayashi, S. Thakur. *Applied Environmental Microbiology*. 2012. 78(8):2698-705.

Summary: Reports on the prevalence and antibiotic resistance of *Campylobacter* found in antibiotic-free and conventional swine operations at the farm and at slaughter facilities. The prevalence of *Campylobacter* isolated from swine raised on antibiotic-free and conventional operations was similar. *Campylobacter* from conventionally raised swine had a greater prevalence of resistance to ciprofloxacin (17 vs. 1 percent), tetracycline (88 vs. 48 percent), and naladixic acid (1 vs. 17 percent) as compared to antibiotic-free swine. *Campylobacter* from antibiotic-free swine had greater prevalence of resistance to clindamycin (13 vs. 4 percent), and environmental samples from antibiotic-free operations had greater prevalence of resistance to azithromycin (34 vs. 15 percent), erythromycin (34 vs. 15 percent), and clindamycin (20 vs. 3 percent). Similar results were observed at slaughter among samples from swine carcasses and the environment. Associations were seen between types of antibiotics used at conventional operations and resistance to the same antimicrobial class isolated from these operations. Antibiotic resistant *Campylobacter* was found among both antibiotic-free and conventionally raised swine during production and slaughter, but there were differences in the antibiotic resistance profiles between the two systems.

Phylogenetic analysis reveals common antimicrobial resistant *Campylobacter coli* population in antimicrobial-free (ABF) and commercial swine systems. M.P. Quintana-Hayashi, S. Thankur. *PLoS One.* 2012, 7(9): 1-6.

Summary: Examines the genetic diversity and persistence of *Campylobacter coli* among swine raised in a conventional setting and those raised in an antibiotic-free setting. Samples were taken from swine on the farm and at slaughter as well as from the environment on the farms and slaughterhouses. About two thirds of *C. coli* isolates were from one distinct group. Antimicrobial resistance was observed among samples from both production systems indicating a shared common ancestry, with some variability in the predominate resistance patterns. Authors conclude that the presence of antimicrobial-resistant *C. coli* in the absence of selective pressure on antibiotic-free operations may be explained by common ancestry of these isolates to those on conventional operations and the persistence of *C. coli* in the farm and slaughter environments.

Isolation and characterization of Methicillin-resistant *Staphylococcus aureus* from pork farms and visiting veterinary students. T.S. Frana, A.R. Beahm, B.M. Hanson, J.M. Kinyon, L.L. Layman, L.A. Karriker, A. Ramirez, T.C. Smith. *PLoS One.* 2013. 8(1): e53738.

Summary: Discusses the prevalence and characteristics of methicillin-resistant *Staphylococcus aureus* (MRSA) among pigs and in the environment on pork farms in the Midwestern United States as well as the transmission dynamics of MRSA isolated from these farms. MRSA was detected among pigs and in the environment. Twenty-nine veterinary students visiting the sampled farms provided 604 nasal samples at multiple points before and after visiting pork farms. Among these individuals, there were 27 visits made to MRSA-positive farms and MRSA was detected in the nares of 5 students with at least one visit to a MRSA-positive farm immediately following the visit. MRSA was not detected in the nares of these students more than 24 hours after the visit, potentially indicating short-term contamination of the nasal passage as opposed to colonization. MRSA isolates identified in pigs, the environment, and humans belonged mainly to sequence types (ST) ST398, ST5, ST72 with a high level of concordance between the samples from pigs, the environment, and humans at the same farms. MRSA in this study had high levels of resistance to tetracyclines (chlortetracycline, oxytetracycline), neomycin, and spectinomycin with some differences in resistance profiles observed between STs. Following short-term exposure to MRSA-positive pork farms, MRSA may be easily shared between pigs and humans but may not become an established colonizer of humans.

POULTRY

The effects of poultry production on farm workers, public health and the spread of antibiotic-resistant bacteria.

Direct transmission of *Escherichia coli* from poultry to humans. A.A. Ojenyiyi. *Epidemiology and Infection*, 1989. 103(3): 513-522.

Summary: Compares the resistance traits of *E.coli* collected from free-range poultry with those from poultry in a large-scale commercial facility. Reports that resistance to the antibiotics tested occurred only in those samples collected from birds in a commercial setting. Attendants from the commercial facilities also were found to contain resistant bacteria while samples from villagers in the community were negative. The authors also demonstrated that attendants contract bacteria from birds in their care by conducting a study where they infected birds with a known type of resistant *E. coli* and screened the attendants for the same bacteria.

Quinolone resistance in *Campylobacter* isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. H.P. Endtz, G.J. Ruijs, B. van Klingeren, W.H. Jansen, T. van der Reyden, and R.P. Mouton. *The Journal of Antimicrobial Chemotherapy*, 1991. 27(2): 199-208.

Summary: Reports the results of tests for quinolone resistance in 883 strains of *Campylobacter* bacteria isolated between 1982 and 1989 from human stool and poultry products. *Campylobacter* isolated from poultry increased in resistance from 0 percent to 14 percent in that time, while resistance in human isolates rose from 0 percent to 11 percent. Results suggest that the increase is mainly due to use of enrofloxacin, a fluoroquinolone, in poultry.

High-frequency recovery of quinupristin-dalfopristin-resistant *Enterococcus faecium* isolates from the poultry-production environment. J.R. Hayes, A.C. McIntosh, S. Qaiumi, J.A. Johnson, L.L. English, L.E. Carr, D.D. Wagner, and S.W. Joseph. *Journal of Clinical Microbiology*, 2001. 39(6): 2298-2299.

Summary: Studies the extent of resistance to quinupristin-dalfopristin, a drug reserved for human use to treat vancomycin-resistant enterococci, in *Enterococcus faecium*. Finds that resistance to this antimicrobial ranged between 51 percent and 78 percent in isolates screened from the food-production environment.

Antibiotic resistance of faecal *Escherichia coli* in poultry, poultry farmers and poultry slaughterers. A.E. van den Bogaard, N. London, C. Driessen, and E.E. Stobberingh. *Journal of Antimicrobial Chemotherapy*, 2001. 47:763-771.

Summary: Reports a survey of *E. coli* in poultry and workers who were in close contact with animals. Finds that the highest resistance rates were in turkeys, closely followed by broilers. Isolates collected from the laying-hen population were much lower, possibly because of the infrequent use of antibiotics in these animals. In the human population the same results followed, with turkey workers' isolates showing greater resistance than those from broilers or laying-hens. Results also strongly suggest the transmission of resistant clones and resistance plasmids of *E. coli* from broilers and turkeys to humans.

The dioxin crisis as experiment to determine poultry-related *Campylobacter enteritis*. A. Vellinga and F. Van Loock. *Emerging Infectious Diseases*, 2002. 8(1): 19-22.

Summary: Poultry was withdrawn in Belgium in June 1999 after a contaminant was found in feed. According to a model designed from the sentinel surveillance system, *Campylobacter* infections decreased by 40 percent during that month—from 153 cases per week to 94 cases. States that by using the ban as an epidemiologic tool, the rate of *Campylobacter* infections attributable to poultry was determined to be greater than 40 percent.

The effect of withdrawing growth promoting antibiotics from broiler chickens: A long-term commercial industry study. H.M. Engster, D. Marvil, and B. Stewart-Brown. *The Journal of Applied Poultry Research,* 2002. 431-436.

Summary: A comprehensive study where removal of growth promoting antibiotics (GPA) from broiler chickens was compared with those still receiving GPA. Average reduction of livability was only 0.2 percent on the Delmarva Peninsula (DMV) and 0.14 percent in North Carolina (NC). However, fluctuations were noted in livability from a reduction of 0.5 percent to a positive impact on livability of 0.3 percent. The average reduction in body weight was 0.03 lb on DMV and 0.04 lb in NC but this decline did not start until after the first year of the trial. Feed conversion (weight of food/body weight gain) was not adversely affected in the study for either location. Removal of GPA also resulted in no reports of field outbreaks of disease and total farm condemnations were not affected.

Fluoroquinolone-resistant *Campylobacter* isolates from conventional and antibiotic-free chicken products. L.B. Price, E. Johnson, R. Vailes, and E. Silbergeld. *Environmental Health Perspectives,* 2005. 113: 557-560.

Summary: Concludes that there is no difference in *Campylobacter* contamination between conventionally raised chickens and poultry raised antibiotic-free; however, conventionally raised poultry is more likely to be resistant to antibiotics than chickens raised antibiotic-free. The findings also suggest that fluoroquinolone-resistant isolates of *Campylobacter* may persist after the usage of fluoroquinolones in poultry production has ceased.

Similarity between human and chicken *Escherichia coli* isolates in relation to ciprofloxacin resistance status. J.R. Johnson, M.A. Kuskowski, M. Menard, A. Gajewski, M. Xercavins, and J. Garau. *The Journal of Infectious Diseases,* 2006. 194(1): 71-78.

Summary: Studies the similarities of *E. coli* isolates collected from humans and chickens that were resistant to ciprofloxacin. Finds that 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 though contaminated meats.

Use of streptogramin growth promoters in poultry and isolation of streptogramin-resistant *Enterococcus faecium* from humans. A.L. Kieke, M.A. Borchardt, B.A. Kieke, S.K. Spencer, M.F. Vandermause, K.E. Smith, S.L. Jawahir, and E.A. Belongia. *The Journal of Infectious Diseases,* 2006. 194(9): 1200-1208.

Summary: Examines virginiamycin use in poultry and its effect on cross-resistance to quinupristin-dalfopristin, a drug also in the streptogramin category that is intended for treating vancomycin-resistant *Enterococcus faecium* infections in humans. The study enrolled patients from hospitals and vegetarians and compared the samples from humans with samples collected from retail poultry meats. Reports that "poultry exposure is associated with a quinupristin-dalfopristin resistance gene and inducible quinupristin-dalfopristin resistance in human fecal *E. faecium.* The continued use of virginiamycin may increase the potential for streptogramin-resistant *E. faecium* infection in humans."

Subtherapeutic tylosin phosphate in broiler feed affects *Campylobacter* on carcasses during processing. M.E. Berrang, S.R. Ladely, R.J. Meinersmann, and P.J. Fedorka-Cray. *Poultry Science*, 2007. 86:1229-1233.

Summary: Studies cross-resistance of tylosin and erythromycin (both macrolide drugs). Erythromycin is often the drug of choice for treating campylobacteriosis, and tylosin is approved at subtherapeutic levels for use in broiler feed for growth promotion. Seventy chicks were divided into two groups, half raised on tylosin, half without. Carcasses of broilers fed tylosin had lower numbers of *Campylobacter*, but all the *Campylobacter* found were resistant to erythromycin. No *Campylobacter* isolated from the control carcasses were resistant. Concludes that application of tylosin phosphate in feed results in lower numbers of *Campylobacter*, but those that remain are resistant to erythromycin.

Growth promoting antibiotics in food animal production: An economic analysis. J.P. Graham, J.J. Boland, and E. Silbergeld. *Public Health Reports*, 2007. 122:79-87.

Summary: Examines the economic effect of removing antibiotics used for growth promotion in broiler chickens using data published by Perdue. Positive production changes were associated with use, but were insufficient to offset the cost of the antibiotics. The net effect of using growth-promoting antibiotics was a lost value of $.0093 per chicken (about 0.45 percent of total cost).

Development of macrolide-resistant *Campylobacter* in broilers administered subtherapeutic or therapeutic concentrations of tylosin. S.R. Ladely, M.A. Harrison, P.J. Fedorka-Cray, M.E. Berrang, M.D. Englen, and R.J. Meinersmann. *Journal of Food Protection*, 2007. 70(8):1915-1951.

Summary: Looks at the impact of antibiotic use on increasing the amount of resistant bacteria in an environment. Poultry were divided into groups of 25 birds: the treatment group was given either therapeutic or subtherapeutic doses of tylosin beginning at two weeks of age while the control group was isolated and not given any antimicrobials. The animals fed subtherapeutic and therapeutic doses of tylosin tested positive for resistant bacteria; no resistant strains were found among the birds that did not get treated with tylosin. The birds treated with subtherapeutic doses of tylosin also showed increased resistance compared with the birds treated with therapeutic doses.

Elevated risk of carrying gentamicin-resistant *Escherichia coli* among U.S. poultry workers. L.B. Price, J.P. Graham, L.G. Lackey, A. Roess, R. Vailes, and E. Silbergeld. *Environmental Health Perspectives*, 2007. 15(12):1738-1742.

Summary: Examines poultry workers and residents on the eastern shore of Maryland and Virginia. Poultry workers had 32 times the odds of being colonized with gentamicin-resistant *E. coli* as community residents; the poultry workers also had an elevated risk of carrying multidrug-resistant *E. coli.* Concludes that "occupational exposure to live animals in the broiler chicken industry may be an important route of entry for antimicrobial-resistant bacteria in to the community."

Effect of macrolide usage on emergence of erythromycin-resistant *Campylobacter* isolates in chickens. J. Lin, M. Yan, O. Sahin, S. Pereira, Y. Chang, and Q. Zhang. *Antimicrobial Agents and Chemotherapy.* 2007. 51(5): 1678-1686.

Summary: Erythromycin is a macrolide antimicrobial often used to treat *Campylobacter* infection in humans. This article presents information from experiments conducted to determine the emergence of erythromycin-resistant (Ery^r) *Campylobacter jejuni* and *Campylobacter coli* under selection pressure of macrolide use in a laboratory setting. Further discusses mechanisms associated with resistance to erythromycin. Results are presented from three experiments examining treatment of chickens with water containing tylosin, a macrolide-class antibiotic, and two experiments examining treatment of chickens with feed containing tylosin. Experiments show that chickens receiving a three-day therapeutic dose of tylosin in water (0.53 g/liter) shed significantly less *C. jejuni* and *C. coli* during treatment, but when treatment ended, resumed shedding a similar amount of the organisms as the control group that did not receive treatment. No Ery^r mutants were found in the treatment or control group in these experiments. Effects of long-term exposure to tylosin are examined by two experiments one which chickens were inoculated with *C. jejuni* at 3 days of age and one at 17 days of age. Treatment groups in each experiment were given feed containing tylosin at a subtherapuetic dose used for growth promotion (50 mg/kg) and control groups were provided unmedicated feed. Both experiments showed an initial reduction in shedding of *C. jejuni* in the medicated group; however, by day 31 and 17 in the two experiments respectively, Ery^r mutants were observed in chickens receiving medicated feed. No Ery^r mutants were observed in the control group in either experiment. Concludes that *C. jejuni* and *C. coli* have low rates of spontaneous mutation to Ery^r when therapeutic dosing is used but extended use of a macrolide drug as a growth promoter resulted in the emergence of Ery^r *C. jejuni* under laboratory conditions. However, the results presented here may not be used to predict development of antibiotic resistance on poultry farms as many factors may differ between the laboratory and poultry farm setting.

Antimicrobial resistance of old and recent *Staphylococcus aureus* isolates from poultry: First detection of livestock-associated methicillin-resistant strain ST398. M. Nemati, K. Hermans, U. Lipinska, O. Denis, A. Deplano, M. Struelens, L.A. Devriese, F. Pasmans, and F. Haesebrouck. *Antimicrobial Agents and Chemotherapy*, 2008. Oct: 3817-3819.

Summary: Compares the resistance profiles of *Staphylococcus aureus* isolates collected from chickens in the 1970s with profiles from healthy chickens in 2006. Finds that resistant levels to eight of the drugs tested were significantly greater in the 2006 samples.

Food animal transport: A potential source of community exposures to health hazards from industrial farming (CAFOs). A.M. Rule, S.L. Evans, and E.K. Silbergeld. *Journal of Infection and Public Health*, 2008. 1(1): 33-39.

Summary: Compares air samples collected while cars with bacterial-collection equipment were driven behind poultry transport vehicles with background samples taken during normal driving conditions. Twenty-five percent of samples collected while following poultry transport vehicles were resistant at least one antimicrobial, while all background samples were susceptible. Suggests that open-air poultry transport vehicles may play a role in spreading resistant bacteria that originated from the administration of antimicrobials to food animals.

Relationships between multidrug-resistant *Salmonella enterica* Serovar Schwarzengrund and both broiler chickens and retail chicken meats in Japan. T. Asai, K. Murakami, M. Ozawa, R. Koike, and H. Ishikawa. *Japanese Journal of Infectious Diseases,* 2009. 62: 198-200.

Summary: A *Salmonella* strain that causes invasive salmonellosis in humans was isolated from broiler chickens and retail chicken meats in Japan. Numerous isolates showed multidrug resistance.

Fate of antimicrobial-resistant *Enterococci* and *Staphylococci* and resistance determinants in stored poultry litter. J.P. Graham, S.L. Evans, L.B. Price, and E.K. Silbergeld. *Environmental Research,* 2009. 109: 682-689.

Summary: Studies the storage of poultry litter and the stability of bacteria and resistance genes during storage. Finds that over a 120-day period, typical storage practices of poultry litter are not sufficient for eliminating drug-resistant *Enterocci* and *Staphylococci,* which may then be delivered to the environment by land application, aerosolization or water contamination during runoff.

Antibiotic-resistant *Enterococci* and *Staphylococci* isolated from flies collected near confined poultry feeding operations. J.P. Graham, L.B. Price, S.L. Evans, T.K. Graczyk, and E.K. Silbergeld. *Science of the Total Environment,* 2009. 407(8): 2701-2710.

Summary: Investigators collected poultry litter and trapped flies around poultry farms to determine the extent of bacteria present and their resistance-gene profile. Results suggest that flies around poultry operations harbor resistant bacteria in their digestive tracts and exterior surfaces. This could result in human exposure to resistant bacteria that arise from antimicrobial use on poultry farms. Highlights the persistence of resistant genes in the environment and the pool of resistance associated with the use of antibiotics in feed additives.

***Salmonella Heidelberg* Ceftiofur-related resistance in human and retail chicken isolates.** Public Health Agency of Canada. 2009.

Summary: In response to public health concerns about the rise of resistance in isolates of *Salmonella* and *E. coli* to ceftiofur, all broiler chicken hatcheries in Québec voluntarily stopped using ceftiofur in February 2005. This publication reports a decrease in the number of ceftiofur-resistant isolates in both chicken and human *S. heidelberg* isolates and in chicken *Escherichia coli* following the voluntary withdrawal of ceftiofur in hatching and day-old chicks in Québec.

Antibiotic resistance of *Escherichia Coli* isolated from poultry and poultry environment of Bangladesh. M.A. Akond, S.M.R. Hassan, S. Alam, and M. Shirin. *American Journal of Environmental Sciences,* 2009. 5 (1): 47-52.

Summary: A study of *E. coli* isolated from poultry sources in Bangladesh. Resistance was high to many antibiotics including: penicillin, streptomycin, kanamycin, ampicillin and erythromycin. Resistance was not seen to gentamicin. The authors state that the widespread use of antibiotics has lead to resistance development that can be transmitted to human pathogens; they suggest that excess use or abuse of antibiotics should be reduced or stopped to ensure public safety.

Ceftiofur resistance in *Salmonella enterica* Serovar Heidelberg from chicken meat and humans, Canada. L. Dutil, R. Irwin, R. Finley, L. King Ng, B. Avery, P. Boerlin, A. Bourgault, L. Cole, D.

Daignault, A. Desruisseau, W. Demczuk, L. Hoang, G.B. Horsman, J. Ismail, F. Jamieson, A. Maki, A. Pacagnella, and D.R. Pillai. *Emerging Infectious Diseases*, 2010. 16(1): 48-54.

Summary: Studies *Salmonella* Heidelberg, a frequently reported cause of infections in North America with sources linked to consumption of poultry, eggs or egg-containing products. Compares resistance rates of *Salmonella* Heidelberg isolates collected from retail chicken to ceftiofur, a third-generation cephalosporin, with rates of human infections that also were resistant to ceftiofur during a period from 2003 to 2008. During this time frame ceftiofur was removed from extralabel use in chicken hatcheries in Québec, resulting in a dramatic decrease in ceftiofur resistance in *Salmonella* Heidelberg and *E. coli* in retail chicken. A similar decrease is shown in resistant human infections of *Salmonella* Heidelberg. Suggests that managing ceftiofur use at the hatchery level may control resistance rates to extended-spectrum cephalosporins. A partial reintroduction of ceftiofur use in hatcheries in 2007 caused a rise in ceftiofur resistance in *E. coli,* but at lower levels than those seen in 2003 to 2004.

Veterinary pharmaceuticals and antibiotic resistance of Escherichia coli isolates in poultry litter from commercial farms and controlled feeding trials. V. Furtula, E.G. Farrell, F. Diarrassouba, H. Rempel, J. Pritchard, and M.S. Diarra. *Poultry Science*, 2010. 89:180-188.

Summary: This study found that there were antimicrobial residues in broiler litter from both a controlled environment, where chickens were fed a diet of feed with additives of bacitracin, chlortetracycline, monensin, narasin, nicarbazin, penicillin, salinomycin and virginiamycin and from commercial farms where the same feed additives were also used. Antimicrobials are not fully absorbed by animals in some cases and will be excreted into the litter leaving a residue of antibiotics that may then be applied to soil for crop fertilization. If application occurs, soil microbes will be subjected to these antibiotic pressures and may develop resistance themselves. There is also evidence for plants to uptake antimicrobial agents and can become a source of exposure to such compounds. *E. coli* isolates were collected from poultry litter from commercial farms and were found to be resistant to at least seven different antibiotics. Isolates from commercial farms showed a higher rate of resistance possibly due to the frequent use of feeds that are available with multiple antibiotics incorporated causing increased resistance. Resistance to such antibiotics as trimethoprim-sulfamethoxazole from isolates collected on commercial farms is of concern as this is a leading treatment of urinary tract infections.

Prevalence and distribution of *Salmonella* in organic and conventional broiler poultry farms. W.Q. Alali, S. Thakur, R.D. Berghaus, M.P. Martin, and W.A. Gebreyes. *Foodborne Pathogens and Disease.* 2010. 7(11): 1363-1371.

Summary: Studies the prevalence of *Salmonella* and antimicrobial resistance on one company's USDA-certified organic broiler chicken operations and conventional broiler operations in North Carolina. Samples from fecal floor droppings, the feed hopper, feed lines, house main water line, and in-house drinking nipples were taken from three organic barns and four conventional barns. *Salmonella* was present in 13 of 300 samples (4 percent) taken from organic operations and 115 of 400 samples (29 percent) from conventional operations. Conventional operations demonstrated 11.9 times the prevalence odds of *Salmonella* in fecal samples as compared to organic operations. The prevalence odds ratio for *Salmonella* in feed samples from conventional vs. organic farms was 7.2. Approximately, 25 percent of isolates from organic operations and 1.7 percent of isolates from conventional operations were susceptible to all antimicrobial agents tested. Additionally, 41 percent (5/12) of isolates from organic operations and 62 percent (36/58) of isolates from conventional operations were resistant to two or more antimicrobial agents. The study demonstrates that within one poultry company in North Carolina, the prevalence of *Salmonella* and antibiotic-resistant *Salmonella* was greater on conventional operations as compared to organic operations. However, as antibiotic resistance was found in both operations this may signal circulation of organisms within a company's farms.

Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. M.A. Leverstein-van Hall, C.M. Dierikx, J. Cohen Stuart, G.M. Voets, M.P. van den Munckhof, A. van Essen-Zandbergen, T. Platteel, A.C. Fluit, N. van de Sande-Bruinsma, J. Scharinga, M.J.M.Bonten, and D.J. Mevius. *Clinical Microbiology and Infection*. 2011, 17(6):873-880.

Summary: An increase in infections caused by Gram-negative bacteria producing extended spectrum beta-lactamases (ESBL) has been observed globally. In The Netherlands, there is low human use of antibiotics but higher levels of use in poultry production. This study examined the distribution of ESBL genes, plasmids, and strain genotypes in *Escherichia coli* found in retail chicken in 2006, in poultry in 2010, and determined the distribution of isolates from Dutch patients with "poultry associated" (PA) ESBL genes, plasmids, and strains in 2009. Of 98 samples from chicken retail meat, 94 percent contained at least one isolate thought to be positive for ESBL. Of 409 ESBL-positive *E. coli* isolates from humans, 35 percent contained ESBL genes and 19 percent had ESBL genes located on plasmids that were indistinguishable from those found in poultry isolates. The most common genes found in human isolates, $bla_{CTX\text{-}M\text{-}1}$ and $bla_{TEM\text{-}52}$, were also the most common genes found in poultry and retail chicken meat and 39 percent of ESBL-producing *E. coli* found in retail meat belonged to genotypes also found in humans. Study results suggest transmission of ESBL-producing *E. coli* between poultry and humans, potentially through contact with retail chicken; however, due to study limitations, further research is required.

Prevalence of types of methicillin-resistant *Staphylococcus aureus* in turkey flocks and personnel attending the animals. A. Richter, R. Sting, C. Popp, J. Rau, B.A. Tenhagen, B. Guerra, H.M. Hafez, A. Fetsch. *Epidemiology and Infection*. 2012. 140(12): 2223-2232.

Summary: The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) among turkeys was 143/200 turkeys (72 percent) from 90 percent of the 20 flocks examined. Among 59 people sampled from 12 farms, 22 (37 percent) were positive for MRSA carriage. Thirteen people tested were found to carry the same type of MRSA as that isolated from the animals or in the environment from the operation, while five carried a different type. Increased contact with turkeys per week increased the odds of MRSA carriage. Almost all MRSA isolates found in this study were also resistant to tetracycline (98 percent) and large proportions were resistant to clindamycin and erythromycin (83 percent), kanamycin (42 percent), gentamicin (27 percent) and ciprofloxacin (31 percent).

Foregoing Sub-therapeutic Antibiotics: the Impact on Broiler Grow-out Operations. J.M. MacDonald and S.-L. Wang. Applied Economic Perspectives and Policy (2011): 1-20. Advance Access published January 6, 2011. doi:10.1093/aepp/ppq030

Summary: Data from a national survey of broiler to analyze the use of subtherapeutic antibiotics (STAs) among broiler growers. About 55% of farms may use STAs. Those who don't use STAs clean out their barns more consistently and use all-in all-out production, feed an all-vegetable diet, follow some sort of animal welfare guidelines, have newer houses, and are also more likely to have tunnel ventilation and evaporative cooling in their houses. Producers who do not use

STAs had no statistically significant impact on production given other inputs. The estimates indicate that growers and integrators can adapt to STA suspensions without declines in production.

RETAIL PRODUCTS

How industrial food animal production affects the food supply.

An evaluation of methods to assess the effect of antimicrobial residues on the human gut flora. D. Corpet. *Veterinary Microbiology,* 1993. 35(3-4):199-212.

Summary: Reviews the effects of antimicrobial residues on the human gut flora and concludes that "most resistant enterobacteria in the human gut of untreated people come from bacterial contamination of raw foods." This assumption stems from a study previously completed by the author in which a sterile diet was given to seven healthy volunteers with an outcome of reduced antibiotic-resistant bacteria in stools.

Quinoline-resistant *Campylobacter jejuni* infections in Minnesota, 1992–1998. K.E. Smith, J.M. Besser, C.W. Hedberg, F.T. Leano, J.B. Bender, J.H. Wickland, B.P. Johnson, K.A. Moore, and M.T. Osterholm. *New England Journal of Medicine,* 1999. 340(20):1525-1532.

Summary: Reports that ciprofloxacin-resistant *C. jejuni* was isolated from 14 percent of 91 domestic chicken products obtained from retail markets in 1997. The number of quinolone-resistant infections acquired domestically has increased, largely because of the acquisition of resistant strains from poultry. Resulting infections may require additional antimicrobial therapy, as fluoroquinolones such as ciprofloxacin are commonly prescribed for diarrheal illnesses caused by *Campylobacter jejuni.*

Isolation of antimicrobial-resistant *Escherichia coli* from retail meats purchased in Greater Washington, DC, USA. C.M. Schroeder, D.G. White, B. Ge, Y. Zhang, P.F. McDermott, S. Ayers, S. Zhao, and J. Meng. International Journal of Food Microbiology, 2003. 85: 197-202.

Summary: Retail meat samples were collected and analyzed from the DC area for presence of *E. coli.* Data on resistance to 11 antimicrobials are given with a large portion showing resistance to such antibiotics as tetracycline (59 percent), sulfamethoxazole (45 percent), streptomycin (44 percent), ampicillin (35 percent) and gentamicin (12 percent). The authors conclude that their findings suggest retail meats may often be contaminated with resistant *E. coli.*

The incidence of antimicrobial-resistant *Salmonella* spp. on freshly processed poultry from US Midwestern processing plants C.M. Logue, J.S. Sherwood, P.A. Olah, L.M. Elijah, and M.R. Dockter. *Journal of Applied Microbiology,* 2003. 94: 16-24

Summary: A study to determine the occurrence of antimicrobial-resistant *Salmonella* spp. on processed turkey at poultry plans in the Midwestern U.S. Samples (surface swabs from carcasses: pre- and post chill and chill water from tanks) were taken from two plants at monthly intervals for one year. Overall incidence of *Salmonella* was around 16.7 percent, with a greater percentage of the pathogen observed on carcasses both pre- and post-chill, with post-chill showing decreased occurrence compared to pre-chill. *Salmonella* from the study had varying levels of antimicrobial resistance. The most common resistance was seen to tetracycline, streptomycin, sulfamethaxozole and ampicillin. Chlorination of chill water is thought to cause this reduction in contamination; however, the authors state that infections would be difficult to treat in the future if chlorine resistance is a factor in promoting selection of bacteria that have other resistance mechanisms.

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. R. Nannapaneni, R. Story, K.C. Wiggins, and M.G. Johnson. *Applied and Environmental Microbiology*, 2005. 71(8): 4510-4515.

Summary: Analyzes the total amount of *Campylobacter* present in retail chicken as well as in ciprofloxacin-resistant isolates. Finds that ciprofloxacin-resistant *Campylobacter* persisted throughout the two-and-a-half-year study, showing a reservoir of resistance in the U.S. food market.

Sulfamethazine uptake by plants from a manure-amended soil. H. Dolliver, K. Kumar, and S. Gupta. *Journal of Environmental Quality,* 2007. 36:1224-1230.

Summary: Studies the uptake of sulfamethazine, an antibiotic extensively used in animal agriculture for therapeutic and subtherapeutic purposes, in corn, lettuce and potatoes when manure-amended soil is used as the growing medium. Following 45 days of growth, all plants tested were contaminated with the antibiotic in varying concentrations.

Antimicrobial drug-resistant *Escherichia coli* from humans and poultry products, Minnesota and Wisconsin, 2002–2004. J.R. Johnson, M.R. Sannes, C. Croy, B. Johnston, C. Clabots, M.A. Kuskowski, J. Bender, K.E. Smith, P.L. Winokur, and E.A. Belongia. *Emerging Infectious Diseases,* 2007, 13(6): 838-846.

Summary: Studies susceptible and resistant *E. coli* collected from hospital patients, healthy vegetarians and poultry that were raised conventionally and without antibiotics. Suggests that many resistant human isolates may originate from poultry. Isolates from healthy vegetarians also follow this pattern, suggesting that avoidance of poultry consumption does not decrease the possibility of carrying drug-resistant *E. coli* from poultry.

The isolation of antibiotic-resistant *Salmonella* from retail ground meats. D.G. White, S. Zhao, R. Sudler, S. Ayers, S, Friedman, S. Chen, P.F. McDermott, S. McDermott, D.D. Wagner, and J. Meng. *New England Journal of Medicine*, 2007. 345(16):1147-1154.

Summary: Researchers tested *Salmonella* from samples of ground chicken, pork, beef and turkey purchased at three supermarkets in the Washington, DC, area. Of 200 samples, 41 (20 percent) contained *Salmonella.* Eighty-four percent of those were resistant to at least one antibiotic and 53 percent were resistant to at least three antibiotics. Sixteen percent were resistant to ceftriaxone, the drug of choice for treating salmonellosis in children.

Antimicrobial-resistant and extraintestinal pathogenic *Escherichia coli* in retail foods. J.R. Johnson, M.A. Kuskowski, K. Smith, T.T. O'Bryan, and S. Tatini. *Journal of Infectious Diseases*. 2005. 191:1040-1049.

Summary: Presents results from a two-year survey of the presence of antimicrobial-resistant *Escherichia coli*, and specifically, extraintestinal pathogenic *E. coli* (ExPEC), in a sampling of foods. To determine differences between retail markets and food types, samples of meat and other foods were systematically taken on a weekly basis from a range of retail markets based on a pre-determined schedule. Approximately 24 percent (396/1648) of samples were positive for *E. coli* with proportions varying by food type (miscellaneous foods: 9 percent; pork: 69 percent; poultry: 92 percent). Among beef and pork being ground was a risk factor for the presence of *E. coli* while natural-store source was associated with a reduction in the presence of the bacteria and antimicrobial resistance. Antibiotic-free labeling was identified as a risk factor for contamination. ExPEC was found in 4 percent of miscellaneous food, 19 percent of pork, and 46 percent of poultry samples and resistance to at least one antibiotic was present in 27, 85, and 94 percent, respectively. Four of the ExPEC positive isolates from food closely resembled positive isolates from humans. Concludes that retail foods are often contaminated with antibiotic-resistant *E. coli* and ExPEC *E. coli* is also present. Food may serve as an important vehicle for the transmission of antibiotic resistant ExPEC bacteria.

Contamination of retail foods, particularly turkey, from community markets (Minnesota, 1999-2000) with antimicrobial-resistant and extraintestinal pathogenic *Escherichia coli*. J.R. Johnson, P. Delavari, T.T. O'Bryan, K.E. Smith, and S. Tatini. *Foodborne Pathogens and Disease*. 2005. 2(1):38-49.

Summary: Provides results from a one-year retail market survey of the prevalence of antimicrobial-resistant *Escherichia coli* in a range of retail foods. Food products were purchased systematically from 16 retail markets, including large economy and luxury chains, small economy chains, locally owned cooperatives, and farmer's markets (only during the summer). Sixteen percent (35/222) of vegetables sampled were positive for *E. coli*, as well as 5 percent (4/74) of fruit items, 100 percent (10/10) beef, (3/3) pork, (28/28) turkey products, and 89 percent (8/9) chicken products. Ten extraintestinal pathogenic *E. coli* (ExPEC) positive samples containing a range of virulence genes were found in turkey products that differed by type, store, and purchase date. ExPEC isolates were missing several virulence genes commonly found in human clinical *E. coli* isolates; however, four of the ExPEC isolates had virulence profiles, phylogenetic backgrounds, and O antigens that resembled clonal groups associated with human infection. Susceptibility testing for 12 antimicrobial agents demonstrated that resistance to tetracycline and sulfisoxazole was most common, followed by resistance to ampicillin, cefazolin, and gentamicin. No resistance to nitrofurantoin or ciprofloxacin was identified. Resistance was more common in meat products than other products and isolates resistant to more than 4 drugs were recovered from one beef item and 29 percent of turkey items. Suggests meat is more frequently contaminated with *E. coli* and meat-source and produce-source *E. coli* differs in virulence, phylogenetic background, and antimicrobial resistance, and therefore in public health implications. Additionally, turkey may be an important source of human exposure to resistant and potentially pathogenic *E. coli* including ExPEC.

Resistance in bacteria of the food chain: Epidemiology and control strategies. F.M. Aarestrup, H.C. Wegener, and P. Collignon. *Expert Reviews,* 2008. 6(5): 733-750.

Summary: Reviews bacterial resistance due to the use of antimicrobials in food animals and their transferability to humans in the form of pathogens. States that limiting the selective pressure in food animal production, especially those antibiotics that are critically important to human health, will help control the emergence of resistant bacteria most efficiently.

Molecular analysis of *Escherichia coli* from retail meats (2002–2004) from the United States National Antimicrobial Resistance Monitoring System. J.R. Johnson, J.S. McCabe, D.G. White, B. Johnston, M.A. Kuskowski, and P. McDermott. *Clinical Infectious Diseases,* 2009. 49: 195-201.

Summary: Researchers screened 287 *E. coli* isolates collected by the National Antimicrobial Resistance Monitoring System (NARMS) for virulence-associated genes. Resistant and susceptible strains differed minimally based on the assessed virulence factors; however, the four meat types screened showed a great variance as chicken and turkey isolates had consistently higher virulence scores than beef and pork samples. These results support 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.

Transient intestinal carriage after ingestion of antibiotic-resistant *Enterococcus faecium* from chicken and pork. T.L. Sorensen, M. Blom, D.L. Monnet, N. Frimodt-Moller, R.L. Poulsen, and F. Espersen. *New England Journal of Medicine,* 2009. 345(16): 1161-1166.

Summary: Reports on a study designed to test the ability of *Enterococci* from various meat sources to have sustained viability in the human intestine. Twelve volunteers ingested a suspension of *Enterococci* that originated from either a pig or chicken source that was resistant to at least one antibiotic. None of the 12 volunteers was colonized with resistant *Enterococci* at the onset of the experiment; however, eight of the 12 had antibiotic-resistant *Enterococci* isolated at six days following ingestion, and one had resistant *Enterococci* at 14 days' post ingestion. Concludes that ingestion of resistant *Enterococci* of animal origin leads to detectable concentrations of the same resistant strain in stools for up to 14 days.

Isolation and characterization of Methicillin-resistant *Staphylococcus aureus* strains from Louisiana retail meats. S. Pu, F. Han, and B. Ge. *Applied and Environmental Microbiology*. 2009. 75(1): 265-267.

Summary: Examines the presence of *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) in raw pork and beef products purchased from retail grocery stores consisting of seven supermarket chains in Baton Rouge, LA. Out of 90 pork samples, 41 were positive for *S. aureus* and 5 of those were found to be MRSA providing a prevalence of MRSA in pork of 6 percent. For beef products, 6/30 samples were positive for *S. aureus* and among those 1 was found to be MRSA for a prevalence of MRSA in beef products of 3 percent. Two of the six MRSA-positive pork samples contained the Panton-Valentine Leukocidin gene, which is considered the main virulence factor associated with skin and soft tissue infections.

Methicillin-resistant *Staphylococcus aureus* in food products: Cause for concern or complacency? J. A. J. W. Kluytmans. Clinical Microbiology and Infection, 2010. 16(1): 11-15.

Summary: A review on an emerging sequence type of MRSA ST398, which has been isolated from various food animals. A recent study in the U.S. observed a contamination rate of 39.2 percent for *S. aureus* on retail meats and in that group 5 percent was MRSA. Studies abroad have shown rates of MRSA contaminating retail meats as high as 11.9 percent. The author suggests that even though ST398 does not appear to spread easily among humans this assumption needs to be confirmed in well-designed studies. 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.

Multidrug-resistant *Salmonella* isolates from retail chicken meat compared with human clinical isolates. N.M. M'ikanatha, C.H. Sandt, A.R. Localio, D. Tewari, S.C. Rankin, J.M. Whichard, S.F. Altekruse, E. Lautenbach, J.P. Folster, A. Russo, T.M. Chiller, S.M. Reynolds, and P.F. McDermott. *Foodborne Pathogens and Disease,* 2010. 7:8 929-934.

Summary: Salmonella isolates from retail chicken were collected in central Pennsylvania from 2006-2007. Overall prevalence rates of Salmonella were 22.2 percent for a combination of open-air market samples, pre-packaged, organic and raised antibiotic free. Prevalence rates were not significantly different between these groups. These isolates were characterized by pulsed-field gel electrophoresis (PFGE) and compared to PulseNet data collected up to 2008. One collected poultry isolate matched directly to a human isolate that was acquired from a 17-year-old Philadelphia resident. The two isolates were collected within five months from each other and poultry consumption was listed as a possible risk factor suggesting that disease was likely caused from contaminated poultry.

Characterization of toxin genes and antimicrobial susceptibility of *Staphylococcus aureus* isolates from Louisiana retail meats. S. Pu, F. Wang, and B. Ge. *Foodborne Pathogens and Disease,* 2010. 1-8.

Summary: This study focuses on *Staphylococcus aureus* collected from retail meats in Louisiana. Isolates characterized included 152 *S. aureus* isolates, with 22 MRSA, for prevalence of 9 enterotoxin and 4 exotoxin genes as well as susceptibility profiles to 20 antimicrobials. Researchers found 85 percent were positive for at least one enterotoxin gene and 66 percent contained 2 to 4 enterotoxin genes. Staphylococcal enterotoxins cause approximately 185,000 food poisoning illnesses annually and occur upon ingestion of the carrier strains with symptoms such as vomiting, nausea, abdominal cramps and diarrhea. Antibiotic resistance was seen most often to penicillin (71 percent), ampicillin (68 percent) and tetracycline (67 percent). Erythromycin resistance (30 percent) and clindamycin resistance(18 percent) were also observed. Multidrug resistance was common in MRSA isolates and those samples from pork. The authors conclude that stringent food safety practice is needed for people who handle raw meat products to prevent food borne infections due to *S. aureus* contamination.

Antimicrobial susceptibility of *Staphylococcus aureus* from retail ground meats. A. Kelman, Y. Soong, N. Dupuy, D. Shafer, W. Richbourg, K. Johnson, T. Brown, E. Kestler, Y. Li, J. Zheng, P. McDermott, and J. Meng. *Journal of Food Protection,* 2011. 24(10). 1625-1629.

Summary: Retail ground beef, pork, and turkey were purchased at grocery stores in the Washington, D.C. area between March and August 2008. Reports 56 percent of 196 ground turkey samples, 28 percent of 198 ground beef samples, and 12 percent of 300 ground pork samples were positive for *Staphylococcus aureus*. Information on resistance to 22 antimicrobial agents is provided. 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. More than half of the *S. aureus* found was resistant to tetracycline. One sample was positive for methicillin-resistant *S. aureus* (MRSA). Concludes that *S. aureus* in retail ground meats is not uncommon and many of these bacteria are resistant to at least one antimicrobial agent.

Multidrug-resistant *Staphylococcus aureus* in U.S. meat and poultry. A.E. Waters, T. Contente-Cuomo, J. Buchhagen, C.M. Liu, L. Watson, K. Pearce, J.T. Foster, J. Bowers, E.M. Driebe, D.M. Engelthaler, P.S. Keim, and L.B. Price. *Clinical Infectious Diseases,* 2011. 52(10). 1227-30.

Summary: Examines the presence and antibiotic-resistance patterns of *Staphylococcus aureus* in meat and poultry products in the U.S. Shows that 77 percent of 26 turkey products, 42 percent of 26 pork products, 41 percent of chicken products, and 37 percent of 38 beef products sampled were positive for *S. aureus.* An evaluation of resistance to 17 antimicrobials is provided and shows that 96 percent of the *S. aureus* positive-samples demonstrated resistance to at least one antimicrobial agent. Additionally, 52 percent of all *S. aureus* were classified as multidrug resistant, meaning resistant to 3 or more antimicrobial classes. Samples showed resistance to several clinically important antibiotics including ciprofloxacin, quinupristin/dalfopristin, clindamycin, erythromycin, oxacillin, and daptomycin.

Identification and antimicrobial resistance of extraintestinal pathogenic *Escherichia coli* from retail meats. X. Xia, J. Meng, S. Zhao, S. Bodeis-Jones, S.A. Gaines, S.L. Ayers, and P.E. McDermott. *Journal of Food Protection*. 2011. 74(1). 38-44.

Summary: Extraintestinal *Eschericia coli* (ExPEC) is a type of *E. coli* that can cause infections outside of the intestines including urinary tract infections, meningitis, and wound infections. This study determines the prevalence of ExPEC in retail meat purchased in Georgia, Maryland, Oregon, and Tennessee in 2006. Reports 16 percent of 1,275 *E. coli*-positive samples were found to be ExPEC. The authors provide information on the distribution of serotypes and virulence genes found among positive samples. Concludes that many of the strains of ExPEC found in meat samples were of strains that can cause disease in humans and 80 percent were shown to be resistant to at least one antimicrobial agent, many of which are clinically relevant.

Prevalence of *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) on retail meat in Iowa. B.M. Hanson, A.E. Dressler, A.L. Harper, R.P. Scheibel, S.E. Wardyn, L.K. Roberts, J.S. Kroeger, and T.C. Smith. *Journal of Infection and Public Health*. 2011. 4: 169-174.

Summary: Investigates the prevalence and types of *Staphylococcus aureus* present on retail pork, chicken, beef, and turkey products purchased at urban and rural stores across Iowa. Turkey demonstrated the highest prevalence of *S. aureus* with the bacteria found in 7/36 samples (19 percent). Turkey was followed by pork with 10/55 samples (18 percent), chicken with 8/45 samples (18 percent), and beef with 2/29 samples (7 percent) positive for *S. aureus*. Methicillin-resistant *S. aureus* (MRSA) was present in 2/55 pork samples (4 percent) only. Based on molecular methods, 7/27 *S. aureus* positive isolates (26 percent) were identified as ST398 and 4/27 were ST9, both livestock associated types. The two ST8 isolates also carried the Panton-Valentine Leukocidin virulence gene. Based on antibiotic susceptibility testing 5/27 isolates (19 percent) were susceptible to all antibiotics, 21/27 (78 percent) were resistant to penicillin, 18/27 (67 percent) were resistant to tetracycline, 6/27 were resistant to clindamycin (22 percent), 4/27 (15 percent) were resistant to erythromycin, and 2/27 (7 percent) were resistant to oxacillin. This study was focused on the potential for human contact with *S. aureus* and MRSA through contact with retail meat. For this reason, laboratory methods focused on the presence of these bacteria on the surface of retail meat and did not use more destructive laboratory methods that measure the prevalence of the bacteria anywhere in the meat samples as many other studies have done. Authors conclude that although this study showed lower prevalence of *S. aureus* and MRSA in retail meats than other studies, it shows that *S. aureus* and MRSA are present on the surface of retail meat and may be a source of human exposure.

Extended-spectrum β-Lactamase-producing *Escherichia coli* from retail chicken meat and humans: Comparison of strains, plasmids, resistance genes, and virulence factors. J.A.J.W. Kluytmans, I.T.M.A. Overdevest, I. Willemsen, M.F.Q. Kluytmans-van den Bergh, K. van der Zwaluw, M. Heck, M. Rijnsburger, C.M.J.E. Vandenbroucke-Grauls, P.H.M. Savelkoul, B.D. Johnston, D. Gordon, J.R. Johnson. *Clinical Infectious Diseases*. 2013. 56: 478-487.

Summary: Builds on previous work examining the similarities between extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) isolated from chicken meat and human diagnostic specimens in the Netherlands. Multilocus sequence typing (MLST) revealed that 51 percent (22/43) of isolates from human rectal samples and 27 percent (4/15) of isolates from human blood cultures were the same as or related to ESBL-EC isolates from chicken meat. When the genetic composition of *E. coli* isolates from the three sources were compared, there was substantial overlap, especially between isolates from chicken meat and those from human rectal samples (representing the bacteria in the human gut). The similarities among ESBL-EC isolated from humans and chicken illustrates that food, specifically chicken meat, may contribute to the emergence of ESBL-EC infections among humans, raising questions about the use of antimicrobials and the presence of antimicrobial resistant bacteria among food animals.

MRSA

The impacts of methicillin-resistant Staphylococcus aureus *(MRSA) on certain areas across the country, veterinarians, health care employees and farmers.*

An outbreak of community-acquired foodborne illness caused by Methicillin-resistant *Staphylococcus aureus*. T.F. Jones, M.E. Kellum, S.S. Porter, M. Bell, and W. Schaffner. *Emerging Infectious Diseases.* 2002. 8(1): 82-84.

> **Summary:** Describes an outbreak of acute gastroenteritis caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Three family members consumed coleslaw and barbeque pork purchased from a market-delicatessen and after consuming the products experienced nausea, vomiting, and stomach cramps. Two of the three individuals sought treatment at a hospital. Indistinguishable MRSA isolates were found in a nasal swab from one asymptomatic food preparer at the market-delicatessen, a sample from the coleslaw, and stool cultures from the three patients. This is the first report of gastroenteritis due to MRSA however, *S. aureus* is a common cause of gastrointestinal illness in the US and therefore MRSA may play a larger role than previously thought.

Methicillin-resistant *Staphylococcus aureus* in pig farming. A. Voss, F. Loeffen, J. Bakker, C. Klaassen, and M. Wulf. *Emerging Infectious Diseases*, 2005. 11(12): 1965-1966.

> **Summary:** Examines cases of MRSA colonization resulting from farmers' contact with pigs, how it moved though their families and was transmitted between a hospital patient and nurse. 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.

Methicillin-resistant *Staphylococcus aureus* colonization in veterinary personnel. B.A. Hanselman, S.A. Kruth, J. Rousseau, D.E. Low, B.A. Willey, A. McGeer, and J.S. Weese. *Emerging Infectious Diseases*, 2006. 12(12): 1933-1938.

> **Summary:** Reports a comprehensive evaluation of veterinary personnel for carriage of MRSA. Samples were taken from participants who resided in 19 different countries and rates of colonization were determined. Of the volunteers, 6.5 percent were positive for MRSA; those working with larger animals showed higher carriage rates (15.6 percent).

Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus* aureus, United States, 1999–2005. E. Klein, D.L. Smith, and R. Laxminarayan. *Emerging Infectious Diseases,* 2007. 13(12): 1840-1846.

> **Summary:** Reports on trends in MRSA infections between 1999 and 2005. The estimated rise in hospitalizations due to *Staphylococcus aureus* infections during this time was 62 percent, while the rate of MRSA infections more than doubled.

Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. R.M. Klevens, M.A. Morrison, J. Nadle, S. Petit, K. Gershman, S. Ray, L.H. Harisson, R. Lynfield, G. Dumyati, J.M. Townes, A.S. Craig, E.R. Zell, G.E. Fosheim, L.K. McDougal, R.B. Carey, and S.K. Fridkin. *Journal of the American Medical Association*, 2007. 285(15):1763-1771.

> **Summary:** Finds that MRSA affects certain populations disproportionately, particularly African Americans. After researching invasive MRSA infections reported in hospitals in eight U.S. cities

and the state of Connecticut, the authors estimate that in 2005 more than 94,000 cases of such infections occurred, 18,650 of which were fatal.

Emergence of methicillin-resistant *Staphylococcus aureus* of animal origin in humans. I. van Loo, X. Huijsdens, E. Tuemersma, A. de Neeling, N. van de Sande-Bruinsma, D. Beaujean, A. Voss, and J. Kluytmans. *Emerging Infectious Diseases*, 2007. 13(12):1834-1839.

Summary: Reports that a new type of MRSA from an animal reservoir (pigs in the Netherlands) has recently entered the human population and is now responsible 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.

Methicillin-resistant *Staphylococcus aureus* ST398 in humans and animals, Central Europe. W. Witte, B. Strommenger, C. Stanek, and C. Cuny. *Emerging Infectious Diseases*, 2007. 13(2): 255-258.

Summary: Studies recent human colonization by MRSA ST398, which in previous years had not been seen in humans. Animal-to-human transmission may occur with this strain; for example, a dog being treated for a wound infection transmitted ST398 to the staff of the veterinary practice where the dog was treated. Concludes that "MRSA exhibiting ST398 may colonize and cause infections in humans and in certain animal species such as dogs, horses and pigs."

Methicillin-resistant *Staphylococcus aureus* colonization in pigs and pig farmers. T. Khanna, R. Friendship, D. Dewey, and J.S. Weese. *Veterinary Microbiology,* 2008. 128:298-303.

Summary: This study, the first of MRSA and pig farms in Canada, found that the prevalence of MRSA colonization on pig farms was 45 percent; prevalence in pig farmers was 20 percent. Humans residing on farms where pigs were free of MRSA also tested negative for MRSA. The authors note another study in which MRSA was identified in food products intended for human consumption, but none originated in pigs. This study adds support to the hypothesis that MRSA can be transmitted between pigs and humans.

Pigs as source of methicillin-resistant *Staphylococcus aureus* CC398 infections in humans, Denmark. H.C. Lewis, K. Molbak, C. Reese, F.M. Aarestrup, M. Selchau, M. Sorum, and R.L. Skov. *Emerging Infectious Diseases,* 2008. 14(9): 1383-1389.

Summary: 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.

Methicillin-resistant and -susceptible *Staphylococcus aureus* sequence type 398 in pigs and humans. A.van Belkum, D.C. Melles, J.K. Peeters, W.B. van Leeuwen, E. van Duijkeren, X.W. Huijsdens, E. Spalburg, A.J. de Neeling, and H.A. Verbrugh. *Emerging Infectious Diseases*, 2008. 14(3):479-483.

Summary: 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.

Transmission of methicillin-resistant *Staphylococcus aureus* strains between different kinds of pig farms. E. van Duijkeren, R. Ikawaty, M.J. Broekhuizen-Stins, M.D. Jansen, E.C. Spalburg, A.J. de Neeling, J.G. Allaart, A.van Nes, J.A.Wagenaar, and A.C. Fluit. *Veterinary Microbiology,* 2008. 126: 383-389.

Summary: MRSA strains were found in 23 percent of the farms tested. States that the use of standard antimicrobials "seems to be a risk factor for finding MRSA-positive pigs on a farm. Pig farms on which the pigs were treated with antimicrobials as group medication had a higher risk of being MRSA positive, whereas farms on which antimicrobials were used restrictively had a much lower chance of being MRSA positive."

Increase in a Dutch hospital of methicillin-resistant *Staphylococcus aureus* related to animal farming. M.M.L. van Rijen, P.H. Van Keulen, and J.A. Kluytmans. *Clinical Infectious Diseases*, 2008. 16:261-263.

Summary: Reports on a study 2002–2006 in the Netherlands involving hospital patients who had MRSA. Patients exposed to pigs or veal calves were shown to be at higher risk for MRSA as there was an emergence of nontypable MRSA during this time. Nontypable MRSA is assumed to stem from pigs and calves.

Methicillin-resistant *Staphylococcus aureus* (MRSA) strain ST398 is present in Midwestern U.S. swine and swine workers. T.C. Smith, M.J. Male, A.L. Harper, J.S. Kroeger, G.P. Tinkler, E.D. Moritz, A.W. Capuano, L.A. Herwaldt, and D.J. Diekema. *PLoS ONE,* 2009. 4(1): e4258.

Summary: Investigates MRSA in the Midwestern U.S. Samples were taken from swine and production workers in two commercial operations. MRSA prevalence was 49 percent in swine and 45 percent in workers. Results show that MRSA is common in swine production in the U.S. and that these animals could be harboring the bacterium.

Methicillin-resistant *Staphylococcus aureus*: A new zoonotic agent? B. Springer, U. Orendi, P. Much, G. Hoger, W. Ruppitsch, K. Krziwanek, S. Metz-Gercek, and H. Mittermayer. *The Middle European Journal of Medicine,* 2009. 121: 86-90.

Summary: Discusses changes in MRSA over the past decade. Once known almost completely as a hospital pathogen, MRSA is now emerging in the community in persons without hospital-related risk factors. Recent evidence also has shown a link between livestock colonization and MRSA infections in persons working with these animals. Identifies three potential transmission routes of MRSA: from animal origin into the population; human-to-human contact from farm workers to the community; via food or by environmental contamination.

Methicillin-resistant *Staphylococcus aureus* (MRSA) strain ST398 is present in Midwestern swine and swine workers. T.C. Smith, M.J. Male, A.L. Harper, J.S. Kroeger, G.P. Tinkler, E.D. Mortiz, A.W. Capuano, L.A. Herwaldt, and D.J. Diekema. *PLoS One*. 2009. 4(1).

Summary: Establishes evidence of methicillin-resistant *Staphylococcus aureus* (MRSA) ST398 in swine and humans in the U.S. Swine and humans from two conventional swine production systems in Iowa and Illinois participated. MRSA was found in swine and humans working in close contact with the swine on one of the swine operations, the other operation had no MRSA-positive swine or employees. On the operation where MRSA was isolated, an inverse association between MRSA colonization of the nostrils of swine and age was observed with swine 15 weeks old or younger having higher odds of MRSA colonization than adult swine. Of 14 participating employees in close contact with swine, 9 were found to carry MRSA. Risk factors including age, gender, use of tobacco products, use of antimicrobial agents in the prior 3 months, having MRSA in the prior 12 months, and duration of employment were not associated with MRSA colonization. All MRSA isolated was confirmed to be ST398 and negative for the Panton-

Valentine Leukocidin virulence gene. All MRSA isolates were resistant to penicillin, oxacillin, and tetracycline.

Methicillin resistant Staphylococcus aurues ST398 in veal calf farming: Human MRSA carriage related with animal antimicrobial usage and farm hygiene. H. Graveland, J.A. Wagenaar, H. Heesterbeek, D. Mevius, E. van Duijkeren, and D. Heederik. *PLoS One,* 2010. 5(6): 1-6.

Summary: Studies MRSA ST398 carriage in veal calves, farmers, their family members and employees. A large sampling size of veal calf farms in the Netherlands was selected at random to be screened for ST398. All participants were given a questionnaire to fill in describing their contact and role on the farm as well as how farm operations were conducted. Samples from both humans and veal calves were cultured and categorized using molecular techniques. The data presented show that direct associations between human and animal carriage of MRSA ST398 exist and that carriage was shown to increase in calves as antibiotic use on the farm increased. Duration of contact to veal calves showed a highly elevated risk of MRSA ST398 carriage in humans and a decrease in MRSA was seen in farms with better hygiene practices (ie cleaning of stables before new claves were brought on the farm). Disinfection was applied in less than 20 percent of the farms in the study and was not associated with prevalence of MRSA carriage in calves. Overall the prevalence of MRSA was 15.9 percent in participants who lived or worked on veal calf farms, which is far greater than the general population carriage rate in the Netherlands estimated to be below 1 percent.

***Staphylococcus aureus* CC398: Host adaptation and emergence of methicillin resistance in livestock.** L.B. Price, M. Stegger, H. Hasman, M. Aziz, J. Larsen, P.S. Andersen, T. Pearson, A.E. Waters, J.T. Foster, J. Schupp, J. Gillece, E. Driebe, C.M. Liu, B. Springer, I. Zdovc, A. Battisti, A. Franco, J. Zmudzki, S. Schwarz, P. Butaye, E. Jouy, C. Pomba, M. Concepcion Porrero, R. Ruimy, T.C. Smith, D.A. Robinson, J.S. Weese, C.S. Arriola, F. Yu, F. Laurent, P. Keim, R. Skov, F.M. Aarestrup. *mBio*. 2012. 3(1).

Summary: Authors applied whole genome sequence typing (WGST) to 89 CC398 *Staphyloccocus aureus* isolates from around the world and examined the origins and evolution of CC398. The article provides phylogenetic evidence that suggests that CC398 originated in humans as a methicillin susceptible *S. aureus* (MSSA) strain. Authors further suggest that this strain spread to livestock where it then acquired the SCC*mec* cassette and resistance to methicillin and tetracycline. Results presented also suggest that the transfer between humans and animals was followed by a reduced capacity for human colonization, transmission, and virulence despite the fact that MRSA CC398 is thought to be associated with an increase in MRSA infections in parts of Europe.

Antimicrobial resistance of *Staphylococcus aureus* strains acquired by pig farmers from pigs. A. Oppliger, P. Moreillon, N. Charrière, M. Giddey, D. Morisset, O. Sakwinska. *Applied Environmental Microbiology*. 2012. 78(22): Epub ahead of print.

Summary: Examines the genotype and antimicrobial resistance patterns of *Staphylococcus aureus* isolated from pigs, pig farmers, and veterinarians on 41 farms in Western Switzerland. This information is compared to characteristics of *S. aureus* isolated from people with no agricultural exposures and from cow farmers. Of 343 pigs tested, 123 (36 percent) were found to carry *S. aureus* while 44/75 pig farmers and veterinarians carried *S. aureus*. Eleven pigs (3 percent) from three farms were positive for MRSA as were five farmers (7 percent). The *S. aureus* found among pigs and pig farmers and veterinarians was similar. *S. aureus* isolated from cow farmers and non-farmers were similar to each other but different than those from pigs and pig farmers. A greater proportion of *S. aureus* isolates from pig farmers and veterinarians were resistant to antibiotics, especially tetracycline and similar to the resistance patterns in pigs. These results support the idea that zoonotic transmission of antimicrobial-resistant *S. aureus* may occur frequently between pigs and caretakers.

A metapopulation model to assess the capacity of spread of methicillin-resistant *Staphylococcus aureus* ST398 in humans. T. Porphyre, E.S. Giotis, D. H. Lloyd, K. Dorothea, C. Stärk. *PLoS One.* 2012. 7(10).

Summary: A mathematical model was used to investigate the ability of methicillin-resistant *Staphylococcus aureus* (MRSA) ST 398, a livestock-associated sequence type, to spread into a hypothetical human population from a commercial pig farm. Results showed that repeated exposures of humans working in direct contact with pigs carrying MRSA ST398, allowed for MRSA ST398 to persist in the human population even at low levels of persistence. Based on the results, the authors recommend farm-level interventions to reduce exposure to MRSA ST398 in order to control spread of MRSA ST398 in the greater population.

Whole genome sequencing identifies zoonotic transmission of MRSA isolates with the novel *mecA* homologue *mecC*. E.M. Harrison, G.K. Paterson, M.T.G. Holden, J. Larsen, M. Stegger, A.R. Larsen, A. Petersen, R.L. Skov, J.M. Christensen, A.Bak Zeuthen, O. Heltberg, S.R. Harris, R.N. Zadoks, J. Parkhill, S.J. Peacock, M.A. Holmes. *EMBO Molecular Medicine.* 2013, 5: 1-7. http://onlinelibrary.wiley.com/doi/10.1002/emmm.201202413/pdf

Summary: Presents findings from a molecular investigation of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates carrying a novel *mecA* gene (*mecC*) recovered from two human cases of infection and from livestock that live on the same property as each respective human case. Results revealed genotypic similarity between isolates collected from each case and their respective livestock, providing evidence that MRSA carrying *mecC* may be transmitted between livestock and humans. This finding is of public health importance as *mecA* is the gene that confers resistance to β-lactam antibiotics and consequently the presence of the *mecA* gene is often used to define the presence of MRSA as a causal agent of infection. Using current diagnostic testing, MRSA isolates carrying *mecC* instead of *mecA* may be found incorrectly to be negative for MRSA. Authors recommend that larger investigations and continued surveillance are needed to understand and monitor bacterial evolution and transmission between animals and humans.

ANTIMICROBIAL-RESISTANT INFECTIONS

Infections arising with implications toward the use of antimicrobials in food animal production.

Molecular epidemiology of antibiotic resistance in *Salmonella* from animals and human beings in the United States. T.F. O'Brien, J.D. Hopkins, E.S. Gilleece, A.A. Medeiros, R.L. Kent, B.O. Blackburn, M.B. Holmes, J.P. Reardon, J.M. Vergeront, W.L. Schell, E. Christenson, M.L. Bisset, and E.V. Morse. *New England Journal of Medicine* 1982. 307:8 1-6.

Summary: Restriction-endonuclease digestion (a method by which DNA is cleaved at specific locations, then these digestion patterns are observed by gel-electrophoresis to compare similarity between samples) was used to analyze plasmids from *Salmonella* isolates collected from animals and humans. Results show that identical or nearly identical antibiotic resistance gene carrying plasmids are found between human and animal strains of *Salmonella*. Plasmid fragments were found not to cluster by human or animal grouping, rather they are intermixed suggesting that the strains developed in one host then were spread to the other, as both share similar characteristics. The infected patients observed had no prior farm exposure, this leaves meat or food preparation as a plausible route for infection, and also points toward the spread of disease from animals to humans.

Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group. A.R. Manges, J.R. Johnson, B. Foxman, T.T. O'Bryan, K.E. Fullerton, and L.W. Riley. *New England Journal of Medicine,* 2001. 345(14): 1007-1013.

Summary: Studies urinary tract infections (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.

De Novo* acquisition of resistance to three antibiotics by *Escherichia coli. M.A. van der Horst, J.M. Schuurmans, M.C. Smid, B.B. Koenders, and B.H. ter Kuile. *Microbial Drug Resistance.* 2001, 17(2): 141-147.

Summary: Explores *de novo* acquisition of resistance by *Escherichia coli* bacteria after varying levels of exposure to three antibiotics – amoxicillin, enrofloxacin, and tetracycline. *E. coli* samples were exposed to sub-lethal concentrations of each antibiotic. If normal growth occurred, colonies were selected and re-plated and exposed to a concentration of the antibiotic at a level doubling the previous exposure. *E. coli* grown in the absence of the amoxicillin had a minimum inhibitory concentration (MIC) that varied between 4 and 8 μg/ml. When grown with 1.25 or 2.5 μg/ml, the MIC reached a maximum of 32 μg/ml, and when grown for another 15 days without antibiotics, the MIC returned to control levels. However, colonies exposed to increasing amounts of amoxicillin reached a maximum MIC of 512 μg/ml and maintained a MIC of 256 μg/ml when grown without antibiotics for another 15 days demonstrating the ability to maintain resistance to amoxicillin. *E. coli* grown in the presence of tetracycline had increasing MIC levels with those exposed to increasing levels of tetracycline demonstrating a maximum MIC of 32 μg/ml. However, all MICs returned to control level when tetracycline was removed. Resistance among *E. coli* exposed to levels of enrofloxacin below the susceptible MIC built quickly, increasing by a factor of up to 100. The increased MIC remained after 15 days of growth in the absence of enrofloxacin. Growth rate of *E. coli* was also examined for each scenario. Differences in resistance and growth rate between the three antibiotics may be due to differences in resistance mechanisms. Moderate amounts of cross-resistance to all three antibiotics were also detected. Concludes that exposure to low levels of antibiotics poses a risk and resistance selected for in the agricultural sector will transfer to the human sector over time and this transfer is already occurring.

Fluoroquinolone resistance in *Camplyobacter* absent from isolates, Australia. L. Unicomb, J. Ferguson, T.V. Riley, and P. Collignon. *Emerging Infectious Diseases,* 2003. 9(11): 1482-1483.

Summary: Reports on a study of fluoroquinolone resistance in New South Wales, Australia, over a three-year period. Only 12 *Campylobacter* isolates were found to be resistant to fluoroquinolones. Ten of these were related to travel; travel status of the other two is unknown. Australia has never allowed the use of fluoroquinolones in food animal production, a policy that may have impacts on human health for countries with fluoroquinolone-resistant cases of *Campylobacter.*

Antibiotic selection pressure and resistance in Streptococcus pneumoniae and Streptococcus pyogenes. W.C. Albrich, D.L. Monnet, and S. Harbarth. *Emerging Infectious Diseases,* 2004. 10:3 514-517.

Summary: Study designed to assess emerging antibiotic resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes* in 20 countries by comparing resistance rates to the dose of antibiotics given to outpatients. The authors find that resistance to penicillin and macrolides in these species in outpatients is directly correlated with increased antibiotic selection pressure on a national level and suggest that these findings lend support to policymakers and professional organizations to discourage the overuse of antibiotics in the community.

Possible animal origin of human-associated, multidrug-resistant, uropathogenic *Escherichia coli.* M. Ramchandi, A.R. Manges, C. DebRoy, S.P. Smith, J.R. Johnson, and L.W. Riley. *Clinical Infectious Disease,* 2005. 40: 251-257.

Summary: Reviews a collection of 495 animal and environmental *E. coli* isolates collected by the Gastroenteric Disease Center and determines that 26 percent had indistinguishable characteristics from human isolates. Concludes that the data suggest that drug-resistant, uropathogenic, human-associated *E. coli* strains may have an animal origin and that drug-resistant urinary tract infections in humans could be derived from foodborne illnesses.

The rising influx of multidrug-resistant gram-negative bacilli into a tertiary care hospital. A.E. Pop-Vicas, E. M. and C. D'Agata. *Clinical Infectious Diseases*, 2005. 40: 1792-8.

Summary: Studies multi-drug resistant (MDR) *E. coli*, *Klebsiella* species, *Enterobacter cloacae*, and *Pseudomonas aeruginosa* isolates from patients harboring these bacteria upon entering a hospital in Israel (within 48 hours of admittance). Finds that between 1998 and 2003 the prevalence of MDR isolates of all listed species increased significantly except *Pseudomonas aeruginosa.* Of the 464 isolates collected 12 percent, 35 percent and 53 percent were resistant to 5, 4 and 3 antimicrobial groups, respectively.

Analysis of a uropathogenic *Escherichia coli* clonal group by multilocus sequence typing. S.Y. Tartof, O.D. Solberg, A.R. Manges, and L.W. Riley. *Journal of Clinical Microbiology*, 2005. 5860-5864.

Summary: Forty-five strains of uropathogenic *E. coli* were analyzed by a molecular typing method called multi-locus sequence typing (MLST). The research shows that one sample from a cow grouped with other human isolates collected from urinary tract infections and bacteremia . This shows that *E. coli* from animals may be a cause of UTIs and bactermia in humans.

Low-level fluoroquinolone resistance among *Camplyobacter jejuni* isolates in Australia. L. Unicomb, J. Ferguson, R.J. Stafford, R. Ashbolt, M.D. Kirk, N.G. Becker, M.S. Patel, G.G. Gilbert, M. Valcanis, and L. Mickan. *Clinical Infectious Diseases,* 2006. 42: 1368-1374.

Summary: Reports a study from five Australian states between 2001 and 2002 that looked into the susceptibility patterns of *Campylobacter jejuni*. Only two percent of isolates from locally acquired infections were resistant to ciprofloxacin, likely reflecting Australia's policy of restricting the use of fluoroquinolones in food production animals.

First report of the emergence of CTX-M-type extended spectrum ß-Lactamases (ESBLs) as the predominant ESBL isolated in a U.S. health care system. J. S. Lewis II, M. Herrena, B. Wickes, J.E. Patterson, and J. H. Jorgensen. Antimicrobial Agents and Chemotherapy, 2007. 51(11): 4015-4021.

Summary: A study on Extended spectrum beta-lactamases (ESBLs) from a clinic in San Antonio Texas. ESBLs are enzymes produced by bacteria that can negate the use of certain newer antibiotics used in treating infections of *E. coli* or similar bacteria. The new ESBL enzyme described here as seen for the first time in the U.S. is located on a plasmid (a mobile element of DNA) within the bacterium. As plasmids can be readily passed between bacteria this new finding could have a wide health impact. The authors state "a worrisome trend with the emergence of these enzymes has been an increasing frequency of *E. coli* isolates from outpatients or patients hospitalized for a very brief period, suggesting community acquisition of these strains."

Endemic and epidemic lineages of *Escherichia coli* that cause urinary tract infections. A.R. Manges, H. Tabor, P. Tellis, C. Vincent, and P. Tellier. *Emerging Infectious Diseases,* 2008. 14(10): 1575-1583.

Summary: Studies urinary tract infections (UTI) in women from California and Canada. Relatedness of the infections is apparent, as the profiles of the bacteria are identical. Multidrug-resistant *E. coli* outbreaks are the causative agent of the disease, and how these bacteria are acquired by the gut is unclear; however, the authors cite a previous study indicating that poultry and pork consumption may lead to the development of drug-resistant UTIs.

Temporal changes in the prevalence of community-acquired antimicrobial-resistant urinary tract infection affected by *Escherichia coli* clonal group composition. S.P. Smith, A.R. Manges, and L.W. Riley. Clinical Infectious Diseases, 2008. 46: 689-695.

Summary: Reports on urinary tract infections (UTIs) from 1,667 patients over the course of 6 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* that had been 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.

Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: Implications for antibiotic stewardship. R.R. Roberts, B. Hota, I. Ahmad, R.D. Scott II, S.D. Foster, F. Abbasi, S. Schabowski, L.M. Kampe, G.G. Ciavarella, M. Supino, J. Naples, R. Cordell, S.B. Levy, and R.A. Weinstein. *Clinical Infectious Diseases,* 2009. 49: 1175-1184.

Summary: Assesses the attributable cost associated with antimicrobial-resistant infections (ARI). Data were collected from patients admitted to a public teaching hospital in the Chicago area in the year 2000. Of 188 patients that met eligibility of ARI, the attributable medical cost of treatment ranged from $18,588 to $29,069 per patient. Social costs were $10.7 to $15.0 million, and total cost corrected to 2008 dollars was $13.35 million.

World health organization ranking of antimicrobials according to their importance in human medicine: A critical step for developing risk management strategies for the use of antimicrobials in food production animals. P. Collignon, J.H. Powers, T.M. Chiller, A. Aidara-Kane, and F.M.Aarestrup. *Clinical Infectious Diseases*. 2009. 49: 132-41.

Summary: Presents information regarding antimicrobial agents used to treat disease in humans. Ranks antimicrobial agents and classes as critically important, highly important, and important to human health and reviews changes in the rankings made in 2007. Antimicrobial rankings are based on two main criteria: 1) the agent or class is the sole therapy or one of few alternatives to treat serious human disease; 2) the antimicrobial agent or class is used to treat diseases cause by organisms that may be transmitted via nonhuman sources or diseases caused by organisms that may acquire resistance genes from nonhuman sources. Within the list of critically important antimicrobial agents a committee designated quinolones, third- and fourth-generation cephalosporins and macrolides as the classes for which immediate action should be taken to reduce unnecessary use in food animals and humans.

Antibiotic management of Staphylococcus aureus infections in US children's hospitals, 1999-2008. J.C. Herigon, A.L Hersh, J.S. Gerber, T.E. Zaoutis, and J.G. Newland. *Pediatrics*, 2010. 125:e1294-e1300.

Summary: This study focuses on the rates of *S. aureus* infection in children under the age of 18 from 1999 until 2008. The authors also track the trend of antimicrobial use during that time period. Finds that *S. aureus* infections increased by a rate of more than 10-fold over the course of 10 years from 14.8 per 1000 admissions in 1999 to 35.7 per 1000 admissions in 2008. MRSA infections also increased 10-fold during the same period from 2.0 cases per 1000 admissions in 1999 to 20.7 cases per 1000 admissions in 2008. Increased use of clindamycin was most substantial (21 percent in 1999 to 63 percent in 2008) while linezolid also saw increased use between 2001 (when it became available) and 2008. The substantial use of clindamycin may lead to greater resistance and ineffective treatment of future *S. aureus* infections. The authors note that continuous monitoring of local *S. aureus* susceptibility patterns is needed as treatment patterns have changed over the past decade due to the emergence of community-associated MRSA.

Genetic identity of aminoglycoside-resistance genes in *Escherichia coli* isolates from human and animal sources. P. Ho, R.C. Wong, S.W. Lo, K. Chow, S.S. Wong, and T. Que. *Journal of Medical Microbiology*, 2010. 59: 702-707.

Summary: A study in Hong Kong on *E. coli* isolates collected from food producing animals and humans (most from urinary tract infections). The group looked at the aminoglycocide (gentamicin) resistance characteristics of these isolates and found the main source of resistance was due to a gene called aacC2. The aacC2 gene was shown to exist in both human and animal *E. coli*. This suggests that gentamicin resistance in human *E. coli* urinary isolates can be attributed to resistance genes that are present in food-producing animals. Study illustrates when humans are in close contact with contaminated food, there is a risk of picking up antibiotic resistant *E. coli* that could lead to UTIs that are more difficult to treat.

Food reservoir for *Escherichia coli* causing urinary tract infections. C. Vincent, P. Boerlin, D. Daignault, C.M. Dozois, L. Dutil, C. Galanakis, R.J. Reid-Smith, P-P. Tellier, P.A. Tellis, K. Ziebell, and A.R. Manges. Emerging Infectious Diseases, 2010. 16(1):88-95.

Summary: The design of this study was to see if a food reservoir exists for *E. coli* that may cause urinary tract infections. Sampling for *E. coli* was completed between 2005 and 2007 comprising clinical UTI samples, retail meats and restaurant/ready-to-eat foods. Upon comparison of these collected isolates by molecular methods the author's report that *E. coli* identified from retail chicken and other food sources are identical or nearly the same as those from human UTIs.

***Escherichia coli* isolates from broiler chicken meat, broiler chickens, pork, and pigs share phylogroups and antimicrobial resistance with community-dwelling humans and patients with urinary tract infection.** L. Jakobsen, A. Kurbasic, L. Skj∅t-Rasmussen, K. Ejrnaes, L.J. Porsbo, K. Pedersen, L.B. Jensen, H.D. Emborg, Y. Agerso, K.E.P. Olsen, F.M. Aarestrup, N.Frimodt-Moller, and A.M. Hammerum. *Foodborne Pathogens and Disease,* 2010. 7:5 537-547

Summary: Study in Denmark comparing phylogroups and antimircrobial resistance patterns among *E. coli* collected from UTI patients, community-dwelling humans, broiler chicken meat, broiler chickens, pork meat and pigs. The study finds that the presence of specific *E. coli* phylogroups, that are the main cause of UTIs, exist in samples of animal origin. The collected animal isolates also 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. Samples from humans were predominantly B2, which is the most commonly found type in UTIs, most likely due to virulence factors associated with the group allowing colonization in humans. Only 6 to 15 percent of isolates of animal origin were found to fall into group B2, but these may still pose a risk for acquiring uropathogenic *E. coli*.

Risk factors for antibiotic-resistant *Escherichia coli* carriage in young children in Peru: Community –based cross sectional prevalence study. H.D. Kalter, R.H. Gilman, L.H. Moulton, A.R. Cullotta, L. Cabrera, and B. Velapatiño . *American Journal of Tropical Medicine and Hygiene,* 2010.

Summary: A study in Peru focused on the carriage and antimicrobial resistance characteristics of *E. coli* from children and their living environments that included animals, market chickens and mothers' hands. The study concludes that data from surveys and sampling for *E. coli* in several regions of Peru shows there were four main factors contributing to antibiotic-resistant *E. coli* carriage in children. Use of antibiotics by anyone in the household increased risk. Residing in an area where a larger proportion of households served home-raised chicken seemed to protect against resistant bacteria, however residing in an area that severed market-raised chicken was a risk factor for carriage of resistant *E. coli*. Also, living in environments contaminated with a higher level of multi-drug resistant bacteria were found to increase the risk of carriage of resistant *E. coli*.

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. K.K. Kumarasamy, M.A. Toleman, T.R. Walsh, J. Bagaria, F. Butt, R. Balakrishnan, U. Chaudhary, M. Doumith, C.G., Giske, S. Irfan, P. Krishnan, A.V. Kumar, S.

Maharjan, S. Mushtaq, T. Noorie, D.L. Paterson, A. Pearson, C. Perry, R. Pike, B. Rao, U. Ray, J.B. Sarma, M. Sharma, E. Sheridan, M.A. Thirunarayan, J. Turton, S. Upadhyay, M. Warner, W. Welfare, D.M. Livermore, and N. Woodford. *The Lancet*, 2010. 10(9): 597-602.

Summary: Presents information about antibiotic resistance in gram-negative bacteria. Fewer antibiotic agents exist to treat gram-negative bacterial infections and therefore resistance to antibiotics among these bacteria may be especially concerning. Antibiotic-resistance is shared by bacteria mainly through the transfer of plasmids (a mobile piece of DNA). After the discovery of CTX-M-15 extended-spectrum β-lactamase (ESBL), which confers resistance to cephalosporins, was reported in India, a greater reliance on carbapenems to treat infection has been observed. The article presents molecular and epidemiologic information on New Delhi metallo-β-lactamase 1 (NDM-1) positive Enterobacteriaceae in India, Pakistan, and the United Kingdom in 2008 and 2009. NDM-1 is a recently identified carbapenem resistance gene which has been shown to readily transfer between bacteria in vitro. Of 3,521 Enterobacteriaceae recovered in Chennai in 2009, 141 were carbapenem resistant, and 44 were positive for NDM-1 (1 percent of all isolates). In Haryana, 47 of 198 isolates were carbapenem resistant and 26 of those were positive for NDM-1. All 44 isolates from Chennai were resistant to all β-lactam antibiotics, fluoroquinolones, and aminoglycosides (except two susceptible to gentamicin) and came from community acquired urinary tract infections, pneumonia, and blood-stream infections. Isolates from the UK were mostly from samples from urine, blood, burn or wound, sputum, central line tip, and throat swabs. All UK NDM-1 positive isolates were resistant to imipenem and ertapenem. A majority of NDM-1 positive isolates from the UK and Chennai carried the NDM-1 gene on plasmids that could be transferred between bacteria. Isolates from Haryana were not transferable. The authors conclude Enterobacteriaceae with the NDM-1 enzyme are resistant to many antibiotic classes and may present a great deal of difficulty in treating Gram-negative infections with available drugs.

Association between antimicrobial resistance in *Escherichia coli* isolates from food animals and blood stream isolates from humans in Europe: An ecological study. A.R. Vieria, P. Collignon, F.M. Aarestrup, S.A. McEwen, R.S. Hendriksen, T. Hald, and H.C. Wegener. *Foodborne Pathogens and Disease*. 2011. Sep 1. [Epub ahead of print].

Summary: Estimates the correlation between antimicrobial resistance of *Escherichia coli* from human blood stream infections and from *E. coli* isolated from poultry, pigs, and cattle in eleven European countries. Reports strong correlations between antimicrobial resistance found in *E.coli* from human blood stream infections and poultry and human blood stream infections and pigs. States that in addition to contributions from human use of antimicrobials, a proportion of resistant *E. coli* implicated in human blood infections may be from food animal sources.

Selection of resistant bacteria at very low antibiotic concentrations. E. Gullberg, S. Cao, O.G. Berg, C. Ilbäck, L. Sandegren, D. Hughes, and D.I. Anderson. *PLoS Pathogens*. 2011. 7(7). E1002158.

Summary: Demonstrates through experiments with *Eschericia coli* and *Salmonella enterica* that the presence of levels of tetracycline and streptomycin several-hundred fold lower than previously considered important, may lead to selection for resistant strains of these bacteria over susceptible strains. The authors state that very low levels of antibiotics, which can be found in the environment or in the human body when undergoing treatment, are important in the development and maintenance of antibiotic resistance in pathogens.

Antibiotic resistance in foodborne pathogens: Evidence of the need for a risk management strategy. (CSPI White Paper). C. Smith DeWaal, C. Roberts, and C. Catella. Center for Science in the Public Interest, January 25, 2011.

Summary: Provides general background concerning the use of antibiotics in food animal-production and documents foodborne outbreaks due to antibiotic resistant bacteria. Focuses on documenting outbreaks due to antibiotic-resistant bacteria as antibiotic resistance is not required to be reported to other agencies in the U.S. Notes an increase in outbreaks due to antibiotic-resistant pathogens over the past several decades, although it is not clear whether this is due to a true increase or an increase in testing and reporting. A total of 35 outbreaks due to antibiotic-resistant pathogens were documented between 1973 and 2009. Source of the outbreaks were dairy products (34 percent), ground beef (26 percent), and poultry, pork, produce, and seafood (6 percent each), as well as eggs and multi-ingredient food (3 percent each). Outbreaks lead to 19,897 sick, 3.061 hospitalizations, and 26 deaths. *Salmonella typhimurium* was the most common pathogen implicated in outbreaks. Other *Salmonella* species were the causative agent in outbreaks as well as *Escherichia coli*, *Campylobacter jejuni*, and *Staphylococcus aureus*. These bacteria demonstrated a range of resistance patterns that included resistance to a total of 14 antibiotics including seven classified as "critically important" to human medicine by the World Health Organization.

Chicken as a reservoir for extraintestinal pathogenic *Escherichia coli* in humans, Canada. C.R. Bergeron, C. Prussing, P. Boerlin, D. Daignault, L. Dutil, R.J. Reid-Smith, G.G. Zhanel, A.R. Manges. *Emerging Infectious Diseases*. 2012. 18(3): 415-421.

Summary: Examined the potential for a food-animal reservoir for extraintestinal pathogenic *Escherichia coli* (ExPEC), a common cause of urinary tract infection (UTI) in humans. To address this question, researchers analyzed *E. coli* isolates obtained between 2005 and 2008 from humans with a diagnosed UTI, retail meat (chicken, beef, pork), and industrially raised food animals (chicken, beef cattle, pigs) in Canada. Fifteen distinct groups, containing 22 human isolates and 41isolates from retail meat were identified, with 71 percent of the retail meat isolates originating from chicken. Eight distinct groups, containing 17 human isolates and 29 isolates from animals at slaughter were identified, again with a majority of isolates from animals originating from chicken (79 percent). Three groups included isolates from all three sources. Among these distinct groups, genetic mapping of the isolates from humans, animals, and meat indicates that they may have originated from a recent common ancestor. The findings support the idea that food animals, and specifically chicken, may serve as a reservoir for ExPEC, allowing humans to become exposed through handling or consumption of retail chicken.

***Enterococcus faecalis* clones in poultry and in humans with urinary tract infections, Vietnam.** L.L. Poulsen, M. Bisgaard, N.T. Son, N.V. Trung, H.M. An, A. Dalsgaard. *Emerging Infectious Diseases*. 2012. 18(7): 1096-1100.

Summary: Presents information on *Enterococus faecalis* isolates from 31 humans with a urinary tract infection (UTI) and from poultry living in the same household as the infected individual. Sequence types (ST) of *E. faecalis* isolated from 23 percent (7/31) of UTI patients were identical to the types isolated from poultry living within the same household. For these seven pairs, the drug resistance patterns and the presence of virulence genes were also similar for human and poultry isolates. This report illustrates the potential for zoonotic transmission of *E. faecalis* between humans and poultry.

Food-borne origins of *Escherichia coli* causing extraintestinal infections. A.R. Manges, J.R. Johnson. *Clinical Infectious Diseases*. 2012. 55(5): 712-719.

Summary: A literature review of the strength of evidence linking human extraintestinal *Escherichia coli* (ExPEC) infections with a food-animal reservoir. Studies indicate a strong link between *E. coli* found in poultry and ExPEC strains recovered from humans, including genetic similarities and common antimicrobial-resistance patterns. Evidence reviewed demonstrates five of nine human ExPEC groups have also been identified in poultry, with one of these groups also found in pigs and cattle and one found also among pigs. Only three human ExPEC groups were determined to have no known food animal reservoir based on the available literature. Many of identified strains express extensive antibiotic-resistance, observed both among animals and humans. Authors indicate that although there are no known studies that can prove direct transmission between humans and food-animals, the weight of available evidence supports the presence of a food-animal reservoir for ExPEC. A discussion of public health interventions is also given.

Antimicrobial-resistant *Campylobacter* in the food chain in Mexico. M.B. Zaidi, P.F. McDermott, F. D. Campos, R. Chim, M. Leon, G. Vazquez, G. Figueroa, E. Lopez, J. Contreras, T. Estrada-Garcia. *Foodborne Pathogens and Disease*. 2012, 9(9): 841-847.

Summary: Describes the prevalence of *Campylobacter* from the intestines of food-animals at the time of slaughter, retail meat, and kindergarten-aged children in four regions of Mexico. Samples from chickens showed 94 percent of the 1,087 samples with *Campylobacter*. Seventy-one percent of 968 samples from swine, and 25 percent of 645 samples from cattle were also positive for *Campylobacter*. The same trend in retail meat was observed with 58, 15, and 5 percent of chicken, pork, and beef found to contain *Campylobacter*, respectively. Of 3,610 children with diarrhea 5 percent were found to be shedding *Campylobacter* as were 3 percent of asymptomatic children. Resistance to ciprofloxacin among *Campylobacter* from all sources was common with isolates from meat sources demonstrating the greatest proportion of resistance (approximately 85 percent) while a lower proportion of isolates from ill (62 percent) and healthy children (54 percent) were resistant to ciprofloxacin. Tetracycline resistance was also common (approximately 80 percent) among *Campylobacter* found in pork and beef and lower in ill (43 percent) and healthy children (37 percent). Resistance to other antimicrobials was also observed but at a lower rate. The presence of high proportions of resistance to ciprofloxacin and tetracycline observed among food-animals, meat, and children is of public health concern as fluoroquinolones are one of the drug classes of choice for treatment of severe *Campylobacter* infections in humans. Fluoroquinolones are not licensed for children and tetracyclines are prohibited for children under the age of eight years yet both of these antimicrobial classes are used in food-animal production in Mexico. This supports the role antimicrobial use has in food-animals contributing to antimicrobial resistance among human pathogens.

For additional information on the Pew Campaign on Human Health and Industrial Farming, or on any of these studies, please contact Laura Rogers, project director, Pew Health Group, at (202) 552-2018 or **lrogers@pewtrusts.org**.

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Food Animals and Antimicrobials: Impacts on Human Health

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INTRODUCTION

For many decades, antibiotic resistance has been recognized as a global health problem. It has now been escalated by major world health organizations to one of the top health challenges facing the 21st century (40, 65). Some of its causes are widely accepted, for example, the overuse and inappropriate use of antibiotics for nonbacterial infections such as colds and other viral infections and inadequate antibiotic stewardship in the clinical arena (109). But the relationship of drug-resistant bacteria in people to antibiotic use in food animals continues to be debated, particularly in the United States (11, 14, 38, 44, 48, 96, 124).

Many have delved into this question, producing volumes of direct and indirect evidence linking animal use to antibiotic resistance confronting people. Among these are a number of studies which unequivocally support the concern that use of antibiotics in food animals (particularly nontherapeutic use) impacts the health of people on farms and, more distantly, via the food chain (69, 88, 90, 111). While it was hoped by many that the years of experience following the bans on nontherapeutic use of antimicrobials in Europe would clearly signal an end to this practice, arguments continue, largely along the lines of a cost/benefit ratio and perceived deficits in solid scientific evidence. Action in the United States continues to lag far behind that of the European Union, which has chosen to operate proactively based on the "precautionary principle," a guiding tenet of public health. This principle states that "when evidence points toward the potential of an activity to cause significant widespread or irreparable harm to public health or the environment, options for avoiding that harm should be examined and pursued even if the harm is not yet fully understood or proven" (103).

This communication summarizes a large number of studies on the links between antimicrobials used for growth promotion, in particular, as well as other nontherapeutic antimicrobial (NTA) use in animal husbandry and aquaculture, and the emergence of antibiotic-resistant bacteria in humans. The *FAAIR Report* (*Facts about Antibiotics in Animals and the Impact on Resistance*) of the Alliance for the Prudent Use of Antibiotics (APUA) cites areas where antibiotic use can be curtailed and proposes several viable recommendations that could be utilized to reduce the burden of resistance genes created by nontherapeutic antibiotic use in animals (22).

Lastly, we consider whether knowledge gaps exist that need addressing in order to answer persisting questions that fuel the controversy over NTA use in food animals.

ANTIMICROBIAL USE IN ANIMALS: EFFECTS ON ANTIBIOTIC RESISTANCE EMERGENCE

Antimicrobials are delivered to animals for a variety of reasons, including disease treatment, prevention, control, and growth promotion/feed efficiency. Antimicrobial growth promotants (AGPs) were first advocated in the mid-1950s, when it was discovered that small, subtherapeutic quantities of antibiotics such as procaine penicillin and tetracycline (1/10 to 1/100 the amount of a therapeutic dose), delivered to animals in feed, could enhance the feed-to-weight ratio for poultry, swine, and beef cattle (142). For many years, the positive effects of this practice were championed, while the negative consequences went undetected. But microbiologists and infectious disease experts facing antibiotic resistance questioned the possible harm from this use (74, 89, 109, 136). They found that farms using AGPs had more resistant bacteria in the intestinal

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floras of the farm workers and farm animals than in those for similar people and animals on farms not using AGPs. A prospective *in vivo/in situ* study in 1975 was performed to evaluate the effect of introducing low-dose in-feed oxytetracycline as an AGP on the intestinal floras of chickens and farm dwellers (111). The results showed not only colonization of the chickens with tetracycline-resistant and other drug-resistant *Escherichia coli* strains but also acquisition of resistance in *E. coli* in the intestinal flora of the farm family. Other studies over the ensuing 3 decades further elucidated the quantitative and qualitative relationships between the practice of in-feed antimicrobials for animals and the mounting problem of hard-to-treat, drug-resistant bacterial infections in humans (83, 162).

Nontherapeutic Agents and Practices

The chief agricultural NTAs, used extensively in the United States and also used in Europe until the 1970s, include drugs that have likewise been employed widely in human medicine. In the absence of complete, unbiased data, this NTA use in the United States is estimated to be equal to (159) or as much as eight times greater than (67, 117) the quantity administered for therapeutic use.

More recently, concerns have arisen over the extensive use of antimicrobials in the burgeoning aquaculture industry, which more than doubled between 1994 and 2004 (36, 84). Eighty to 90 percent of total production occurs in Asia, with 67% occurring in China alone (64). In many parts of the world, fish farming is integrated with sewage or industrial wastewater or with land agriculture, as manure and other agricultural residues are commonly employed in fish feed (123). The overcrowding, unhygienic measures, and other manipulations in this intensive, industrial-scale production act as stressors to the fish and promote an increased use of antibiotic prophylaxis, particularly in the shrimp and carnivorous fish (such as salmon) industries. Moreover, even though the aquaculture use of AGPs in Western Europe and North America has been discontinued, therapeutic treatment of fish generally occurs *en masse* via inclusion in fish food, which results in exposure of the entire body of water to the antibiotic. The broad application of antibiotics in fish food leads to leaching from unconsumed food and feces into the water and pond sediments, where it not only exerts selective pressures on the sediment and water microflora but also can be washed to more distant sites, exposing wild fish and shellfish to trace antimicrobials (36). In this environment, the role of transduction (infection by bacterial phages) is considered highly important in facilitating lateral gene transfer (71). Sorum suggested that, historically, the transfer and emergence of resistance have occurred faster from aquatic bacteria to humans than from terrestrial animal bacteria to humans (141).

In the United States, the total fish industry use of antibiotics was estimated to be 204,000 to 433,000 pounds in the mid-1990s (25) (about 2% of the nonmedical use in cattle, swine, and poultry [117]). In much of the world, however, antibiotics are unregulated and used indiscriminately, and use statistics are rarely collected (25, 157). Although the total quantities of antibiotics employed in aquaculture are estimated to be smaller than those used in land animal husbandry, there is much greater use of antibiotic families that are also used in human medicine (Table 1). In Chile, for example, ~100 metric tons of quinolones are used annually (10-fold greater than the amount used in human medicine), mostly in aquaculture (35). At least 13 different antimicrobials are reportedly used by farmers along the Thai coast (75).

Salmonella and the *Swann Report*

Alarmed by the rise in multidrug-resistant *Salmonella* in the 1960s, the United Kingdom's *Swann Report* of 1969 recognized the possibility that AGPs were contributing largely to the problem of drug-resistant infections (144). It concluded that growth promotion with antibiotics used for human therapy should be banned. The recommendation was implemented first in England and then in other European countries and Canada. The practice continued unchanged, however, in the United States and ultimately also continued in Europe, but with agents that were not used therapeutically in humans. Antibiotics such as bacitracin, avoparcin, bambermycins, virginiamycin, and tylosin gained in popularity as narrower-spectrum substitutes that had a smaller impact on the broad range of gut flora. Unforeseen, however, was the structural relationship between some of these agents and agents used clinically in humans (Table 1). This similarity meant that they shared a single bacterial target and that use of one agent could produce cross-resistance to the other.

Impacts of Nontherapeutic Use

Therapeutics applied properly for the treatment of individual animals tend to control the emergence and propagation of antimicrobial-resistant strains, in large part due to their relatively short-term application and relatively small numbers of animals treated. The resistant strains which may appear are generally diluted out by the return of normal, drug-susceptible commensal competitors (110). In contrast, any extended antibiotic applications, such as the use of AGPs, which are supplied for continuous, low-dose application, select for increasing resistance to the agent. Their use in large numbers of animals, as in concentrated animal feeding operations (CAFOs), augments the "selection density" of the antibiotic, namely, the number (density) of animals producing resistant bacteria. An ecological imbalance results—one that favors emergence and propagation of large numbers of resistance genes (113). The selection is not linked merely to the total amount of antibiotic used in a particular environment but to how many individuals are consuming the drug. Each animal feeding on an antibiotic becomes a "factory" for the production and subsequent dispersion of antibiotic-resistant bacteria. NTA uses are also clearly linked to the propagation of multidrug resistance (MDR), including resistance against drugs that were never used on the farm (10, 52, 59, 60, 92, 107, 111, 132, 141, 153, 154, 164). The chronic use of a single antibiotic selects for resistance to multiple structurally unrelated antibiotics via linkage of genes on plasmids and transposons (111, 143).

Studies on the impact of NTA use on resistance in land food animals have focused primarily on three bacterial genera—*Enterococcus*, *Escherichia*, and *Campylobacter*—and, to a lesser extent, on *Salmonella* and *Clostridium*. All of the above may be members of the normal gut flora (commensals) of food animals

TABLE 1. Antimicrobials used in food animal production[a]

Antibiotic	Purpose	Antimicrobial class	Spectrum of activity	Use in human medicine	Structurally related antibiotic(s)/antibiotic(s) with shared cross-resistance	Comments[c]
Ardacin	Bovine AGP	Glycopeptides	Gram-positive organisms	No	Vancomycin, teicoplanin	Withdrawn from EU in 1997; not licensed in U.S.
Amoxicillin,[b] ampicillin[b]	Aquaculture, oral treatment of swine colibacillosis, treatment of bovine bacterial enteritis and subclinical mastitis	Aminopenicillins	Moderate	Yes	All penicillins	
Avilamycin	AGP for broilers	Orthosomysins	Gram-positive organisms	No	Everninomycin	Withdrawn from EU; not licensed in U.S.
Avoparcin[b]	AGP	Glycopeptides	Gram-positive organisms	No	Vancomycin, teicoplanin	Withdrawn from EU in 1997; not licensed in U.S.
Bacitracin/zinc bacitracin	AGP for poultry, beef cattle, and swine; control of swine dysentery and bacterial enteritis; control of poultry enteritis	Polypeptides	Gram-positive organisms	Yes (zinc bacitracin)	Actinomycin, colistin, polymyxin B	Withdrawn from EU in 1999; available in U.S.; used in Japan
Bambermycin	AGP for poultry, swine, and cattle	Phosphoglycolipids	Gram-positive organisms	No	Vancomycin, teicoplanin	Withdrawn from EU in 2006; available in U.S.
Carbadox	Control of swine dysentery	Quinoxalines	Gram-positive and -negative organisms	No	Other quinoxolines	Withdrawn due to worker toxicity in EU and Canada; available in U.S. and Mexico
Carbomycin[b]	Respiratory disease prevention and treatment in poultry	Macrolides	Gram-positive organisms	No	Other macrolides	
Chloramphenicol	Aquaculture (oral/bath/injection)	Amphenicols	Broad	Yes	All amphenicols	Chloramphenicol approved in U.S. for dogs only
Colistin	Broiler, swine, and cattle feed	Cyclopolypeptides	Gram-negative organisms	Yes	All polymyxins	Used in Japan
Efrotomycin	AGP for swine	Elfamycins	Gram-positive organisms	No	Other elfamycins only	Not marketed
Enrofloxacin[b]	Therapy for bovine and swine respiratory disease, use in aquaculture (oral/bath)	Fluoroquinolones	Broad	No	All quinolones	Banned for use in poultry by FDA in 2005; not approved for aquaculture in U.S.
Erythromycin[b]	Aquaculture (oral/bath/injection); AGP for poultry, cattle, and swine; therapy for poultry respiratory disease and bovine mastitis	Macrolides	Gram-positive organisms	Yes	Oleandomycin and other macrolides and lincosamides	
Florfenicol	Respiratory disease treatment of cattle and swine	Amphenicols	Broad	No	All amphenicols	
Flumequin[b]	Aquaculture (oral)	Fluoroquinolones	Broad	No	Fluoroquinolones and quinolones	Not approved in U.S.
Furazolidone	Aquaculture (oral/bath)	Nitrofurans	Broad	Yes		Banned in U.S. food animals in 2005
Gentamicin[b]	Therapy for swine colibacillosis and dysentery, prevention of early poultry mortality, turkey egg dip	Aminoglycosides	Gram-positive and -negative organisms	Yes	Other aminoglycosides	
Lasalocid	AGP for cattle, poultry, sheep, and rabbits; coccidiosis prevention in poultry and sheep	Ionophores	Gram-positive organisms	No	Not demonstrated	Approved in EU and U.S.
Lincomycin	AGP for chickens and swine; therapy for swine dysentery, pneumonia, chicken necrotic enteritis, and respiratory disease	Lincosamides	Gram-positive organisms	Rare	Erythromycin and other macrolides and lincosamides, clindamycin	Approved in U.S.
Maduramycin	Poultry coccidiostat	Ionophores	Coccidia, Gram-positive organisms	No	Not demonstrated	Approved in EU and U.S.
Monensin	Bovine AGP; prevention/control of coccidiosis in bovines, poultry, and goats	Ionophores	Coccidia, Gram-positive organisms	No	Not demonstrated	Withdrawn from EU as bovine AGP but authorized as poultry coccidiostat

Neomycin[b]	AGP for swine and poultry; treatment/control of swine enteritis and pneumonia; control of mortality from *E. coli* in turkeys, bovines, swine, sheep, and goats; control of respiratory and other poultry diseases; aquaculture (bath)	Aminoglycosides	Gram-positive and -negative organisms	Yes	Gentamicin and other aminoglycosides	Approved in U.S.
Narasin	Poultry feed coccidiostat, prevention of necrotic enteritis in chickens, AGP for cattle	Ionophores	Coccidia, Gram-positive organisms	No	Not demonstrated	Approved in U.S.
Nourseothricin	Swine AGP	Streptothricins	Gram-negative organisms	No	None	Withdrawn from EU; never used in U.S.
Novobiocin	Treatment of staph infections, treatment and control of fowl cholera, treatment of bovine mastitis	Aminocoumarins	Gram-positive organisms	Yes		
Olaquindox	Swine AGP, control of swine dysentery/enteritis	Quinoxalines	Gram-positive and -negative organisms	No	Other quinoxolines	Withdrawn due to worker toxicity in EU and Canada; available in U.S.
Oleandomycin[b]	Poultry and swine AGP	Macrolides	Gram-positive organisms	Yes	Erythromycin and other macrolides	
Ormetoprim	Poultry AGP, prevention of fowl cholera and other infections	Diaminopyrimidines	Broad	No	Trimethoprim	
Oxolinic acid[b]	Aquaculture (oral)	Quinolones	Broad	No	Other quinolones	Not approved in U.S.
Pristinamycin	AGP	Streptogramins	Gram-positive organisms	Yes	Other streptogramins (virginiamycin, quinupristin/dalfopristin)	
Procaine penicillin[b]	AGP in poultry and swine	Beta-lactams	Gram-positive organisms	Yes	Other beta-lactams	Withdrawn in EU; available in U.S.
Roxarsone	AGP for poultry and swine, poultry coccidiostat, treatment of swine dysentery	Arsenicals	Coccidia	No	Other arsenicals	
Salinomycin	Swine AGP, prevention/control of swine dysentery and porcine intestinal adenomatosis, control of *Clostridium perfringens* in growers	Ionophores	Gram-positive organisms	No	Not demonstrated	Withdrawn from EU
Spiramycin[b]	Swine AGP, treatment of bovine mastitis	Macrolides	Gram-positive organisms	Yes	Erythromycin and other macrolides and lincosamides	AGP use withdrawn from EU in 1999; not approved in U.S.
Streptomycin[b]	Aquaculture (bath)	Aminoglycosides	Broad	Yes	All aminoglycosides	
Sulfonamides	Aquaculture (sulfamerazine [oral] and sulfadimethoxine [oral]), swine AGP (sulfamethazine), chicken AGP (sulfadimethoxine)	Sulfonamides	Broad	Yes	All sulfonamides	Sulfamerazine authorized for U.S. aquaculture, but not marketed
Tetracyclines (oxy- and chlor-)[b]	AGP for poultry, swine, and cattle; treatment and control of multiple livestock diseases; aquaculture (oral/bath/injection); control of fish and lobster disease	Tetracylines	Broad	Yes	All tetracyclines	Withdrawn from EU; authorized in U.S.
Tiamulin	Swine AGP; treatment of swine enteritis, dysentery, and pneumonia	Pleuromutilins	Gram-positive organisms, mycoplasmas, spirochetes	No	Tylosin, erythromycin, and other macrolides	Used for disease prevention and treatment in chickens outside the U.S.
Tylosin[b]	Swine AGP, therapeutic treatment of mastitis	Macrolides	Gram-positive organisms	No	Erythromycin and other macrolides and lincosamides	AGP use withdrawn from EU; available in U.S.
Virginiamycin	AGP for broilers	Streptogramins	Gram-positive organisms	Yes	Quinupristin/dalfopristin and other streptogramins	Withdrawn from EU; available in U.S.

[a] Based on data from references 7, 32, 34, 53, 84, 96, 98, 133, and 162.
[b] Highly important in human medicine or belongs to critically important class of human antimicrobials.
[c] EU, European Union.

but possess the potential to become serious human pathogens. The prospective farm study by Levy in 1975 (111) and studies of others in the following decades clearly demonstrated the selective nature of low-dose, nontherapeutic AGPs on both the pathogenic and commensal flora of food animals such as poultry, swine, and cattle (8, 16, 18, 90, 98, 146, 149). Likewise, in the past decade, studies have demonstrated the selective nature of mass treatment with antimicrobials in aquaculture (36, 62, 84). In the latter, studies have focused on *Aeromonas* pathogens of both fish and humans and the subsequent high-frequency transfer of their resistance plasmids to *E. coli* and *Salmonella* (36).

Aarestrup and Carstensen found that resistance derived from use of one NTA (tylosin) was not confined to swine gut bacteria only but could cross species and appear in staphylococci isolated from the skin. While the conversion of gut enterococci to erythromycin (a related human therapeutic) resistance occurred rapidly (within 1 week) the skin-derived resistant organism *Staphylococcus hyicus* appeared more gradually, escalating to a 5-fold increase over 20 days (5).

The finding of bacterial cross-resistance between NTAs used in food animals and human drugs was aptly demonstrated with avoparcin (an AGP) and its close relative vancomycin (an important human therapeutic) when vancomycin-resistant enterococci (VRE) emerged as a serious human pathogen. A connecting link between resistance in animals and humans was revealed when Bates et al. found avoparcin- and vancomycin-coresistant enterococci in pigs and small animals from two separate farms. Ribotyping methods showed that some of the patterns from farms and sewage exactly matched those of *Enterococcus* spp. from the hospital (24). The structures of the two drugs are similar: they are both members of the glycopeptide family (24).

Since that time, numerous studies have examined the impacts of newer NTAs on the floras of animals. The use of tylosin and virginiamycin in Norwegian swine and poultry led to high prevalences of resistance to both these agents in *Enterococcus faecium* (75% to 82% for tylosin and 49 to 70% for virginiamycin) (1). Avilamycin resistance, while significantly associated with avilamycin use, has been observed on both exposed and unexposed farms and was significantly higher in isolates from poultry than in those from swine, despite its use in both these species (4). These findings suggest that other selective agents may be present in the environment or that substances related to avilamycin were not recognized. As described above, not only the drug choice and amount but also the number of animals treated can affect the consequence of its use.

Other findings suggest that complex ecologic and genetic factors may play a role in perpetuating resistance (63). Resistance (particularly to tetracycline, erythromycin, and ampicillin) has been found inherently in some antibiotic-free animals, (10, 45, 93, 130), suggesting that its emergence is related to other factors, such as diet, animal age, specific farm type, cohort variables, and environmental pressures (26). While Alexander et al. found MDR (tetracycline plus ampicillin resistance) in bacteria in control animals, the strains that emerged after AGP use were not related to these (10). In addition, resistance to tetracycline was higher for a grain-based diet than a silage-based one. Costa et al. found non-AGP-related resistances in enterococci, most likely derived from previous flocks, i.e., the farm environment and the feed source appeared to be responsible for the emergence of the unrelated resistances (45). Khachatryan et al. found an MDR phenotype (streptomycin, sulfonamide, and tetracycline [SSuT] resistance phenotype) propagated by oxytetracycline in a feed supplement, but upon removal of the drug, the phenotype appeared to be maintained by some unknown component of the unmedicated feed supplement, possibly one that selects for another gene that is linked to a plasmid bearing the SSuT resistance phenotype (100). The persistence may also relate to the stability of the plasmid in its host and the fact that expression of tetracycline resistance is normally silent until it is induced by tetracycline. Thus, the energy demands exerted on the host by tetracycline resistance are lower. One can conclude that removal of the antibiotic may not lead to rapid loss of the resistant strain or plasmid.

EFFECTS OF BANNING GROWTH PROMOTANTS IN ANIMAL FEEDS IN EUROPE

One of the first bans on AGP use was that imposed on tetracycline by the European Common Market in the mid-1970s (39). Prior to institution of the ban in the Netherlands (1961 to 1974), Van Leeuwen et al. had tracked a rise in tetracycline-resistant *Salmonella* spp. Following the ban, however, they observed a decline in tetracycline resistance in both swine and humans (150).

More than 10 years have passed since the final 1999 European Union ban, during which a plethora of studies from multiple European countries, Canada, and Taiwan have examined antibiotic use and resistance trends subsequent to the removal of key AGP drugs, especially avoparcin, and the consequences on vancomycin resistance in *Enterococcus* (7, 15, 17, 21, 29, 30, 76, 85, 97, 102, 107, 121, 148, 150, 156a). Its structural relationship to and cross-resistance with avoparcin render vancomycin a drug of prime interest for determining the impact of avoparcin in triggering and promoting resistance in human infection.

Avoparcin

In many European countries, the use of avoparcin as a feed additive led to frequent isolation of VRE from farm animals and healthy ambulatory people (3, 18, 102). Since the emergence of the enterococcus as a major MDR pathogen, vancomycin has evolved as a key therapy, often as the drug of last resort. Following the 1995 ban on avoparcin, several investigators reported a decline in animal VRE. In Denmark, frequencies peaked at 73 to 80% and fell to 5 to 6% (7, 18) in poultry. In Italy, VRE prevalence in poultry carcasses and cuts decreased from 14.6% to 8% within 18 months of the 1997 ban (121), and in Hungary, a 4-year study showed not only a decline in prevalence of VRE among slaughtered cattle, swine, and poultry after removal of avoparcin but also a decrease in vancomycin MICs (97). In surveillance studies both before and after the German ban in 1996, Klare et al. showed a high frequency of VRE in 1994, followed by a very low frequency of just 25% of poultry food products in 1999 (102). Similar declines were reported in broiler farms following a ban on avoparcin in Taiwan in 2000 (107).

A dramatic reduction in human carriage of VRE also followed the ban on avoparcin. Parallel surveillances of the gut floras of healthy ambulatory people showed that VRE colonization in Germany declined from 13% in 1994 to 4% in 1998 (102), and in Belgium, it declined from 5.7% in 1996 to ~0.7% in 2001 (68).

Virginiamycin and Other Antibiotics

Increased virginiamycin use in Danish broilers during the mid-1990s correlated with a rise in resistant *E. faecium* prevalence, from 27% to ~70% (7). Following the ban, resistance declined to 34% in 2000. Likewise, in Denmark, the 1998 ban on the use of tylosin in swine resulted in a decline in erythromycin (a structurally related macrolide) resistance, from 66% to 30% (49). Avilamycin use in 1995 and 1996 increased resistance in broiler *E. faecium* strains, from 64% to 77%, while declining applications after 1996 lowered the prevalence to 5% in 2000 (7).

Some of these studies revealed a genetic linkage between bacterial macrolide and glycopeptide resistances in swine, such that neither resistance declined in prevalence until both avoparcin (a glycopeptide) and tylosin (a macrolide) use was limited. With a reduction in tylosin use, the prevalence of glycopeptide-resistant enterococci fell to 6% and macrolide resistance fell from nearly 90% to 47% in *E. faecium* and to 28% in *Enterococcus faecalis* (7). Notably, the first report of transfer of vancomycin resistance from *Enterococcus* to *Staphylococcus aureus* was demonstrated in laboratory mice because of its linkage to macrolide resistance on the same plasmid (119).

One concern voiced following the banning of NTAs was that the incidence of disease in animals would rise and result in a parallel increase in therapeutic use. This has become the subject of some debate. Some countries encountered rises in necrotic enteritis in chickens and colitis in swine soon after the institution of AGP bans (33, 159). In Norway, an abrupt increase in necrotizing enteritis (NE) in poultry broilers was reported following the removal of avoparcin, with a coincident rise in antibiotic therapy. When the ionophore feed additive narasin was approved, NE declined once again (77). It was concluded that the ban on avoparcin consumption produced a negligible effect on the need for antibiotic therapy (76). Likewise, in Switzerland, Arnold et al. reported a postban increase in overall antibiotic quantities used in swine husbandry but observed a stable therapy intensity (prescribed daily dose) (15). By 2003, total animal use of antibiotics in Denmark, Norway, and Sweden had declined by 36%, 45%, and 69%, respectively (76). The most thorough postban analysis of this phenomenon comes from Denmark. In a careful review of swine disease emergence, animal production, and antibiotic use patterns over the years 1992 to 2008, Aarestrup et al. reported no overall deleterious effects from the ban on finishers and weaners in the years 1998 and 2000, respectively. Despite an increase in total therapeutic antibiotic consumption immediately following the ban, no lasting negative effects were detected on mortality rate, average daily weight gain, or animal production (6). Moreover, even if therapeutic use increased, the numbers of animals treated would be reduced compared to those with growth promotion use, so selection density would be decreased (113).

In summary, the in-depth, retrospective analyses in Denmark shed a different perspective on postban concerns over increased therapeutic use. Over time, it appears that the negative after-effects of the ban have waned. As farmers modified their animal husbandry practices to accommodate the loss of banned NTAs, these disease outbreaks became less prominent. Improved immunity and reduced infection rates led to fewer demands for therapeutic antibiotics.

Interestingly, recent studies have shown that the original beneficial aspects observed with AGP use (i.e., weight gain and feed efficiency) appear to have diminished, although the results are mixed and depend upon the kind of animals and type of antibiotic involved. Diarra et al. found no effect on body weight or feed intake in poultry from five different AGPs, and feed efficiency was improved with penicillin only (52). In contrast, Dumonceaux et al. reported a significantly increased body weight (10%) and a 7% increase in feed efficiency with the AGP virginiamycin, but only for the first 15 days (55a). In short, improved farming practices and breeding programs, which may include reduced animal density, better hygiene, targeted therapy, and the use of enzymes, prebiotics, probiotics, and vaccines, appear to have at least partially replaced the beneficial aspects of antibiotic growth promoters (27, 158, 160).

EVIDENCE FOR ANIMAL-TO-HUMAN SPREAD OF ANTIBIOTIC RESISTANCE

Any use of antibiotics will select for drug-resistant bacteria. Among the various uses for antibiotics, low-dose, prolonged courses of antibiotics among food animals create ideal selective pressures for the propagation of resistant strains. Spread of resistance may occur by direct contact or indirectly, through food, water, and animal waste application to farm fields. It can be augmented greatly by the horizontal transfer of genetic elements such as plasmids via bacterial mating (conjugation). We summarize here the evidence for animal-to-human transfer of resistant bacteria on farms using antibiotics for treatment and/or nontherapeutic use.

Resistance Acquisition through Direct Contact with Animals

Farm and slaughterhouse workers, veterinarians, and those in close contact with farm workers are directly at risk of being colonized or infected with resistant bacteria through close contact with colonized or infected animals (Table 2). Although this limited transmission does not initially appear to pose a population-level health threat, occupational workers and their families provide a conduit for the entry of resistance genes into the community and hospital environments, where further spread into pathogens is possible (118, 155).

The majority of studies examining the transmission of antibiotic-resistant bacteria from animals to farm workers document the prevalence of resistance among farmers and their contacts or among farmers before and after the introduction of antibiotics at their workplace. Direct spread of bacteria from animals to people was first reported by Levy et al., who found

TABLE 2. Key evidence for transfer of antibiotic resistance from animals to humans

Transfer type	Species tracked	Animal host(s)	Recipient host(s)	Resistance transferred	Evidence	Reference
Human colonization via direct or indirect animal contact	*E. coli*	U.S. chickens	Animal caretakers, farm family	Tetracycline	Following introduction of tetracycline on a farm, resistant *E. coli* strains with transferable plasmids were found in caretakers' gut floras, with subsequent spread to the farm family	111
	S. aureus, *Streptococcus* spp., *E. coli* and other enterobacteria	French swine	Swine farmers	Erythromycin, penicillins, nalidixic acid, chloramphenicol, tetracycline, streptomycin, cotrimoxazole	Phenotypic antibiotic resistance was significantly higher in the commensal floras (nasal, pharyngeal, and fecal) of swine farmers than in those of nonfarmers	16
	E. coli	U.S. chickens	Poultry workers	Gentamicin	Increase in phenotypic gentamicin resistance in workers through direct contact with chickens receiving gentamicin prophylactically	126
	E. coli	Chinese swine and chickens	Farm workers	Apramycin (not used in human medicine)	Detection of *aac(3)-IV* apramycin resistance gene in humans, with 99.3% homology to that in animal strains	164
	MRSA ST398	Dutch veal calves	Veal farmers	MDR	Human nasal carriage of the *mecA* gene was strongly associated with (i) greater intensity of animal contact and (ii) the number of MRSA-positive animals; animal carriage was related to animal antibiotic treatment	78
Human infection via direct or indirect animal contact	*Salmonella* Newport	Beef cattle (ground beef) receiving chlortetracycline AGP	*Salmonella*-infected patients with diarrhea	Ampicillin, carbenicillin, tetracycline	Direct genetic tracking of resistance plasmid from hamburger meat to infected patients	87
	E. coli	German swine (ill)	Swine farmers, family members, community members, UTI patients	Streptothricin	Identification of transferable resistance plasmids found only in human gut and UTI bacteria when nourseothricin was used as swine AGP	90
	E. coli, *Salmonella enterica* (serovar Typhimurium)	Belgian cattle (ill)	Hospital inpatients	Apramycin, gentamicin	Plasmid-based transfer of *aac(3)-IV* gene bearing resistance to a drug used only in animals (apramycin)	42
	Enterococcus faecium	Danish swine and chickens	Hospital patients with diarrhea	Vancomycin	Clonal spread of *E. faecium* and horizontal transmission of the *vanA* gene cluster (Tn*1546*) found between animals and humans	80
	E. coli	Spanish chickens (slaughtered)	Bacteremic hospital patients	Ciprofloxacin	Multiple molecular and epidemiological typing modalities demonstrated avian source of resistant *E. coli*	95

the same tetracycline-resistant *E. coli* strains in the gut flora of chicken caretakers as in the chickens receiving tetracycline-laced feed (112). The observation extended to the farm family as well and showed an increased frequency of tetracycline-resistant and multidrug-resistant *E. coli* after several months of use of AGP-laden feed. Studies such as this (which examined a variety of antibiotic classes and assorted pathogens) have consistently shown a higher prevalence of resistant gut bacteria among farm workers than in the general public or among workers on farms not using antibiotics (16, 90, 98, 149).

While gentamicin is not approved for growth promotion in the United States, it remains the most commonly used antibiotic in broiler production, being employed for prevention of early poultry mortality (115). A revelatory 2007 study found that the risk for carrying gentamicin-resistant *E. coli* was 32 times higher in poultry workers than in other members of the community: half of all poultry workers were colonized with gentamicin-resistant *E. coli*, while just 3% of nonpoultry workers were colonized. Moreover, the occupationally exposed population was at significantly greater risk for carriage of multidrug-resistant bacteria (126).

New gene-based methods of analysis provide even stronger evidence for the animal origin of bacteria that colonize or infect humans. Homologous relationships between bacterial resistance genes in humans and farm animals have been identified most commonly for food-borne pathogens such as *Escherichia coli* and *Salmonella* (see below) but have also been recorded for various species of *Enterococcus* and for methicillin-resistant *Staphylococcus aureus* (MRSA). Zhang and colleagues found *E. coli* strains resistant to apramycin (an antibiotic used in agriculture but not in human medicine) in a study of Chinese farm workers. All farms in the study that used apramycin as an AGP had workers that carried apramycin resistance genes. The same resistance gene, *aac(3)-IV*, was present in each swine, poultry, and human isolate, with some resistance profiles also matching across species (164). A group of French scientists found the same resistance gene [*aac(3)-IV*] in cow, pig, and human *E. coli* strains that bore resistance to apramycin and gentamicin (42). In another study, similar resistance patterns and genes were detected in *E. faecalis* and *E. faecium* strains from humans, broilers, and swine in Denmark (2). Lee sampled MRSA isolates from cattle, pigs, chickens, and people in Korea and found that 6 of the 15 animal isolates containing *mecA* (the gene responsible for methicillin resistance in *S. aureus*) were identical to human isolates (108).

Antibiotic Resistance Transmission through the Food Chain

Consumers may be exposed to resistant bacteria via contact with or consumption of animal products—a far-reaching and more complex route of transmission. There is undeniable evidence that foods from many different animal sources and in all stages of processing contain abundant quantities of resistant bacteria and their resistance genes. The rise of antibiotic-resistant bacteria among farm animals and consumer meat and fish products has been well documented (36, 108, 122, 162). Demonstrating whether such reservoirs of resistance pose a risk to humans has been more challenging as a consequence of the complex transmission routes between farms and consumers and the frequent transfer of resistance genes among host bacteria. Such correlations are becoming more compelling with the advent of molecular techniques which can demonstrate the same gene (or plasmid) in animal or human strains, even if the isolates are of different species.

For example, Alexander et al. showed that drug-resistant *Escherichia coli* was present on beef carcasses after evisceration and after 24 h in the chiller and in ground beef stored for 1 to 8 days (9). Others isolated ciprofloxacin-resistant *Campylobacter* spp. from 10% to 14% of consumer chicken products (79, 137). MRSA has been reported to be present in 12% of beef, veal, lamb, mutton, pork, turkey, fowl, and game samples purchased in the consumer market in the Netherlands (50), as well as in cattle dairy products in Italy (120). Likewise, extensive antibiotic resistance has been reported for bacteria, including human pathogens, from farmed fish and market shrimp (56, 84, 140).

Some of the antibiotic resistance genes identified in food bacteria have also been identified in humans, providing indirect evidence for transfer by food handling and/or consumption. In 2001, Sorensen et al. confirmed the risk of consuming meat products colonized with resistant bacteria, showing that glycopeptide-resistant *Enterococcus faecium* of animal origin ingested via chicken or pork lasted in human stool for up to 14 days after ingestion (139). Donabedian et al. found overlap in the pulsed-field gel electrophoresis (PFGE) patterns of gentamicin-resistant isolates from humans and pork meat as well as in those of isolates from humans and grocery chicken (55). They identified that when a gene conferring antibiotic resistance was present in food animals, the same gene was present in retail food products from the same species. Most resistant enterococci possessed the same resistance gene, *aac(6′)-Ie-aph(2″)-Ia* (55).

Emergence of Resistance in Human Infections

There is likewise powerful evidence that human consumption of food carrying antibiotic-resistant bacteria has resulted, either directly or indirectly, in acquisition of antibiotic-resistant infections (Table 2). In 1985, scientists in Arizona traced an outbreak of multidrug-resistant *Salmonella enterica* serovar Typhimurium, which included the death of a 72-year-old woman, to consumption of raw milk. Isolates from most patients were identical to the milk isolates, and plasmid analysis showed that all harbored the same resistance plasmid (145). A 1998 *S.* Typhimurium outbreak in Denmark was caused by strains with nalidixic acid resistance and reduced fluoroquinolone susceptibility. PFGE revealed that a unique resistance pattern was common to *Salmonella* strains from all patients, two sampled pork isolates, the swine herds of origin, and the slaughterhouse (118).

Samples from gentamicin-resistant urinary tract infections (UTIs) and fecal *E. coli* isolates from humans and food animal sources in China showed that 84.1% of human samples and 75.5% of animal samples contained the *aaaC2* gene for gentamicin resistance (86). Johnson et al. used PFGE and random amplified polymorphic DNA (RAPD) profiles of fluoroquinolone-resistant *E. coli* strains in human blood and fecal samples and in slaughtered chickens to determine that the two were virtually identical to resistant isolates from geographically linked chickens. Drug-susceptible human *E. coli* strains, however, were genetically distinct from poultry bacteria, suggesting that the ciprofloxacin-resistant *E. coli* strains in humans were imported from poultry rather than originating from susceptible human *E. coli* (94, 95).

Other reports demonstrate a broader linkage of resistance genes through the farm-to-fork food chain. A resistance-specifying bla_{CMY} gene was found in all resistant isolates of *Salmonella enterica* serotype Newport originating from humans, swine, cattle, and poultry. The host plasmid, which conferred resistance to nine or more antimicrobials, was capable of transmission via conjugation to *E. coli* as well (165). An observed homology between CMY-2 genes in cephalosporin-resistant *E. coli* and *Salmonella* suggested that plasmids conferring resistance had moved between the two bacterial species. The authors found higher rates of CMY-2 in strains from animals than in those from humans, supporting an animal origin for the human pathogen (161). A 2000 study found matching PFGE profiles among vancomycin-resistant *Enterococcus faecium* isolates from hospitalized humans, chickens, and pigs in Denmark. Molecular epidemiology studies have also linked tetracycline resistance genes from *Aeromonas* pathogens in a hospital effluent to *Aeromonas* strains from a fish farm (127). These results support the clonal spread of resistant isolates among different populations (80).

Chronologic studies of the emergence of resistance across the food chain also strongly imply that reservoirs of resistance among animals may lead to increased resistance in consumers of animal food products. Bertrand et al. chronicled the appearance of the extended-spectrum beta-lactamase (ESBL) gene *CTX-M-2* in *Salmonella enterica* in Belgium. This resistance element was identified first in poultry flocks and then in poultry meat and, finally, human isolates (28). A recent Canadian study also noted a strong correlation between ceftiofur-resistant bacteria (the pathogen *Salmonella enterica* serovar Heidelberg and the commensal *E. coli*) from retail chicken and human infections across Canada. The temporary withdrawal of ceftiofur injection from eggs and chicks dramatically reduced resistance in the chicken strains and the human *Salmonella* isolates, but the trend reversed when the antibiotic use was subsequently resumed (57).

In three countries (United States, Spain, and the Netherlands), a close temporal relationship has been documented between the introduction of fluoroquinolone (sarafloxacin and enrofloxacin) therapy in poultry and the emergence of fluoroquinolone-resistant *Campylobacter* in human infections. An 8- to 16-fold increase in resistance frequency was observed—from 0 to 3% prior to introduction to ~10% in the United States and the Netherlands and to ~50% in Spain—within 1 to 3 years of the licensure (61, 128, 137). In the Netherlands, this frequency closely paralleled an increase in resistant isolates from retail poultry products (61), while the U.S. study used molecular subtyping to demonstrate an association between the clinical human isolates and those from retail chicken products (137).

It is now theorized, from molecular and epidemiological tracking, that the resistance determinants found in salmonella outbreaks (strain DT104) in humans and animals in Europe and the United States likely originated in aquaculture farms of the Far East. The transmissible genetic element contains the florfenicol gene (*floR*) and the tetracycline class G gene, both of which were traced to *Vibrio* fish pathogens (*Vibrio damsel* and *Vibrio anguillarum*, respectively). Both drugs are used extensively in aquaculture (36).

In the above examples, the link to nontherapeutic antibiotic use in the farm animals is still circumstantial and largely implied, often because the authors do not report any statistics on farm use of antibiotics. Interpreting these studies is also difficult because of the widespread resistance to some drugs in bacteria of both animals and humans and the ubiquitous nature of resistance genes. Moreover, the same farmer may use antibiotics for both therapeutic and nontherapeutic purposes.

The complexities of the modern food chain make it challenging to perform controlled studies that provide unequivocal evidence for a direct link between antibiotic use in animals and the emergence of antibiotic resistance in food-borne bacteria associated with human disease. While this concrete evidence is limited, a small number of studies have been able to link antibiotic-resistant infection in people with bacteria from antibiotic-treated animals. While not necessarily involving NTAs, these studies substantiate the considerable ease with which bacteria in animals move to people. For example, a multidrug-resistant *Salmonella enterica* strain in a 12-year-old Nebraska boy was traced to his father's calves, which had recently been treated for diarrhea. Isolates from the child and one of the cows were determined to be the same strain of CMY-2-mediated ceftriaxone-resistant *S. enterica* (69). It is now believed that the 1992 multiresistant *Vibrio cholerae* epidemic in Latin America was linked to the acquisition of antibiotic-resistant bacteria arising from heavy antibiotic use in the shrimp industry of Ecuador (13, 156).

By comparing the plasmid profiles of MDR *Salmonella* Newport isolates from human and animal sources, Holmberg et al. provided powerful evidence that salmonella infections in 18 persons from 4 Midwestern states were linked directly to the consumption of hamburger meat from cattle fed subtherapeutic chlortetracycline. A plasmid which bore tetracycline and ampicillin resistance genes was present in the organisms causing serious illness in those persons who ate the hamburger meat and who were also consuming penicillin derivatives for other reasons (87).

One of the most compelling studies to date is still Hummel's tracking of the spread of nourseothricin resistance, reported in 1986. In Germany, nourseothricin (a streptogramin antibiotic) was used solely for growth promotion in swine. Resistance to it was rarely found and was never plasmid mediated. Following 2 years of its use as a growth promotant, however, resistance specified by plasmids appeared in *E. coli*, not only from the treated pigs (33%) but also in manure, river water, food, and the gut floras of farm employees (18%), their family members (17%), and healthy outpatients (16%) and, importantly, in 1% of urinary tract infections (90). Ultimately, the resistance determinant was detected in *Salmonella* and *Shigella* strains isolated from human diarrhea cases (146).

The movement of antibiotic resistance genes and bacteria from food animals and fish to people—both directly and indirectly—is increasingly reported. While nontherapeutic use of antibiotics is not directly implicated in some of these studies, there is concern that pervasive use of antimicrobials in farming and widespread antimicrobial contamination of the environment in general may be indirectly responsible. For instance, within the past 5 years, MRSA and MDR *Staphylococcus aureus* have been reported in 25 to 50% of swine and veal calves in Europe, Canada, and the United States (51, 78, 101, 114). Graveland et al. noted that this frequency was higher in veal calves fed antibiotics (78). Studies also show that colonization among farmers correlates significantly with MRSA colonization among their livestock (78, 101, 114, 138). In the Netherlands, colonization of swine farmers was found to be more than 760 times greater than that of patients admitted to Dutch hospitals (155). In a study of nasal swabs from veal and veal calf growers, family members, and employees at 102 veal calf farms in the Netherlands, Graveland et al. found that human MRSA sequence type ST398 carriage among the farmers was strongly associated with the degree of animal contact and the frequency of MRSA-colonized animals on the farm. When <20% of calves were carriers, the estimated prevalence in humans was ~1%—similar to that in the general public. With >20% carriage in calves, the prevalence in humans was >10% (78).

Recently, MRSA ST398 has appeared in the community. A Dutch woman without any known risk factors was admitted to a hospital with endocarditis caused by MRSA ST398, suggesting a community reservoir which passed on to people (58). Voss et al. demonstrated animal-to-human and human-to-human transmission of MRSA between a pig and pig farmer, among the farmer's family members, and between a nurse and a patient in the hospital. All isolates had identical random amplified polymorphic DNA profiles (155). Examples of similar MRSA strains among animals and people are mounting (82, 108, 147, 151, 152, 163).

ADDRESSING KNOWLEDGE GAPS: RESERVOIRS OF ANTIBIOTIC RESISTANCE

Historically, considerable attention has been focused on a very small minority of bacterial species that actually cause disease. However, a vast "sea" of seemingly innocuous commensal and environmental bacteria continuously and promiscuously exchange genes, totally unnoticed (116). A staggeringly diverse group of species maintain a large capacity for carrying and mobilizing resistance genes. These bacteria constitute a largely ignored "reservoir" of resistance genes and provide multiple complex pathways by which resistance genes propagated in animals can directly, or more likely indirectly, make their way over time into human pathogens via food, water, and sludge and manure applied as fertilizer. Horizontal (or lateral) gene transfer studies have identified conjugal mating as the most common means of genetic exchange, and there appear to be few barriers that prevent this gene sharing across a multitude of dissimilar genera (104).

While colonic bacteria have received much focused study, water environments such as aquaculture, sludge, freshwater, and wastewaters are prime sites for gene exchange but have been examined minimally for their roles as "mixing pots" and transporters of genes from bacteria of antibiotic-fed animals to humans (116). Aside from the already described impacts of NTA use on bacterial resistance, food animal use of NTAs has broad and far-reaching impacts on these environmental bacteria. It is estimated that 75% to 90% of antibiotics used in food animals are excreted, largely unmetabolized, into the environment (43, 105). Antibiotics or resistant bacteria have been detected in farm dust (81), the air currents inside and emanating from swine feeding operations (41, 72, 129), the groundwater associated with feeding operations (31, 37), and the food crops of soils treated with antibiotic-containing manure (54). This leaching into the environment effectively exposes countless environmental organisms to minute quantities of antibiotic—enough to select bacteria with resistance mutations to promote the emergence and transfer of antibiotic resistance genes among diverse bacterial types (104). The potentially huge impact of all these residual antibiotics on the environmental bacteria that are directly or indirectly in contact with humans has scarcely been examined.

The multiple pathways and intricacies of gene exchange have so far thwarted attempts to qualitatively or quantitatively track the movement of these genes *in vivo*, and thus we are left with minimal direct evidence for linking resistance in animals to that in humans. With extensive gene movement between disparate hosts, it is less likely that the same bacterial hosts will be found in animals and humans and more probable that only the resistance genes themselves will be identifiable in the final pathogens that infect humans. Even these may be altered in their journey through multiple intermediate hosts (161) (Fig. 1). Mounting evidence exists in reports of complex gene "cassettes" which accumulate resistance genes and express multidrug resistance (106, 125).

A few investigators have undertaken the challenging task of developing mathematical models in order to predict the impacts of NTAs on human disease (12, 19, 20, 46, 91, 99, 134, 135). Models can be very useful in attempting to define the types of diverse data sets that are seen in this field. Some explore the entire "farm-to-fork" transmission process, while others tackle only portions of this extremely complex chain or adopt a novel backwards approach which looks first at human infections and then calculates the fraction that are potentially caused by NTA use in animals. Most models are deliberately simplified and admittedly omit many aspects of transmission and persistence. Moreover, current models are frequently based on multiple assumptions and have been challenged on the basis of certain shortcomings, such as limitation to single pathogens only, the determination of lethality while ignoring morbidity, and dependence on estimates of probabilities (19). Chief among these, however, is the lack of a complete understanding of the contribution made by commensals, which may play an important role in augmenting the link between animals and humans. Some models are driven by findings of dissimilar strains in animals and humans and therefore arrive at very low probabilities for a causal link between the two (47). A finding of dissimilar strains, however, overlooks two possibilities. First, it does not exclude the existence of small subpopulations of homologous strains that have gone undetected within the gut floras of animals. These may have been amplified temporarily by antibiotic selection and transferred their mobile genetic elements in multiple complex pathways. Subsequently, they may have declined to nondetectable levels or merely been outcompeted by other variants. Second, it overlooks dissimilarities that evolve as genes and their hosts migrate in very complex ways through the environment. Figure 1 illustrates the difficulties in tracking a resistance gene, since these genes are frequently captured in bacteria of different species or strains

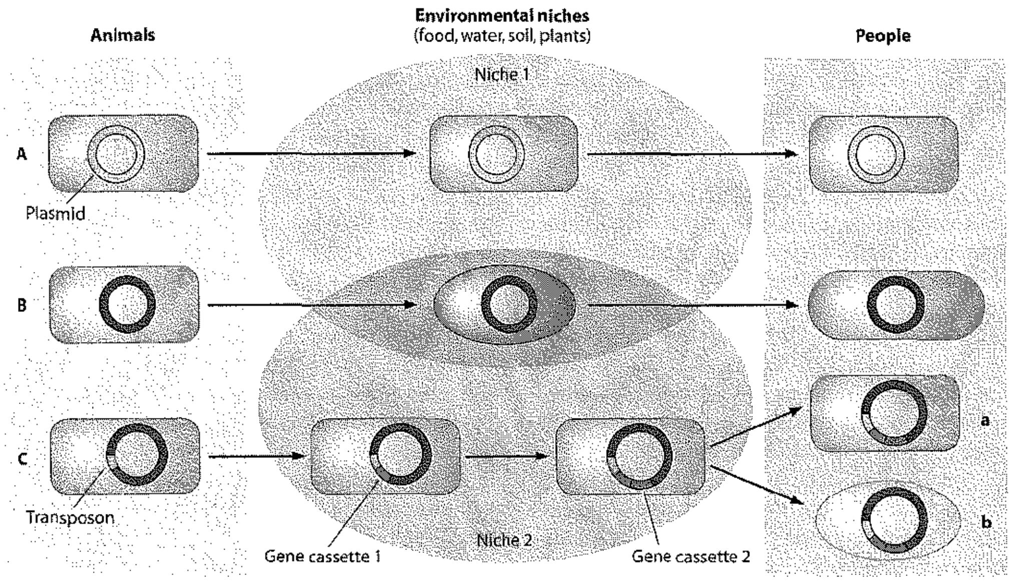

FIG. 1. Several scenarios may present themselves in the genetic transport that occurs as bacteria migrate from animal to human environments. (A) The same host and its indigenous genes in animals are transported unchanged to humans, with a resulting 100% match of the bacterial strain. (B) The genetic structure passes through one or more different hosts, ending in a new host (humans), with a resulting 100% match of DNA. (C) The host and its plasmid-borne genes pass through the environment, picking up gene cassettes en route, with a resulting 100% match for the host only (a) or a low-% match for DNA only (b). In both examples, the plasmid core remains the same.

which no longer resemble the original host. Over time, even the genes themselves may undergo mutations or become entrapped in gene cassettes that alter their genetic landscape. State-of-the-art technology and thoughtful investigation are often necessary to identify and track the actual strains that link animals and humans. These are facets of modeling that have yet to be explored, and obtaining direct evidence for the origins of specific genes can be highly challenging.

In general, the weaknesses of present models lie in their simplicity and the lack of crucial knowledge of microbial loads at each stage of the "farm-to-fork" transmission chain. Many of the available studies that examine links between animals and humans suffer from a failure to examine the antibiotic use practices for the farm animals they investigate. More powerful evidence could have accumulated that would aid in modeling efforts if data on the quantities and uses of farm antibiotics had been reported. These oversights are often due to the lack of registries that record and report the utilization of antibiotics on food animal farms. It is widely advocated that surveillance studies of resistance frequencies at all levels of the transmission chain would aid greatly in reducing our knowledge deficits and would help to inform risk management deliberations (23, 34). A number of localized and international surveillance systems exist for the tracking of human pathogens. In the United States, the National Antimicrobial Resistance Monitoring System (NARMS) has become instrumental in the monitoring of resistance trends in pathogens found in food animals, retail meats, and humans (73). However, at the level of commensals, resistance monitoring is still in its infancy. The Reservoirs of Antibiotic Resistance (ROAR) database (www.roarproject.org) is a fledgling endeavor to promote the accumulation of data that specifically focus on commensal and environmental strains as reservoirs of antibiotic resistance genes. With advances in detection at the genetic level, the potential for tracking the emergence and spread of horizontally transmissible genes is improving rapidly. By capturing geographic, phenotypic, and genotypic data from global isolates from animal, water, plant, and soil sources, the ROAR project documents the abundance, diversity, and distribution of resistance genes and utilizes commensals as "barometers" for the emergence of resistance in human pathogens.

CONCLUSIONS

Data gaps continue to fuel the debate over the use of NTAs in food animals, particularly regarding the contribution and quantitation of commensal reservoirs of resistance to resistance in human disease. Nonetheless, it has been argued reasonably that such deficits in surveillance or indisputable demonstrations of animal-human linkage should not hinder the implementation of a ban on the use of nontherapeutic antibiotics (23). Food animals produce an immense reservoir of resistance genes that can be regulated effectively and thus help to limit the negative impacts propagated by this one source. In the mathematical model of Smith et al., which specifically evaluates opportunistic infections by members of the commensal flora, such as enterococci, it was concluded that restricting antibiotic use in animals is most effective when antibiotic-resistant bacteria remain rare. They suggest that the timing of regulation is critical and that the optimum time for regulating animal antibiotic use is before the resistance problem arises in human medicine (134).

A ban on nontherapeutic antibiotic use not only would help to limit additional damage but also would open up an opportunity for better preservation of future antimicrobials in an era when their efficacy is gravely compromised and few new ones are in the pipeline. Although the topic has been debated for several decades without definitive action, the FDA has recently made some strides in this direction. Officially, the organization now supports the conclusion that the use of medically important antimicrobials for nontherapeutic use in food animal production does not protect and promote public health (131). Although not binding, a guidance document was released in 2010 that recommended phasing in measures that would limit use of these drugs in animals and ultimately help to reduce the selection pressures that generate antimicrobial resistance (66).

The Danish experience demonstrated that any negative disease effects resulting from the ban of NTAs were short-lived and that altering animal husbandry practices could counter expected increases in disease frequency (6). For aquaculture, also, it has been demonstrated that alternative processes in industry management can be instituted that will reduce antibiotic use without detrimental financial effects (141). Still, it has been argued by some in animal husbandry that the different situation in the United States will result in increased morbidity and mortality, projected to cost $1 billion or more over 10 years. Again, however, the Danish postban evaluation found that costs of production increased by just 1% for swine and were largely negligible for poultry production due to the money saved on antibiotics themselves. Models also showed that Danish swine production decreased by just 1.4% (1.7% for exports), and poultry production actually increased, by 0.4% (0.5% for exports) (158). Such calculations still fail to consider the negative externalities that are added by the burden of antibiotic resistance and the antibiotic residue pollution generated by concentrated animal feeding operations.

Opponents of restriction of NTA use argue that a comprehensive risk assessment is lacking, but such an analysis is impossible without the kind of data that would come out of surveillance systems. Although surveillance systems have been advocated repeatedly (23, 70), such systems are sparse and extremely limited in their scope.

In 2002, working with the accumulated evidence and an assessment of knowledge deficits in the area of animal antibiotic use, the APUA developed a set of guidelines that are still viable today and can be used to guide both policy and research agendas. In summary, APUA recommended that antimicrobials should be used only in the presence of disease, and only when prescribed by a veterinarian; that quantitative data on antimicrobial use in agriculture should be made available; that the ecology of antimicrobial resistance in agriculture should be a research priority and should be considered by regulatory agencies in assessing associated human health risks; and that efforts should be invested in improving and expanding surveillance programs for antimicrobial resistance. Suitable alternatives to NTAs can be implemented, such as vaccination, alterations in herd management, and other changes, such as targeted use of antimicrobials with a more limited dosage and duration so as not to select for resistance to critical human therapeutics (23).

There is no doubt that human misuse and overuse of antibiotics are large contributors to resistance, particularly in relation to bacteria associated with human infection. Interventions in medical settings and the community are clearly needed to preserve the efficacy of antibiotics. Efforts in this area are being pursued by the Centers for Disease Control and Prevention, the Alliance for the Prudent Use of Antibiotics, the American Medical Association, the American Academy of Pediatrics, the Infectious Diseases Society of America, and other professional groups. Still, given the large quantity of antibiotics used in food animals for nontherapeutic reasons, some measure of control over a large segment of antibiotic use and misuse can be gained by establishing guidelines for animals that permit therapeutic use only and by then tracking use and health outcomes.

The current science provides overwhelming evidence that antibiotic use is a powerful selector of resistance that can appear not only at the point of origin but also nearly everywhere else (104). The latter phenomenon occurs because of the enormous ramifications of horizontal gene transfer. A mounting body of evidence shows that antimicrobial use in animals, including the nontherapeutic use of antimicrobials, leads to the propagation and shedding of substantial amounts of antimicrobial-resistant bacteria—both as pathogens, which can directly and indirectly infect humans, and as commensals, which may carry transferable resistance determinants across species borders and reach humans through multiple routes of transfer. These pathways include not only food but also water and sludge and manure applications to food crop soils. Continued nontherapeutic use of antimicrobials in food animals will increase the pool of resistance genes, as well as their density, as bacteria migrate into the environment at large. The lack of species barriers for gene transmission argues that the focus of research efforts should be directed toward the genetic infrastructure and that it is now imperative to take an ecological approach toward addressing the impacts of NTA use on human disease. The study of animal-to-human transmission of antibiotic resistance therefore requires a greater understanding of the genetic interaction and spread that occur in the larger arena of commensal and environmental bacteria.

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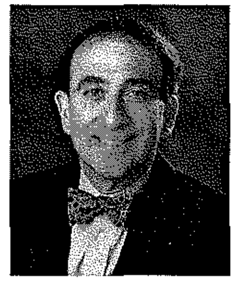

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Ministry of Food, Agriculture and Fisheries
Danish Veterinary and Food Administration

CHECK AGAINST DELIVERY

12 July 2010

Danish testimony on the July 14th Hearing about Antibiotic Resistance in the Livestock Industry organised by the Subcommittee on Health

By Per Henriksen, DVM, PhD, Head of Division for Chemical Food Safety, Animal Welfare and Veterinary Medicinal Products, The Danish Veterinary and Food Administration

Thank you, Mr. Chairman, Mr. Ranking Member, and Members of the Subcommittee, for inviting me to testify.

As a representative of the Danish government I am aware that the use of antibiotic growth promoters is a contentious issue here in the US and that Denmark is often mentioned in the debate. Against this background I wish to emphasize that the Danish government is not represented here today to advocate for or against any specific legislative proposals. However, we are an open nation, willing to share our experience when requested and therefore we have accepted your kind invitation.

I have submitted five fact sheets for the record, and with the Subcommittee's indulgence, I will therefore shorten my remarks to allow for your questions.

....

Denmark is a major livestock producer in Europe, and the worlds' largest exporter of pork. The Danish livestock production is highly industrialised, intensive and applies modern management principles. Due to the significance for the Danish economy the National Government takes the competitiveness of the Danish farmers seriously.

Treatment with antibiotics is in many cases essential for human and animal health and an uncritical use of antibiotics can lead to several antibiotics becoming ineffective.

Because antimicrobial resistance can be transferred between bacteria, regardless of whether the bacteria are pathogenic or not, the development of antimicrobial resistance in any kind of bacteria can constitute a problem.

It is a fact that antimicrobial resistance can be transferred from animals to humans by consumption of meat and every year also Denmark experience human outbreaks caused by consumption of meat, contaminated with antimicrobial resistant bacteria.

A ban on antimicrobial growth promoters was considered necessary for several reasons: There was science-based evidence that the use of antibiotics in animal feed could create resistance in pathogenic bacteria to medically important antibiotics, and there was a real concern that doctors would run out of options for treating life-threatening infections in humans.

Given the fact that very recently, a Danish PhD project concluded that production animals and meat might be a source of human E. coli urinary tract infections, the Danish ban seemed to be an example of due diligence.

....

Among the initiatives, that are all mandated by the Danish government, I would like to mention the following:

- No prophylactic use of antimicrobials and mandatory low fixation of the veterinarians profit from sales of medicine.

- The critically important antibiotics fluoroquinolones can only be used, if a laboratory test shows, that no other antibiotics can be used.

- Treatment guidelines for swine and cattle veterinary practitioners have been issued.

- Each individual veterinary practitioner is subjected to risk management and risk communication on prudent and reduced usage of antibiotics.

- Continuous monitoring and research in antimicrobial resistance in animals, humans and food.

- Monitoring of food borne pathogens in Danish as well as imported meat. Antimicrobial resistance is one of the parameters used to determine whether a shipment of food is dangerous.

- Control and action plans to combat Salmonella bacteria in poultry and pork and Campylobacter in poultry are all implemented.

And the most recent development includes mandatory action plans in swine-herds above a certain threshold value for antibiotics usage – the so called 'yellow card' initiative.

It is important to note that, according to our experience, a ban on antibiotic growth promoters can immediately and dramatically reduce the amount of antibiotics used. In Denmark the decrease was 40%. But such a ban should not stand-alone in the long run. This explains the fact that we have implemented this range of follow up measures and we expect also to have to take additional steps in the future.

....

I would now briefly present some results of the initiatives:

The ban of growth promoters has resulted in a marked reduction in antimicrobial resistance as measured among several different bacterial species in food animals. The percentage of macrolide resistance in porcine Campylobacter has decreased from 80% before the ban to less than 20% in 2006. A similar reduction from more than 75 % vancomycin resistance in enterococci isolated from broilers before the ban to less than 5% in 2006.

Additionally, Denmark has a markedly lower level of resistant bacteria in meat compared to imported meat from other EU member states. I can mention as an example, that the percentage of cephalosporin resistance in E. coli isolated from Danish broiler meat is less than 5%, while more than 35% of E. coli isolated from broiler meat from other EU-member states reveal cephalosporin resistance. This marked difference in resistance can be ascribed to our ban of growth promoters and low usage of antimicrobials compared to other EU countries. According to data from the European Food Safety Authority the total consumption of antimicrobials in food producing animals in 2007 was 120 metric tons in Denmark and almost 600 metric tons in another EU country with a comparable type of pig production.

The ban of growth promoters came into force in 1995 and we noted a substantial decrease of 40% in the consumption of antibiotics in the years thereafter.

The Danish swine industry has been producing pigs without the use of growth promoters for many years now and has increased both the production and the productivity. The same picture applies in the broiler chicken and cattle industries.

15 years after the ban the overall amount of antibiotics used for animals in Denmark is still almost 40% below the pre-ban level. As some US observers has pointed out, there has been an increase in the consumption of antimicrobials for therapeutical use during the post-ban years, but it has to be remembered, that the pig production has increased 25% in the same period, which can account for more than the increase in consumption of antimicrobials.

In the last few years and particularly in 2009 we have noted an increase of usage of antimicrobials above the concurrent increase in pig production. However, as this increase appears more than 10 years after the ban of growth promoters, we do not relate this to the ban. Nevertheless, we take this recent increase in usage seriously and have imposed the above-mentioned recent initiative - the ‘yellow card’ where farms using antibiotics above a certain threshold are mandated to reduce their use.

Salmonella levels have been between 0-2 % in eggs and chicken, and the Salmonella level in pork has remained low.

....

When presenting the Danish experience here in the US, it is important to stress that Denmark is favoured by a range of institutional characteristics which helped implementing the ban and the following steps.

- In Denmark we can identify every herd, farmer and veterinarian and we are able to pinpoint the antimicrobial usage right down to the individual cow and to an age-group of swine. This is due to our many databases on husbandry and medicine usage. And we have also monitored and researched in resistance for the past 15 years in a targeted program called DANMAP.

- Our farming industry is highly organised in a co-operative structure with one common organisation for farmers and food companies. We have a longstanding tradition for working towards a consensus between government and industry and this was also the case with the ban on antimicrobial growth promoters.

- Working as an entity, the Danish swine industry has therefore played an important role and voluntarily stopped all non-therapeutic use of antibiotics, starting in 1998, with a total state ban in place by January 2000. Only two weeks ago the Danish swine industry again issued a voluntary ban; this time against therapeutic treatment with the critically important antibiotic Cephalosporin.

- Danish farmers are well educated and have easily learnt to produce pigs without antibiotic growth promoters. Instead they use good management, weaning at 28 days, initiatives concerning feed and proper care of sick animals.

Thus, institutional advantages have enabled Denmark to take ambitious risk mitigating strategies in order to combat antimicrobial usage and resistance – and without endangering the economic sustainability of the swine industry.

....

In conclusion Denmark can state the following results:

- Antimicrobial resistance is reduced after the ban
- Total antibiotic consumption in food producing animals has been reduced by almost 40% from the mid 1990's till today
- Animal health has not been compromised
- Agricultural productivity has continued to improve
- The farmer's economy has not been significantly threatened
- Food safety in Danish products of animal origin has significantly improved as regards specifically Salmonella and Campylobacter
- A range of institutional factors helped Denmark implement the ban
- A ban on antibiotic growth promoters can be a very substantial and fulfilling first step in combating antimicrobial resistance, but should not stand alone in the long run

If you have any questions I will gladly answer them, and I will also direct our attention to the fact sheets handed out. Thank you for your attention.

Changes in the use of antimicrobials and the effects on productivity of swine farms in Denmark

Frank M. Aarestrup, DVM, PhD; Vibeke F. Jensen, DVM, PhD; Hanne-Dorthe Emborg, DVM, PhD; Erik Jacobsen, MS; Henrik C. Wegener, PhD

Objective—To evaluate changes in antimicrobial consumption and productivity by Danish swine farms during 1992 to 2008.

Sample Population—All Danish swine farms for antimicrobial consumption data and a representative sample of Danish swine herds for productivity data.

Procedures—Antimicrobial consumption by Danish swine farms from 1992 to 2008 was determined and evaluated in light of policies to regulate antimicrobial consumption, changes in disease patterns, and productivity data. Trend analyses of productivity data were conducted before and after a ban on use of antimicrobial growth promoters (AGPs).

Results—Antimicrobial consumption peaked at 100 mg/kg of swine produced in 1992, decreased to 31 mg/kg in 1999, and increased to 49 mg/kg in 2008. Key factors for changes were regulations banning subtherapeutic use of antimicrobials and veterinary profits from the prescription and sale of antimicrobials in 1994 and termination of AGP use by January 2000. Pig production increased from 18.4 to 27.1 million pigs, and the mean number of pigs per sow per year raised for slaughter increased from 21 in 1992 to 25 in 2007. Average daily gain for weaning (< 35 kg) and finishing (> 35 kg) pigs was higher in 2008 than in 1992, but mortality rates for weaning and finishing pigs were similar in 1992 and 2008.

Conclusions and Clinical Relevance—From 1992 to 2008, antimicrobial consumption per kilogram of pig produced in Denmark decreased by > 50%. Furthermore, there was improvement in productivity, suggesting that long-term swine productivity was not negatively impacted by a ban on AGP use. (*Am J Vet Res* 2010;71:726–733)

Soon after their discovery, antimicrobials were used in veterinary medicine for the treatment of bacterial diseases and were also incorporated in animal feed as AGPs.[1] Since the 1950s, antimicrobials have become an integrated part of food animal production, with large quantities of antimicrobials used in food animal production systems globally.[2] However, because of concerns regarding antimicrobial-resistant bacteria being transmitted from food animals to humans, efforts have been launched throughout the world to promote the prudent use of antimicrobials in food animals.[3,4] The criteria that constitute prudent use of antimicrobials among differing production systems continue to be debated. In particular, the widespread subtherapeutic and routine in-feed use of antimicrobials for growth promotion has been a subject of controversy.

Swine are the main food animal species in Denmark. Approximately 90% of pork produced in Denmark is exported, and Denmark is the largest exporter of pork in the world. The consumption of antimicrobial agents by food animals, including swine, has been monitored since 1990.[5] Many factors, including regulatory actions taken by the national authorities in Denmark and the European Union authorities, have influenced the amount and pattern of use of antimicrobials in animals during the past 2 decades. To our knowledge, the change in consumption over these 2 decades and the potential impact on swine productivity and health have not been evaluated.

The purpose of the study reported here was to assess the changes in consumption of antimicrobial agents by swine farms in Denmark from 1992 to 2008, evaluate the effects of factors (eg, regulatory actions, changes in productivity, or emergence of novel diseases) that might affect antimicrobial use, and determine the impact on health and productivity of swine in Denmark.

ABBREVIATIONS

ADG	Average daily gain
AGP	Antimicrobial growth promoter
PMWS	Porcine multisystemic wasting syndrome
PRRS	Porcine reproductive and respiratory syndrome

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Materials and Methods

Sample population—Data for the total production of swine in Denmark were collected from an online database.[a] The consumption of antimicrobial agents by swine farms in Denmark is reported[5] annually. The National Committee for Pig Production operates a swine production records system. Approximately 10% of Danish swine producers voluntarily submit data to the records system on a monthly basis. The records system operates as an efficiency control program for benchmarking production characteristics of swine farms; it was assumed that the production trends determined over time by this program were representative for all swine producers. The sample size during 1992 to 2008 varied from 147 to 2,237 herds/y for herds comprising weaning pigs (< 35 kg) and 282 to 1,742 herds/y for herds comprising finishing pigs (> 35 kg). Results were reported as the mean value of data for 1 year based on records of a minimum of 170 continuous days during a period starting on August 15 and ending on November 14 of the following year.[6–10]

Policies and regulations limiting the use of antimicrobials—In Denmark, a veterinary prescription is required for the use of antimicrobials for disease control. In 1994, public discussions regarding the increased consumption of relatively inexpensive and extemporaneously prepared tetracycline antimicrobials on swine farms prompted the Danish authorities to pass regulations that limited veterinary profits from the prescription and sale of antimicrobials and banned the prophylactic use of antimicrobials in food animals. The new legislation comprised several components. Restrictions were imposed that prohibit the use of extemporaneously prepared drugs when medicinal products could be used for a specific therapeutic indication. Limitations were placed on a veterinarian's ability to prescribe antimicrobial drugs to a maximum of 5 days of treatment for a specifically diagnosed disease, unless herd health contracts between the veterinarian and farmer allowed prescription for up to 35 days of treatment for a diagnosed disease or a disease that was expected in the pigs on the basis of the veterinarian's knowledge of the herd. It was mandated that a veterinarian register the use and delivery of drugs to farmed animals and maintain records of this use (available for inspection by veterinary officials for 3 years). It allowed a pharmacy to divide large boxes that contain several packages into single packages of antimicrobials to sell smaller quantities of antimicrobials at the same price as did veterinarians. Finally, it prohibited pharmacies and the pharmaceutical industry from offering economic incentives to veterinarians or others for the purpose of increasing product sales.

In an attempt to guide the choice of antimicrobial agents, detailed treatment guidelines for veterinarians were developed, and they have been updated annually since 1996.[11] These guidelines have been developed in collaboration with the relevant government authority, practicing veterinarians, and experts employed by universities. The guidelines provide specific recommendations for the selection of the appropriate antimicrobials for the treatment of all common indications in major food animal species.

In 2002, a new regulation was adopted that limited a veterinarian's ability to prescribe fluoroquinolones to animals raised for food consumption. A veterinarian can prescribe a fluoroquinolone for use in food animals only if the need for use can be documented and it can be determined that other approved drugs are ineffective. Furthermore, it is mandatory for the veterinarian to notify the district veterinary officer of this prescription.

Actions limiting the use of AGPs—In Europe, the use of antimicrobials in low doses as feed additives for growth promotion is not regarded as disease control and, consequently, has not required veterinary oversight or a prescription. Contrary to the situation in the United States, all other uses, which include in-feed and in-water use of antimicrobials for metaphylaxis and prophylaxis, require a prescription from a licensed veterinarian.

Concerns were raised during the 1960s in some European countries that the use of antimicrobials in food animals could lead to infections with resistant organisms in humans[12]; this prompted a ban on the use of antimicrobials for growth promotion in food animals if these antimicrobials were also important for therapeutic use in humans. This action was enforced on individual antimicrobials and did not consider potential resistance problems from the use of other antimicrobials belonging to the same class of drug. Thus, a number of antimicrobial compounds belonging to classes of drugs also used for treatment of domestic animals and humans were used as AGPs. Subsequently, this oversight may have allowed for the selection of bacterial resistance to other therapeutic drugs.[1,13] In 1995, glycopeptide-resistant enterococci were detected in pig and poultry production systems.[1,13] This prompted the Danish government to ban the use of avoparcin as an AGP. Furthermore, results of research in Denmark and other countries resulted in a ban for all use of avoparcin in the European Union in 1996. The Danish government banned the use of virginiamycin as an AGP in food animals in 1998.[1,11] This was followed by an overall ban of virginiamycin, bacitracin, tylosin, and spiramycin by the European Union in 1998. In 2003, the European Union made the decision to phase out all use of AGPs by the beginning of 2006.[14] However, the Danish swine industry decided to stop all use of AGPs in finishing pigs by April 1998 and in all swine by January 2000.

Statistical analysis—Trends in productivity data over time were analyzed via linear regression models by use of a statistical software package.[b] Data were analyzed by use of both mixed and generalized linear models. Outcome variables were the various productivity data (ie, ADG in weaning and finishing pigs, mortality rate of weaning pigs, percentage of dead and condemned finishing pigs, number of feed units [usable energy in 1 kg of barley {ie, 7.72 MJ}]/kg of gain in finishing pigs, number of pigs produced per sow per year, and total production of pigs). The explanatory variable was time (continuous variable). Additionally, time was coded as a categorical variable with the first category defined as the time period (1993 to 1998 for finishing pigs and 1993 to 1999 for weaning pigs) before the ban

Table 1—Mean number of feed units* per kilogram of gain for weaning and finishing pigs raised in Danish swine production systems from 1996 to 2008.†

Type of pig	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Weaning‡	—	—	—	—	—	—	—	1.97	2.06	2.07	2.04	2.02	1.97
Finishing§	2.94	2.91	2.9	2.89	2.89	2.89	2.88	2.86	2.87	2.88	2.87	2.89	2.83

*Given as the useable energy in 1 kg of barley (ie, 7.72 MJ). †Productivity data for the Danish swine industry were collected beginning on August 15 and ending on November 14 of the following year and reported as the year in which the data collection period terminated. ‡Weaning refers to pigs that weighed < 35 kg. §Finishing refers to pigs that weighed > 35 kg.
— = Not reported.

on AGP use and the second category defined as the time period after the ban on AGP use. An interaction between time and time before and after the ban on AGP use was included in the model to determine whether the trend in productivity data was significantly different before and after the ban on AGP use. Data for dead and condemned finishing pigs and the mortality rate of weaning pigs were transformed by use of the arc-cosine function. Then, 2 separate models were fitted to both outcome variables (1 model in which the outcome was not transformed for each variable and 1 model in which the outcome was transformed for each variable). The number of farms that provided productivity data varied from year to year; to adjust for this variation in the analyses, data from each year were weighted by the square root of the number of farms reporting productivity for that respective year. A value of $P < 0.05$ was considered significant for all analyses.

Results

Evaluation of statistical methods—Results from the data analysis did not differ significantly between the mixed and generalized linear models. Results of the analyses performed by use of transformed versus nontransformed outcome variables did not differ significantly. Therefore, only the results of the nontransformed outcome were reported. In addition, a dramatic change was observed in the mortality rate of weaning pigs after 2004. Therefore, trend analysis for the mortality rate of weaning pigs was only performed from 1992 until 2004.

Productivity in Danish swine production

Data for the number of feed units per kilogram of gain in weaning pigs were unavailable from 1996 through 2002 (**Table 1**). The number of feed units per kilogram of gain in weaning pigs peaked in 2005; the value then remained relatively constant in 2006 and 2007, but decreased in 2008 to reach a value similar to that for 2005.

Total production of weaning pigs in Denmark was not affected by the ban on AGP use. Analysis of data obtained from a database[a] revealed that production of weaning pigs increased from 18.4 million pigs in 1992 to 27.1 million pigs in 2008, which was an increase of 47% (**Figure 1**). The number of pigs per sow per year steadily increased from approximately 21 to 25 during the 15-year study period. However, the increase was significantly higher after the ban on AGP use, compared with results for the period before the ban on AGP use (**Table 2**).

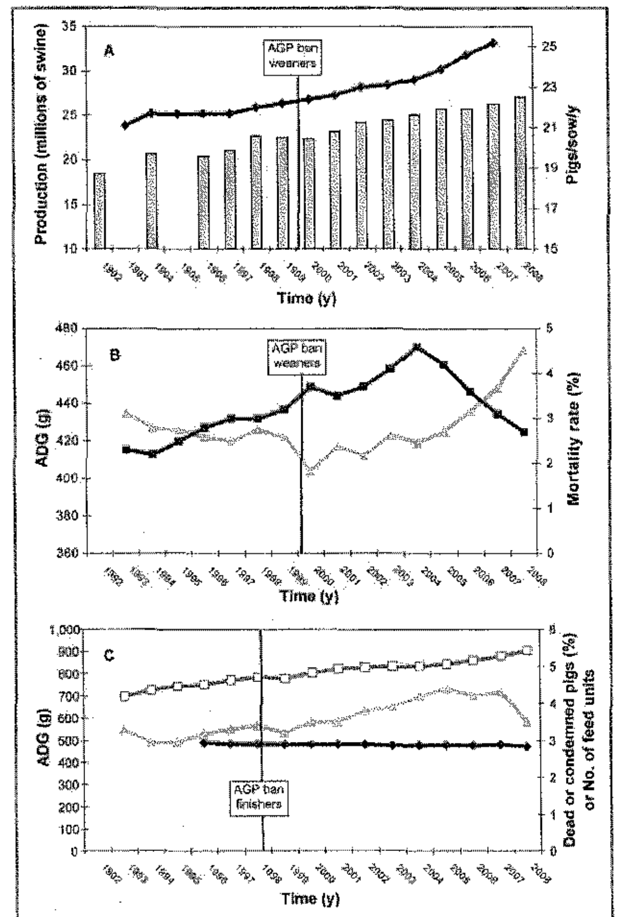

Figure 1—Data[d] of production characteristics for total production of pigs (millions of swine; gray bars) and mean number of pigs farrowed per sow per year (black diamonds; A), ADG (gray triangles) and mortality rate (black squares) in weaning pigs (B), and ADG (white squares), number of feed units (black diamonds) and the percentage of dead or condemned finishing pigs (gray triangles; C) raised in the Danish swine production system from August 15, 1991, through November 14, 2007. Data for total pig production were collected during the calendar year from January 1 through December 31; all other production values were collected from August 15 through November 14 of the following year and reported as the year in which the data collection period terminated. The ban on AGP use (vertical line) was instituted on April 1, 1998, and January 1, 2000, for finishing and weaning pigs, respectively. Weaning and finishing pigs weighed < 35 kg and > 35 kg, respectively.

As a result of the dramatic change observed in the mortality rate of weaning pigs after 2004, trend analysis of the mortality rate of weaning pigs was only performed from 1992 through 2004. A significant increase

Table 2—Results from statistical models constructed for reported variables of production data recorded from a database[c] for weaning (< 35 kg) and finishing (> 35 kg) pigs raised in the Danish swine production system from 1993 to 2008.

Variable	Effect	Estimate	SE	P
No. of pigs produced*	Intercept	18,327.00	266.89	—
	Year	511.84	29.61	< 0.001
No. of pigs born/sow†	Intercept	21.19	0.17	—
	Year	0.13	0.05	< 0.001
	After ban on AGP use	−1.97	0.47	0.002
	Prior to ban on AGP use	0	—	—
	Year after ban on AGP use*	0.24	0.06	0.003
	Year prior to ban on AGP use*	0	—	—
ADG of weaning pigs	Intercept	432.76	4.17	—
	Year	−1.87	1.00	0.009
	After ban on AGP use	−77.87	11.39	< 0.001
	Prior to ban on AGP use	0	—	—
	Year after ban on AGP use*	7.90	1.35	< 0.001
	Year prior to ban on AGP use*	0	—	—
Mortality rate of weaning pigs‡	Intercept	1.95	0.09	—
	Year	0.19	0.01	< 0.001
ADG of finishing pigs	Intercept	685.72	7.35	—
	Year	17.47	2.22	< 0.001
	After ban on AGP use	30.12	11.65	0.024
	Prior to ban on AGP use	0	—	—
	Year after ban on AGP use*	−6.80	2.37	0.014
	Year prior to ban on AGP use*	0	—	—
Mortality rate of finishing pigs§	Intercept	2.87	0.12	—
	Year	0.09	0.01	< 0.001
Feed unit/kg of gain in finishing pigs	Intercept	2.94	0.01	—
	Year	−0.01	0.00	< 0.001

*Analyses included data from 1992. †Analyses included data from 1993 through 2007. ‡Analyses included data from 1993 through 2004 because of a reduction in mortality rate during 2004 through 2008 (ie, from 4.6% to 2.7%). §Analyses did not include data from 2008 because of a major reduction in mortality rate (ie, from 4.3% in 2007 to 3.5% in 2008).

— = Not reported.

in mortality rate of weaning pigs was observed during the study period. However, this was not significantly different when compared with the mortality rate before and after the ban on AGP use.

Among finishing pigs, a significant decrease in feed unit per kilogram of gain was observed over time. Time (categorical variable) before and after the ban on AGP use did not have a significant effect, and there was no significant interaction between these 2 variables. However, as a result of an insufficient number of observations reported before the ban on AGP use, it was not possible to determine whether the apparent trend was significantly different.

The ADG of weaning pigs significantly decreased from 1992 until shortly after the ban on AGP use in January 2000; ADG significantly increased thereafter. Mortality rate of weaning pigs increased after 1994, peaked in 2004, and decreased from 2005 through 2008. The ADG for finishing pigs increased during the period from 1992 through 2008. Trend analysis indicated that this increase was significant over time. However, the increase in ADG was greater before the ban on AGP use than after the ban.

The percentage of dead and condemned finishing pigs increased from 1992 through 1998; there was a decrease in this rate after the ban on AGP use in finishing swine in 1998. However, the percentage of dead and condemned finishing pigs again increased from 3.2% in 1999 to 4.4% in 2005, which was followed by a reduction to 3.5% in 2008. The increase in the percentage of dead and condemned finishing pigs was significant over time. However, this trend did not differ significantly before and after the ban on AGP use.

Consumption of antimicrobials over time

Following the implementation of laws that restricted veterinary profits from antimicrobial sales in May 1995, analysis of data obtained from an aforementioned database[5] revealed that there was a reduction in the consumption of antimicrobials (especially tetracyclines) used for therapeutic indications (**Table 3**). The ban on AGP use of avoparcin (May 1995) and virginiamycin (January 1998) had no or only a marginal effect on the consumption of antimicrobials for therapeutic indications and on overall antimicrobial consumption (**Figure 2**). The phasing out of AGP use in finishing pigs did not result in immediate changes in antimicrobial consumption for therapeutic indications. In 1996, there was an outbreak of PRRS that involved > 1,100 Danish swine herds.[15,c] However, this event did not appear to influence the consumption of antimicrobial agents for therapeutic indications.

Following the termination of AGP use in all pigs by January 2000, there was an increase in antimicrobial

Table 3—Change in antimicrobial consumption* for the Danish swine production system relative to pork production from 1992 to 2008.

Variable	1992	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Production (millions of kg of pigs produced)	1,442	1,604	1,582	1,592	1,639	1,770	1,781	1,748	1,836	1,892	1,898	1,967	1,988	1,957	2,046	1,985
Therapeutic use																
Tetracyclines	13.7	20.5	5.1	7.3	7.5	6.2	8.2	12.4	14.0	11.8	13.2	14.0	14.1	15.5	17.4	17.3
Macrolides, lincosamides, and pleuromutilins	1.1	6.3	5.3	4.2	3.5	3.5	4.3	7.9	8.8	9.2	8.5	11.6	11.0	10.5	11.0	12.8
Aminoglycosides	7.9	4.1	3.7	3.4	2.8	3.3	3.2	4.5	4.9	5.0	5.2	5.0	4.6	4.4	3.2	2.4
β-lactamase sensitive–type penicillins	4.5	3.5	3.3	2.7	4.1	4.8	5.0	5.2	5.4	5.9	6.7	7.6	8.0	8.2	8.2	8.3
Other penicillins and cephalosporins	2.8	1.7	1.8	2.3	2.3	2.3	2.3	2.6	3.1	3.6	4.2	5.1	4.7	4.3	4.2	4.0
Sulfonamide and trimethoprim	4.0	4.0	2.2	1.8	2.1	2.1	1.8	1.9	2.3	2.6	2.5	2.6	2.7	3.1	3.0	3.9
Other antimicrobials†	4.2	2.4	1.0	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2
Total of therapeutic use‡	38.2	40.0	21.3	21.7	22.4	22.3	24.8	34.4	38.5	38.1	40.3	45.1	46.0	46.0	47.0	48.9
Estimated AGP use	62.2	58.6	51.2	59.1	58.8	26.6	6.5	0	0	0	0	0	0	0	0	0
Total antimicrobial use§	100.4	98.6	72.5	80.8	81.2	48.9	31.3	34.4	38.5	38.1	40.3	45.1	46.0	46.0	47.0	48.9

*Antimicrobial consumption is defined as the number of milligrams of active compound consumed per kilogram of pig produced. †Other includes colistin, fluoroquinolones, metronidazole, and nitrofuranthion. ‡Results only include data for antimicrobials used for therapeutic indications in swine. Prior to 2001, consumption of antimicrobials for therapeutic indications in swine was estimated from the total consumption for pigs, assuming that 90% of the macrolide-lincosamide-pleuromutilin group, 77% of aminoglycosides, 90% of tetracyclines, 62% of β-lactamase sensitive–type penicillins, and 64% of the remaining penicillin and cephalosporin groups were used to treat swine (2001 and 2002 data[d]). §Combines the results of antimicrobials used for therapeutic indications and the estimated amount of antimicrobials used as an AGP.

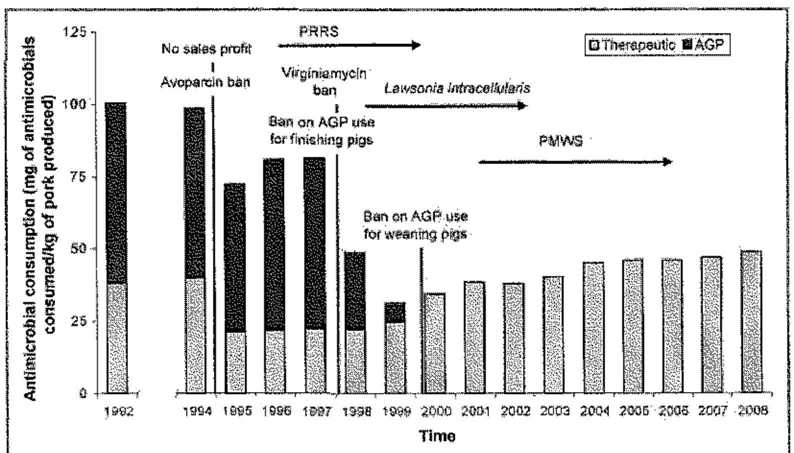

Figure 2—Consumption of antimicrobials for use as AGPs (black bars) or for therapeutic administration (gray bars) from 1992 to 2007 by the Danish swine production system. Notice the ban on use of avoparcin and on veterinary profits from the prescription and sale of antimicrobials, the ban on AGP use in finishing pigs and on use of virginiamycin in all pigs that was instituted in 1998, and the ban on AGP use in weaning pigs that was instituted in January 2000. Outbreaks of PRRS (1996 to 2000), disease attributable to *Lawsonia intracellularis* (1998 to 2002), and PMWS (2001 to 2006) are indicated (arrows). Weaning and finishing pigs weighed < 35 kg and > 35 kg, respectively.

consumption for therapeutic indications in 2000 and 2001. This increase may have been caused by a concurrent outbreak of disease caused by *Lawsonia intercellularis* in weaning pigs.[16] In 2001, PMWS was first diagnosed in a Danish herd; this disease affected 626 herds by December 2005.[17] Since 2002, the consumption of antimicrobials has continued to increase with minor fluctuations; this increase in antimicrobial consumption was mainly the result of the increased use of tetracycline and macrolide antimicrobials. The main AGP used in pigs before the ban on AGP use was tylosin, which was also the main macrolide antimicrobial used for therapeutic indications. The total consumption of macrolides used as an AGP and for therapeutic indications decreased from 62,959 kg in 1997 to 11,446 kg in 2008; this corresponded to a decrease of 82% for antimicrobial consumption per pig produced.

Discussion

The study reported here was an observational study of the relationship between data reported on productivity characteristics of the Danish swine production system and consumption of antimicrobial agents from 1992 to 2008. The reduction in antimicrobial consumption from 1994 to 1995 can be explained by the limitation of sales incentives paid to veterinarians imposed by Danish authorities. The ban on use of avoparcin and virginiamycin (1995 and 1998, respectively) and the prohibition of all AGP use in finishing pigs (after April 1998) appeared to have only a limited effect, if any, on the amount of other antimicrobials used for therapeutic indications; this is in agreement with the findings of a herd-level study.[18]

In 1996, an attenuated vaccine against PRRS was used in > 1,100 Danish swine herds to vaccinate 3- to 18-week-old pigs.[15,c] Unfortunately, this strain reverted to virulence and further advanced the spread of PRRS in Denmark.[15,c] However, this did not seem to influence the consumption of antimicrobials for therapeutic indications. The complete cessation of all AGP use by January 2000 coincided with an increase in the consumption of antimicrobials for therapeutic indications. The ban on AGP use in weaning pigs appears to be the most likely explanation, although the concurrent outbreak of disease attributable to *Lawsonia intercellularis* in Danish swine herds[16] may have contributed to this as well.

From 2001 to 2002, there was a minor reduction in antimicrobial consumption. In 2001, PMWS was first diagnosed in a Danish herd; since that time, the number of herds with PMWS has increased substantially, especially during 2003 to 2005.[17] By December 2005, PMWS had been diagnosed in 626 herds by personnel at the diagnostic laboratory at the National Veterinary Institute. The occurrence of PMWS can cause a significant increase in antimicrobial use at the farm level, with use being greater in sows than in weaning pigs.[19] Thus, PMWS may explain a portion of the increasing antimicrobial consumption in weaning pigs and sows from 2002 to 2004 and the increase in antimicrobial consumption in weaning pigs from 2004 to 2005; this is supported by the geographic distribution of PMWS and increasing antimicrobial use during these years, both of which were localized almost entirely in Jutland and Funen, Denmark.[5]

The continued increase in antimicrobial consumption during 2006 to 2008 is more difficult to explain. It is highly unlikely that this increase can be related to the ban on AGP use that was enacted almost 10 years earlier. Increased antimicrobial consumption was not associated with an increase in the mortality rate of weaning pigs, which has decreased since 2004. One explanation could be the large reduction (50%) in the purchase price of some of the commonly used antimicrobials (eg, tetracycline, tiamulin, and tylosin), which has made it much cheaper to use antimicrobials rather than other disease control measures such as vaccination and infection control practices. These aspects must be investigated.

It is important to recognize that the different classes of antimicrobials are not of equal importance for human and food animal health.[20] Thus, an overall reduction in antimicrobial consumption could be associated with a negative impact on the health of humans or food animals if the consumption was changed toward more critically important drugs. Therefore, it is also important to notice that the main increase in therapeutic antimicrobials has been in macrolides and tetracyclines and not in more potent drugs such as third-generation cephalosporins and fluoroquinolones. Before 2001, third- and fourth-generation cephalosporins and fluoroquinolones were not separately registered, but instead they were summed together with other β-lactam antimicrobials (ie, β-lactam and other penicillins) and other antimicrobials (ie, colistin, metronidazole, and nitrofurantion), respectively. However, the use of third- and fourth-generation cephalosporin antimicrobials has gradually increased from approximately 0.04% of total antimicrobial consumption for swine in 2001 to 0.13% in 2008. Fluoroquinolone consumption has decreased from 0.13% for swine in 2001 to almost nothing (total registered use, 5 g) in 2008.

Few estimates exist on antimicrobial consumption for food animal production in other countries. In 1999, before the ban on AGP use, the European Medicines Agency estimated the consumption for AGP use and therapeutic indications for 1996 and compared this value with food animal production in 15 European countries during 1997.[21] Mean consumption was 98 mg of antimicrobials/kg of meat and poultry produced (range, 24 to 184 mg/kg). In the United States, there are different estimates of antimicrobial consumption. One estimate[22] was 12,630,000 kg for consumption in all animal species (including companion animals) in 2007, whereas another estimate was 11,158,000 kg for nontherapeutic use in cattle, pigs, and poultry in 1999.[23] However, the certainty of these estimates[22,23] is unknown. Total meat production in the United States was 37,258,500,000 kg in 1999 and 41,809,400,000 kg in 2007.[d] Thus, both of these estimates imply that the consumption of antimicrobials in the United States is approximately 300 mg/kg of meat produced. This is considerably higher than the mean European Union value and higher than the mean value for any other country in Europe.

The number of swine in the Danish swine industry has continued to increase from < 20 million swine/y to > 27 million swine/y during the past 15 years. The number of swine produced per sow per year has also steadily increased, which indicates both the efficacy of the Danish swine industry as well as the production pressure that is put on the pigs. Because mortality rate and ADG of weaning pigs are objective criteria that can be measured over time and also are highly reproducible, these factors were used as key indicators for productivity and health of weaning pigs. The mortality rate of weaning pigs increased from 1995 to 2004 but decreased markedly during the subsequent 3 years. It was expected that the ban on AGP use (January 2000) for weaning pigs and the rapidly increasing prevalence of PMWS during 2001 to 2005 would influence the increase in mortality rate of weaning pigs for these years. However, no effect of the ban on AGP use on the mortality rate of weaning pigs was detected. Mortality rates have improved considerably during recent years, and the total number of pigs raised for slaughter per sow per year has increased continuously during this entire time period (1993 to 2007). Similarly, ADG in weaning pigs was not negatively affected when assessing this variable over the entire study period. In fact, ADG decreased from 1992 to approximately the time of the ban on AGP use, which was followed by an increase thereafter. Thus, the potential negative effects of the ban on AGP use on both mortality rate and ADG of weaning pigs seem to be negligible, or there may even have been a benefit, especially when looking at the long-term effects. Similarly for finishing pigs, no effect on mortality rate was observed and ADG continued to increase. However, the increase was slightly but significantly less after the ban on AGP use, compared with the results before the ban on AGP use. Whether this difference in the ADG increase is because ADG was approaching a plateau or because of the ban on AGP use needs to be further evaluated. These findings support conclusions reached in a study[18] conducted at the herd level. The ban on AGP use did not cause any important or lasting effects on productivity, although an increase in diarrhea among weaning pigs was observed during the first year of the ban on AGP use and caused an increase in consumption of antimicrobials for therapeutic indications in weaning pigs.[18]

In addition to the ban on AGP use and the emergence and spread of new pathogens, a number of other factors might directly or indirectly have influenced the consumption of antimicrobials used for therapeutic indications in swine in Denmark. Recommendations for the inclusion of protein in the feed have changed over time, as have the production systems, trade between farmers, and price on antimicrobials and feed; all of these factors might influence antimicrobial use and are difficult to account for in a controlled manner. This also illustrates the complexity of factors that influence the use of antimicrobials in any type of farm animal production system.

It should be mentioned that the aggregate results described in the study reported here suggest minimal detriment to the industry as a whole. However, such an analysis may not reveal all negative and positive impacts of the imposed legislation on antimicrobial use. The data reported here were mean values for the entire Danish swine industry, for all production systems, and among a random subset of monitored herds. Therefore, the negative and positive impacts for individual pigs and farms may have been obscured.

Data regarding the effects of a ban on AGP use are also available from other countries. Switzerland imposed a ban on AGP use for swine farms in 1999, but they found no effect on the use of antimicrobials for therapeutic indications.[24] In Finland, antimicrobials used for the treatment of diarrhea in weaning pigs did not increase significantly after a ban on AGP use in 1999.[25] In Norway, a significant reduction in the consumption of antimicrobials for therapeutic indications followed a ban on AGP use.[26] However, in Sweden, a ban on AGP use in 1986 was followed by an increase in the consumption of antimicrobials for therapeutic indications, with antimicrobial consumption returning to the same level as before the ban on AGP use after almost 10 years.[26] To our knowledge, data on the effects of a ban on AGP use on productivity in the pig industry of other countries are not available. However, in both Denmark[27] and the United States,[28] the effect of a ban on AGP use in poultry is negligible or even nonexistent. Unfortunately, few studies have been conducted following the ban on AGP use in all 27 European Union member states in 2000.

Detailed treatment guidelines for veterinarians in Denmark have been developed and updated annually since 1996. The extent to which veterinarians adhere to these guidelines or the effect they have on the total consumption of antimicrobials or the patterns of antimicrobial consumption has not been assessed. Analysis of results from the study reported here suggests, with 1 exception, that the effect appears to be relatively minor; this may have resulted in a reduction in antimicrobial consumption of macrolides with a concurrent increase in the use of tetracyclines for treatment during 2005 to 2008.

Globally, there is limited experience with various interventions and their effect on antimicrobial consumption for food animal production.[29] On the basis of our experience in Denmark, regulatory actions and financial incentives can be effective in changing the consumption of antimicrobials, whereas the effects of other actions have not been definitively proven.

From 1992 to 2008, a reduction (> 50%) in antimicrobial consumption per kilogram of pig produced was observed in Denmark. This change was associated with the implementation of policies to discontinue the use of antimicrobials as AGPs. During the same period, overall swine productivity improved markedly, which suggests that the change in antimicrobial consumption has not had a negative impact on long-term swine productivity.

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United States General Accounting Office

GAO

Report to Congressional Requesters

April 2004

ANTIBIOTIC RESISTANCE

Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals

GAO Accountability * Integrity * Reliability

GAO-04-490

GAO
Accountability·Integrity·Reliability

Highlights

Highlights of GAO-04-490, a report to congressional requesters

Why GAO Did This Study

Antibiotic resistance is a growing public health concern; antibiotics used in animals raised for human consumption contributes to this problem. Three federal agencies address this issue—the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC), and the Department of Agriculture (USDA). GAO examined (1) scientific evidence on the transference of antibiotic resistance from animals to humans and extent of potential harm to human health, (2) agencies' efforts to assess and address these risks, (3) the types of data needed to support research on these risks and extent to which the agencies collect these data, (4) use of antibiotics in animals in the United States compared with its key agricultural trading partners and competitors, and (5) information on how use has affected trade.

What GAO Recommends

GAO recommends that (1) FDA expedite its risk assessments of drugs used in animals that are critical for human health and (2) USDA and HHS develop and implement a plan to collect data on antibiotic use in animals. USDA and HHS generally agreed with GAO's findings. With respect to the recommendations, HHS agreed that it is important to review animal drugs that are critical to human health and both agencies discussed ways to better collect antibiotic use data.

www.gao.gov/cgi-bin/getrpt?GAO-04-490.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Anu Mittal at (202) 512-3841 or Marcia Crosse at (202) 512-7119.

April 2004

ANTIBIOTIC RESISTANCE

Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals

What GAO Found

Scientific evidence has shown that certain bacteria that are resistant to antibiotics are transferred from animals to humans through the consumption or handling of meat that contains antibiotic-resistant bacteria. However, researchers disagree about the extent of harm to human health from this transference. Many studies have found that the use of antibiotics in animals poses significant risks for human health, but a small number of studies contend that the health risks of the transference are minimal.

Federal agencies have expanded their efforts to assess the extent of antibiotic resistance, but the effectiveness of their efforts to reduce human health risk is not yet known. FDA, CDC, and USDA have increased their surveillance activities related to antibiotic resistance. In addition, FDA has taken administrative action to prohibit the use of a fluroquinolone in poultry. FDA has identified animal drugs that are critically important for human health and begun reviewing currently approved drugs using a risk assessment framework that it recently issued for determining the human health risks of animal antibiotics. However, because FDA's initial reviews of approved animal drugs using this framework have focused on other drugs and have taken at least 2 years, FDA's reviews of critically important drugs may not be completed for some time.

Although federal agencies have made some progress in monitoring antibiotic resistance, they lack important data on antibiotic use in animals to support research on human health risks. These data, such as the type and quantity of antibiotics and purpose for their use by species, are needed to determine the linkages between antibiotic use in animals and emerging resistant bacteria. In addition, these data can help assess human health risks from this use and develop and evaluate strategies for mitigating resistance.

The United States and several of its key agricultural trading partners and competitors differ in their use of antibiotics in animals in two important areas: the specific antibiotics allowed for growth promotion and availability of antibiotics to producers (by prescription or over the counter). For example, the United States and Canada allow some antibiotics important in human medicine to be used for growth promotion, but the European Union (EU) and New Zealand do not. Regarding over the counter sales of antibiotics, the United States is generally less restrictive than the EU.

Antibiotic use in animals has not yet been a significant factor affecting U.S. international trade in meat and poultry, although the presence of antibiotic residues in meat has had some impact, according to government and industry officials. Instead, countries raise other food safety issues, such as hormone use and animal diseases. However, according to these officials, antibiotic use in animals may emerge as a factor in the future. They particularly noted that the EU could object to U.S. use of antibiotics for growth promotion as its member countries are phasing out that use.

Appendix II

Studies of the Economic Impacts of Restricting Antibiotic Uses in Animals

In this appendix we identify and summarize eight recent studies that provide estimates of the potential economic impacts of restrictions on antibiotics used in livestock production. Specifically, these studies estimate the economic effects of a partial and/or total ban of antibiotics used in animals. For several decades, antibiotics have been used for a variety of production management reasons, from therapeutic uses to increased productivity, such as feed efficiency or weight gain. In economic terms, higher productivity results in more final product supplied to the market, at a lower cost to consumers. Despite the use of a variety of economic models, assumptions about model parameters, and data sets, the economic impacts on consumers and producers of the studies that we identified were generally comparable. Overall, the studies conclude that a ban or partial ban on antibiotics in animal production would increase costs to producers, decrease production, and increase retail prices to consumers. For example, the studies indicate that the elimination of antibiotic use in pork production could increase costs to producers ranging from $2.76 to $6.05 per animal,[1] which translates into increased consumer costs for pork ranging from $180 million per year to over $700 million per year. Table 2 summarizes the eight studies.

[1]The WHO study described in this appendix also has estimated a cost of $1.04 per animal; however, the study was done to estimate economic impacts on the Danish swine market. (See World Health Organization, *Impacts of Antimicrobial Growth Promoter Termination in Denmark*, Department of Communicable Diseases, Prevention and Eradication and Collaborating Centre for Antimicrobial Resistance in Foodborne Pathogens, 2003.)

Table 2: Economic Studies That Estimate the Effects of Restrictions on Antibiotic Use

			Economic impacts	
Economic study	**Purpose of the study**	**Year**	**Producers**	**Consumers**
World Health Organization (WHO), *Impacts of Antimicrobial Growth Promoter Termination in Denmark*	To review the economic impacts resulting from the Danish ban of the use of antibiotics for growth promotion purposes in swine and poultry production.	2003	Cost increase of $1.04 per swine or 1 percent of total production costs. No cost changes for poultry.	
Hayes and Jensen, "Lessons from the Danish Ban on Feed-Grade Antibiotics," Center for Agricultural and Rural Development	To determine the economic impacts of a ban on antibiotics in pork production in the United States from the experience with such a ban in Denmark.	2003	Costs increase by $4.50 per head in first year. Total 10-year cost over $700 million.	Retail price increases by 2%.
Miller et al., "Productivity and Economic Effects of Antibiotics Used for Growth Promotion in U.S. Pork Production," *Journal of Agricultural and Applied Economics*	To estimate the net benefit of antibiotics used for growth promotion to swine producers in the United States using the 1990 and 1995 NAHMS swine survey data.[a]	2003	Increased profits of $0.59 per marketed swine or 9% profitability.	
Miller et al., "Producer Incentives for Antibiotic Use in U.S. Pork Production," American Agricultural Economics Association Annual Meetings	To validate the productivity and economic impacts of antibiotic use for swine producers at the farm level using the NAHMS 2000 survey.	2003	Four scenarios:[b] • Ban on AGP: profits decrease by $3,813 • Ban on ADP: profits increase by $2703 • Ban on AGP and ADP: profits decrease by $1128 • Limitation of AGP and ADP: Profits increase by $12,438	
Brorsen, Lehenbauer, Ji, and Conner, "Economic Impacts of Banning Subtherapeutic Use of Antibiotics in Swine Production," *Journal of Agricultural and Applied Economics*	To estimate the economic impacts on producers and consumers of a ban on the use of antibiotics in swine production.	2002	Costs would increase by $2.37 - $3.11 per hog with an average of $2.76 per hog. Total costs would be $153.5 million per year in the short run and $62.4 million per year in the long run.	Costs to consumers increase by $89 million per year in the short run to $180 million per year in the long run.

(Continued From Previous Page)

			Economic impacts	
Economic study	**Purpose of the study**	**Year**	**Producers**	**Consumers**
Mathews, Jr., "Economic Effects of a Ban Against Antimicrobial Drugs Used in U.S. Beef Production," *Journal of Agricultural and Applied Economics*	To examine the economic effects of a ban on antibiotic use in U.S. beef production on two policy alternatives—a partial ban and a full ban.	2002	**Partial ban**: Cattle prices increase by 0.49 percent. Producer income declines by $15 million.[d] **Full ban**: Cattle prices increase by 3.32 percent. Producer income declines by $113.6 million.[d]	**Partial ban**: Costs to consumers increase by $54.7 million.[d] **Full ban**: Costs to consumers increase by about $361 million.[d]
Hayes, Jensen, Backstom, and Fabiosa, "Economic Impact of a Ban on the Use of Over-the-Counter Antibiotics," Center for Agricultural and Rural Development	To estimate the likely economic impacts of a ban on antibiotics in the U.S. pork industry based on the impacts of such a ban in Sweden.	1999	Costs would increase by $5.24 - $6.05 per head. Net profit declines by $0.79/head. Total net present value of forgone profits over 10 years declines by $1.039 billion.	Retail price would increase by 5 cents per pound. Nationally, annual increase of consumer costs of $748 million.
National Research Council "Costs of Eliminating Subtherapeutic Use of Antibiotics" in *The Use of Drugs in Food Animals: Benefits and Risk*	To examine the economic costs to consumers of the elimination of subtherapeutic use of antibiotics for poultry, beef, and pork.	1999		Retail meat price increases (cents per pound):[c] Chicken: (1 – 3) Turkey: (2 – 3) Pork: (3 – 6) Beef: (3 – 6) Total consumer costs for pork: $382 million - $764 million per year. For all meat products, consumer costs increase by $1.2 billion to $2.5 billion per year.

Source: GAO analysis of sources cited.

[a]NAHMS is the National Animal Health Monitoring System.

[b]Within these scenarios, Miller et al. define AGP as antibiotics used for growth promotion and ADP as antibiotics used for disease prevention. The annual estimates of economic impacts for these scenarios are for a producer that has a 1,020-head barn of swine. A swine producer could have many such barns in his/her operation.

[c]The National Research Council estimates of retail price increases are ranges based on whether consumers would substitute other meat. The lower change in price assumes that substitution of other meat mitigates the price impact by 50 percent, while the higher change in retail price assumes no substitution.

[d]These estimates are in 1984 dollars.

While these market effects are important to both producers and consumers of livestock products, they must be balanced against the health care costs of antibiotic resistance due to agricultural uses of antibiotics. Potential health costs imposed by increased antibiotic resistance include more hospitalizations, higher mortality rates, and higher research costs to find new and more powerful drugs.[2] From the point of view of proposals to reduce antibiotic use, these potential costs represent the benefits from reduced antibiotic use. These costs to society, however, are difficult to measure because of limited data on antibiotic use and resistance as well as the problematic nature of measuring the value of a human life. Moreover, while there are some estimates of the costs of antibiotic resistance from both medical and agricultural sources, no estimates exist that directly link the human health costs of antibiotic resistance with antibiotics used in animal production. Nevertheless, studies that have examined the costs of antibiotic resistance from all sources have found a wide range of estimates running into the millions and billions of dollars annually.[3] For example, one recent study (2003) estimated that the health cost to society associated with resistance from only one antibiotic, amoxicillin, was $225 million per year.[4]

We discuss the eight studies we reviewed in reverse chronological order, from 2003 to 1999. Most examine restrictions on antibiotics in the swine industry, but a few look at the beef and poultry industries as well. All of the studies measure the economic impacts of antibiotic restrictions on domestic U.S. markets, except the WHO study of the antibiotic restrictions recently imposed by Denmark. Also, most studies estimate only domestic economic impacts, not impacts on international trade.

[2]Ramanan Laxminarayan, "Fighting Antibiotic Resistance: Can Economic Incentives Play a Role?" *Resources*, Spring 2001, Issue 143.

[3]Phelps (1989) estimated that the annual economic costs of drug resistance range from a best-case scenario of $100 million to a worst-case scenario of $30 billion, with the wide range of estimates accounted for by different assumptions about the economic value of a human life. Also, a study done by the Office of Technology Assessment in 1995 estimated that the cost of antibiotic resistance for six different strains of antibiotic bacteria reached about $1.3 billion in 1992 dollars.

[4]E.H. Elbasha, "Deadweight Loss of Bacterial Resistance Due to Overtreatment," *Health Economics*, 2003, 12(2): 125-138.

WHO (2003) Review of the Economic Impacts of Antibiotics for Growth Promotion in Denmark

In 2002, WHO convened an international expert panel to review, among other issues, the economic impact resulting from the Danish ban of antibiotics for growth promotion, particularly in swine and poultry production.[5] As part of this effort, Denmark's National Committee for Pigs estimated that the cost of removing antibiotic growth promoters in Denmark totaled about $1.04 per pig, or a 1 percent increase in total production costs. In the case of poultry, however, there was no net cost because the savings associated with not purchasing these antibiotics offset the cost associated with the reduction in feed efficiency. Components of these costs included excess mortality, excess feeding days, increased medication, and increased workload.

A subsequent study by Jacobsen and Jensen (2003) used these costs as part of the agriculture sector of a general equilibrium model to estimate the impact on the Danish economy of the termination of antibiotic growth promoters.[6] The model used these cost assumptions in a baseline scenario that projects the likely development of the Danish economy to 2010.

The results of the model indicated a small reduction in pig production of about 1.4 percent per year and an increase in poultry production of about 0.4 percent. The authors explain that the increase in poultry production occurred because of the substitutability of these meats in consumption. In addition, this research included estimates of the consequences of removing antibiotic growth promoters on the export market. The model showed that exports of pork were forecast to be 1.7 percent lower than they would be in the absence of these growth promoters, while poultry exports would increase by about 0.5 percent.

The authors explained that some costs associated with modifications to production systems were difficult to measure and were not included in the analysis, although they may have been substantial for some producers. They also stated that the analysis does not take into account the possible positive effect that the removal of antibiotic growth promoters may have

[5]World Health Organization, *Impacts of Antimicrobial Growth Promoter Termination in Denmark*, Department of Communicable Diseases, Prevention and Eradication and Collaborating Centre for Antimicrobial Resistance in Foodborne Pathogens, 2003.

[6]L.B. Jacobsen and H.G. Jensen, "Sector and Economy Wide Effects of Terminating the Use of Antimicrobial Growth Promoters in Denmark," In: International Invitational Symposium; Beyond Antimicrobial Growth Promoters in Food Animal Production, November 6-7, 2002 (subsequently revised, 2003), Foulum, Denmark.

had on consumer demand, both in the domestic and in the export markets. Moreover, they added that any costs must be set against the likely human health benefits to society.

Hayes and Jensen (2003) Study Based on the Danish Ban of Feed-Grade Antibiotics in the Pork Industry

In 2003, using a 1999 study by Hayes et al. of the potential economic impacts of a U.S. ban based on the ban in Sweden, as described below, and a recent ban on feed-grade antibiotics in Denmark, Hayes and Jensen estimated the economic impacts of a similar ban in the United States.[7] In 1998, the Danish government instituted a voluntary ban on the use of antibiotics in pork production at the finishing stage, and in 2000 it banned antibiotics for growth promotion at both the weaning and the finishing stages. The results of the ban in Denmark, however, may be more applicable than the Swedish experience because, like the United States, Denmark is one of the largest exporters of pork and has somewhat similar production practices.[8] The authors compared the econometric results of a U.S. baseline without a ban with projected results based on assumptions taken from the ban in Denmark. Many of the same technical and economic assumptions that were used in the Swedish study were also used for the impacts based on the Danish ban. For instance, the authors included a sort-loss cost of $0.64 per animal, a similar assumption for loss of feed efficiency, and decreases in piglets per sow.[9] Other key assumptions and features unique to the study include the following:

- the use of only one case or scenario—a "most-likely" scenario—unlike the study based on the Swedish ban;
- increased costs of $1.05 per animal at the finishing stage and $1.25 per animal at the weaning stage;

[7]Dermot J. Hayes and Helen H. Jensen, "Lessons from the Danish Ban on Feed-Grade Antibiotics," Briefing Paper 03-BP 41, Center for Agricultural and Rural Development, Iowa State University, Ames, Iowa, June 2003.

[8]While the United States and Denmark are both leading pork exporters, their market structures are different. In Denmark, unlike in the United States, farmer cooperatives dominate production, processing, and distribution systems.

[9]Sort-loss costs represent discounts or penalties for increased weight variability for marketing swine that are either too light or too heavy. The Swedish experience indicated that removal of antibiotics in feed increased this variability at marketing. However, because they were able to influence the packers to accept more light weight pigs, Swedish producers actually did not have a problem with sort loss.

- a vaccine cost of $0.75 per animal; and
- a capital cost of about $0.55 per animal;

According to the study, a major economic impact in the U.S. pork market of a ban similar to the Danish ban would be a cost increase of about $4.50 per animal in the first year. Across a 10-year period, the total cost to the U.S. pork industry was estimated to be more than $700 million. With a lower level of pork production, retail prices would increase by approximately 2 percent. The authors conclude that a ban at the finishing stage would create very few animal health concerns, while a ban at the weaning stage would create some serious animal health concerns and lead to a significant increase in mortality. They also note that, as happened immediately following the ban at the weaning stage in Denmark, the total use of antibiotics in the United States at this production stage may rise.

Miller et al. (2003) Study Using 1990 and 1995 NAHMS Data on the Economic Effects of Antibiotics Used for Growth Promotion in U.S. Pig Production

Miller et al. (2003) used 1990 and 1995 National Animal Health Monitoring System (NAHMS) swine survey data to estimate the net benefit of antibiotics used for growth promotion to swine producers.[10] The NAHMS database provides statistically valid estimates of key parameters related to the health, management, and productivity of swine operations in the United States.[11] The authors used econometric methods to estimate the relationships between growth-promoting antibiotics and productivity measures, such as average daily weight gain (ADG) and feed conversion ratio (FCR), for grower/finisher pigs. Using these productivity measures, predictions on performance were then generated for an independent, medium-sized, midwestern farrow-to-finish pork producer in 1995. The performance figures were expressed in economic terms, such as profitability, using a swine enterprise budgeting model. The study includes the following key features and assumptions:

[10]Gay Y. Miller, Kenneth A. Algozin, Paul E. McNamara, and Eric J. Bush, "Productivity and Economic Effects of Antibiotics Used for Growth Promotion in U.S. Pork Production," *Journal of Agricultural and Applied Economics*, 35,3(December 2003): 469-482.

[11]The National Animal Health Monitoring System (NAHMS) is a program operated by veterinary and animal science professionals at USDA's Center for Animal Health Monitoring. A primary function of this branch of USDA is to make periodic surveys and assessments of animal health management practices on commercial livestock farms across the United States.

- The productivity measures estimated were ADG, FCR, and mortality rate (MR) during the grower/finisher stage of swine production.
- Explanatory variables included in the model were regional identifiers, size of operation, market structure variables, number of rations, mortality rate, number of days antibiotics were administered, number of antibiotics fed, number of diseases diagnosed in last 12 months, among others.
- The ADG and FCR equations were estimated jointly using the seemingly unrelated regression procedure.
- Because the theory as to an exact specification was unknown, the MR equation was estimated using a backward-stepwise linear regression.

The authors estimated that increases in annual returns above costs from antibiotics for a 1,020-head finishing barn was $1,612, or $0.59 per swine marketed. This represents an improved profitability of approximately 9 percent of net returns in 2000 for Illinois swine finishing operations. The authors also found that there is substitutability between antibiotics as growth promoters and other production inputs (such as number of rations) that could reduce the negative influence of removing antibiotics.

Miller et al. (2003) Study Using 2000 NAHMS Data to Estimate the Productivity and Economic Impacts of Antibiotic Use in U.S. Pig Production

In an updated study, Miller et al. (2003) estimated the combined effects of antibiotics used for growth promotion (AGP) and antibiotics used for disease prevention (ADP) in pork production using the NAHMS 2000 swine survey.[12] Specifically, the authors measured the productivity and the economic impacts of these antibiotics on grower/finisher pigs for individual swine producers. The authors evaluated four scenarios, using varying degrees of bans of both AGP and ADP: (1) a ban on AGP, (2) a ban on ADP, (3) a ban on both AGP and ADP, and (4) a limitation on AGP and ADP to levels that maximize production. These scenarios were chosen because antibiotics that are used for different purposes have different impacts on productivity, improving it on one dimension while possibly diminishing it on another. First, the authors estimated four pork productivity dimensions related to the use of antibiotics using an

[12] Gay Y. Miller, Xuanli Liu, Paul E. McNamara, and Eric J. Bush, "Producer Incentives for Antibiotic Use in U.S. Pork Production," paper prepared for presentation at the American Agricultural Economics Association Annual Meeting, Montreal, Canada, July 2003.

econometric model. Second, using the estimated productivity measures from the econometric model, they estimated economic impacts to pork producers for each antibiotic ban scenario using a spreadsheet farm budget model. The study includes the following key features and assumptions:

- Pork productivity was measured using four measures of productivity, including average daily weight gain, feed conversion ratio, mortality rate, and lightweight rate.
- These productivity measures were estimated using seemingly unrelated regression analysis and are modeled from the perspective of possible structural relationships among the measures.
- The study used the NAHMS 2000 study, which provides the most recent data available to investigate productivity impacts and impacts on farm costs and profitability.

Overall, the authors confirmed their earlier findings that a ban would likely cause substantial short-term losses to producers. However, decreasing the use of certain antibiotics to a more desirable level may be implemented without major losses. For scenario 1, a total ban on AGP would cost producers $3,813 in profits annually.[13] For scenario 2, a ban on ADP would slightly improve profits by a gain of $2703 annually. For scenario 3, a ban on both AGP and ADP would lower producer profits by $1128 annually. For scenario 4, where AGP and ADP are applied at levels where swine productivity is maximized, producers would gain $12,438 annually compared with no antibiotic use. The authors conclude that restrictions on classes of AGP, the amount of time antibiotics are fed, and restrictions on ADP many be implemented by producers without major losses. However, they also note that some time dimensions ignored in their study may be important and that their use of nonexperimental data requires careful interpretation.

[13]Each scenario in the model estimates profit for a 1,020-head barn of swine. A swine producer, however, could have many such barns in his/her operation.

Brorsen et al. (2002) Study on Economic Effects of a Ban on the Use of Antibiotics for Growth Promotion in Swine Production

Brorsen et al. (2002) used a model similar to one developed by Wohlgenant (1993) to estimate the economic impacts on producers and consumers of a ban on antibiotics used for growth promotion in swine production.[14] The authors used a model that allowed for feedback between beef and pork markets and measured changes in producer and consumer surplus resulting from shifts in both supply and demand. Moreover, the authors extended their two-commodity beef and pork model to include poultry. In their model, changes in production costs due to banning the use of antibiotics for growth promotion are measured indirectly by the net benefits from their use. The study includes the following key features and assumptions:

- The ban considered in this model is a complete ban on all antibiotics in feed.
- The effects of using antibiotics for growth promotion were assumed to be from improvements in (1) feed efficiency over drug cost, (2) reduced mortality rate, and (3) reduced sort-loss at marketing.
- The authors assumed a $45.00 per hundredweight market price for hogs.
- All parameters (i.e., demand and supply elasticities) used to solve the model were based on other economic studies, except the parameter that represented the change in production costs. Once these were obtained, retail quantity, retail price, farm quantity, and farm price were determined simultaneously.
- An econometric model was used to obtain the economic benefit from the improvement in feed-to-gain conversions in swine production.
- The mortality benefit in swine was assumed to range from 0 percent, to 0.75 percent (most likely), to 1.5 percent.

[14]B. Wade Brorsen, Terry Lehenbauer, Dasheng Ji, and Joe Conner, "Economic Impacts of Banning Subtherapeutic Use of Antibiotics in Swine Production," *Journal of Agricultural and Applied Economics*, 34,3 (December 2002): 489-500; and M.K. Wohlgenant "Distribution of Gains from Research and Promotion in Multi-Stage Production Systems: The Case of the U.S. Beef and Pork Industries," *American Journal of Agricultural Economics* 75 (1993): 642-651.

- Net benefits of the use of antibiotics for growth promotion were estimated by summing the results of a simulation exercise based on the probability distributions of the three sources of economic benefits at the industry level.

The authors estimated that economic costs to swine producers from a ban on antibiotics used for growth promotion would range from $2.37 per hog to $3.11 per hog, with an average cost of $2.76 per hog. For swine producers, the estimated annual costs would be approximately $153.5 million in the short run to $62.4 million in the long run. Estimated annual costs to pork consumers would increase by about $89 million in the short run to $180 million in the long run.

Mathews, Jr. (2002) Analysis of the Economic Effects of a Ban on Antibiotics in U.S. Beef Production

Mathews, Jr. (2002) examined the economic effects of a ban on antibiotic use in U.S. beef production using two policy alternatives—a partial ban and a full ban.[15] To estimate these effects, the author developed a series of economic models, including a firm-level, cost-minimization model that minimizes the cost of feeding cattle to final output weights for a base case, a full ban, and a partial ban (banning only selected antibiotics) scenario. Imbedded in this model is a growth function that incorporates the interaction between the growth rate of cattle and feed efficiency. The firm-level effects were then aggregated across firms in a partial equilibrium framework to estimate national cattle supply, price, and value of production for the three scenarios. The study includes the following key features and assumptions:

- Variables included in the growth function were lagged average daily weight gain, feed efficiency, seasonal variables, and an interaction variable of average weight gain and feed efficiency. The growth model forms a "dynamic" link to the cost-minimization model by accounting for the impacts of recent feeding experiences.

- In the cost-minimization model, feed costs were minimized, subject to protein levels and other feed constraints. The model finds the minimum cost for feeding a steer to a final weight estimated from the embedded growth function.

[15]Kenneth H. Mathews, Jr., "Economic Effects of a Ban Against Antimicrobial Drugs Used in U.S. Beef Production," *Journal of Agricultural and Applied Economics,* 34, 3 (December 2002): 513-530.

- The resulting model allowed final cattle weights, feeding costs, and the number of cattle fed per year to vary, resulting in livestock supplies that are endogenous to the model.
- In the partial-ban scenario, substitute antibiotics were assumed to be functionally equivalent to and twice as costly as in the base scenario.
- Data for the aggregate analysis included annual average all-cattle prices and commercial beef production for the period 1975 through 1990. A base scenario was estimated using parameter and final steer weight estimates from the growth model for each quarter over an 11-year period, from January 1990 through January 2001.

Results of the partial-ban scenario indicated that aggregate annual income would decrease by nearly $15 million for producers, while annual consumer costs would increase by $54.7 million.[16] For the full ban, a 4.2 percent decline in beef production would yield a 3.32-percent increase in the price of cattle, from $42.60 to $47.12 per hundredweight. Also, the full ban translates into an annual consumer cost increase of $361 million. The author noted that the study did not take into account any effects of a ban or partial ban on trade in beef products.

Hayes et al. (1999) Study Based on the Swedish Ban of Antibiotics in the Pork Industry

A study issued in 1999 by Hayes et al. at Iowa State University estimated the potential economic impacts of a ban on the use of antibiotics in U.S. pork production based on assumptions from a Swedish ban in 1986.[17] To estimate baseline results, the authors used a simultaneous econometric framework of the U.S. pork industry that included several production and marketing segments: live inventory and production, meat supply, meat consumption, meat demand, and retail price transmission. The baseline results, or results with no change in antibiotic use, were compared to a range of estimates of a ban on antibiotics in pork production in the United States based on a set of technical and economic assumptions taken from the Swedish experience. These simulations included three different scenarios: a "most likely," a "best-case," and a "worst-case" scenario if the

[16]All estimates for this study are in 1984 dollars.

[17]Dermot J. Hayes, Helen H. Jensen, Lennart Backstrom, and Jay Fabiosa, "Economic Impact of a Ban on the Use of Over-the-Counter Antibiotics," Staff Report 99-SR 90, Center for Agricultural and Rural Development, Iowa State University, Ames, Iowa, December 1999.

ban were to be implemented in the United States. The key features and assumptions of the model for the "most likely" case included the following:

- a 10-year projection period from 2000 to 2009 from a 1999 baseline, with deviations from the baseline in the projection period reflecting the technical and economic assumptions taken from the Swedish ban;
- the pork, beef, and poultry markets, although the model assumed no change in the regulation of antibiotics on beef and poultry;
- technical assumptions: feed efficiency for pigs from 50 to 250 pounds declines by 1.5 percent, piglet mortality increases by 1.5 percent, and mortality for finishing pigs increases by 0.04 percent. Also, the "most likely" case extends weaning age by 1 week and piglet per sow per year decrease by 4.82 percent.
- veterinary and therapeutic costs would increase by $0.25 per pig, net of the cost for feed additives;
- additional capital costs would be required because of additional space needed for longer weaning times and restricted feeding, including $115 per head for nursery space and $165 per head for finishing space;
- an estimated penalty of $0.64 per head for sort-loss costs; and
- input markets, such as the cost of antibiotics, are exogenous or not a part of the modeling system.

The authors in their "most likely" scenario estimated that the effects of a ban on the use of antibiotics would increase production costs by $6.05 initially and $5.24 at the end of the 10-year period modeled. Because the supply of pork declines, however, net profit to farmers would decline by only $0.79 per head. Over a 10-year period, the net present value of forgone profits would be about $1.039 billion. For consumers, the retail price of pork increases by $0.05 per pound, which sums to a yearly cost of about $748 million for all consumers.

The authors also cited four important limitations to their study: (1) the estimated impacts represent an "average" farm and may mask wide differences across farms; (2) technical evidence from the Swedish experience must be regarded with caution as an indicator of what might happen in the United States; (3) consumers only respond to changes in the price of pork; however, the model does not take into account how such a ban would affect the prices of beef and poultry; and (4) there was no attempt to factor in the positive effects of such a ban on consumer willingness to pay for pork produced without the use of feed-grade antibiotics.

National Research Council's (1999) Economic Analysis of the Costs of Eliminating Subtherapeutic Use of Antibiotics in Animals

The National Research Council (NRC) examined the economic costs to consumers of the elimination of all subtherapeutic use of antibiotics in a chapter of a 1999 report entitled *The Use of Drugs in Food Animals: Benefits and Risks*.[18] Instead of measuring the consequences of eliminating antibiotics on farm costs and profits, NRC decided that a more viable alternative would be to measure costs to consumers in terms of the higher prices that would be passed on to consumers. According to NRC, this measurement strategy was followed for several reasons: changes in production costs do not necessarily translate into lower profits; depending on management practices, not all producers rely on these antibiotics to the same extent and would not all be equally affected by a ban; and some producers, for example those who produce for special niche markets, may actually benefit from such a ban.[19] The study includes the following key features and assumptions:

- All cost increases are passed on to consumers in terms of percentage price changes.
- The model measures how much consumers would need to spend in order to maintain a similar level of consumption as before the ban.
- No change in consumption because of a ban on antibiotics would occur.

[18]National Research Council, "Costs of Eliminating Subtherapeutic Use of Antibiotics," Chapter 7, in *The Use of Drugs in Food Animals: Benefits and Risk*, National Academy Press, Washington, D.C., 1999, 179-187. Although the precise definition is the subject of some debate, subtherapeutic use refers to antibiotic use in animal production to improve animal performance, such as enhanced growth rates or improved feed efficiency, whereas therapeutic use refers to antibiotics used to treat specific health problems.

[19]The NRC cites Colemon Natural Beef of Colorado, a company that raises its beef without antibiotic treatments or exogenous growth promoters, as an example of such a company.

- Per capita costs are estimated as the product of three items: (1) percentage increase in annual production costs, (2) retail prices, and (3) per capita annual retail quantity sold.

- Annual costs of a ban were estimated for four domestic retail markets—chicken, turkey, beef, and pork—as well as a total cost for all meat.

NRC estimated that the average annual cost per capita to consumers of a ban on all antibiotic use was $4.84 to $9.72. On a commodity retail price basis, the change in price for poultry was lowest, from $0.013 per pound to $0.026 per pound; for pork and beef, prices ranged from $0.03 per pound to $0.06 per pound. Retail pork price increases ranged from $0.03 per pound to $0.06 per pound. Total national additional costs per year for pork consumption ranged from $382 million to $764 million, depending on assumptions about meat substitutes. As for all meat products combined, total consumer cost increases ranged from $1.2 billion to $2.5 billion per year. Finally, NRC noted that the reduction in profits and industry confidence that would result from such a ban may cause a reduction in research, and that society would lose the research benefits. Also, to determine whether this cost increase would be justified, the amount should be compared with the estimated health benefits.