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Antibiotic Resistance in Foodborne Pathogens:
Evidence of the Need for a Risk Management Strategy

A CSPI White Paper by
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Contents

"[T]here is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials. These consequences include infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death) and increased severity of infections, as documented for instance by fluoroquinolone resistant human Salmonella infections" (WHO, 2003).

Information on outbreaks of foodborne illness due to antibiotic-resistant bacteria is limited. *Salmonella* and *E. coli* are not routinely tested for antibiotic resistance, and even when tests are performed, results are not required to be reported to the Centers for Disease Control and Prevention (CDC). The Center for Science in the Public Interest (CSPI) documented through literature searches a total of 35 foodborne outbreaks between 1973 and 2009 in which the bacteria identified were resistant to at least one antibiotic (Appendix A). This report illustrates the link between foods, mostly of animal origin, and outbreaks of antibiotic-resistant pathogens (mostly *Salmonella)* in humans. Outbreaks caused by antibiotic-resistant bacteria are not an emerging problem, but an *established* problem that needs more routine scrutiny by public health officials.

The National Antimicrobial Resistance Monitoring System (NARMS) collects data on patterns of emerging resistance from pathogens. Those data are not linked to actual outbreaks. Also, CDC does not track and publish outbreaks or sporadic illnesses caused by resistant bacteria, as it does for pathogens in its FoodNet system. Therefore, CSPI developed this preliminary database of outbreaks due to antibiotic-resistant bacteria in the food chain to encourage health officials to track those outbreaks more closely in the future. Cataloging foodborne illness outbreaks is a critical step in documenting the link between administering antibiotics to farm animals and human illness as it relates to antibiotic resistance.

Antibiotic-Resistant Foodborne Illness Outbreaks in the United States
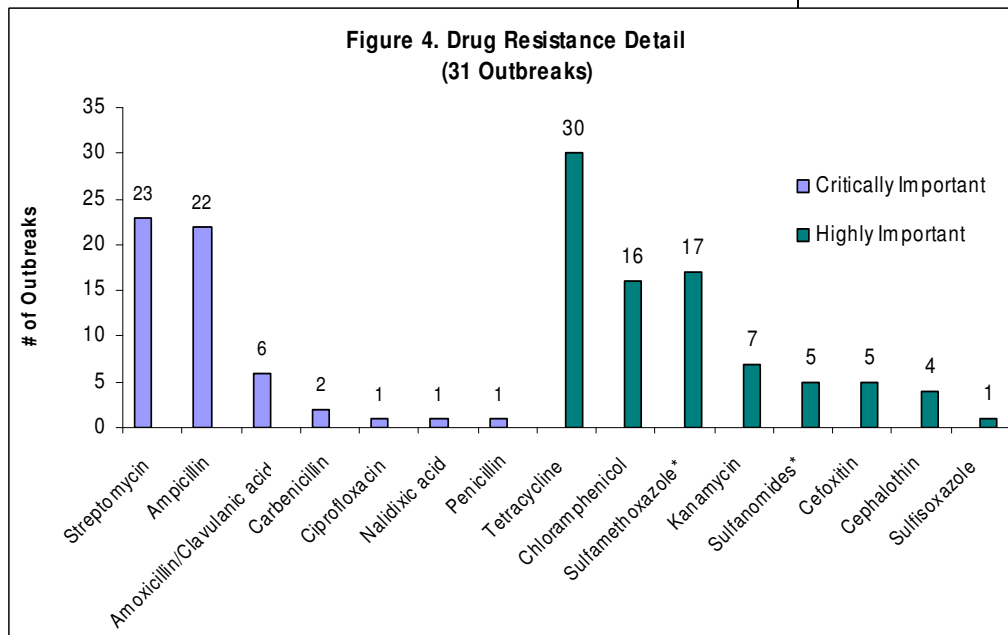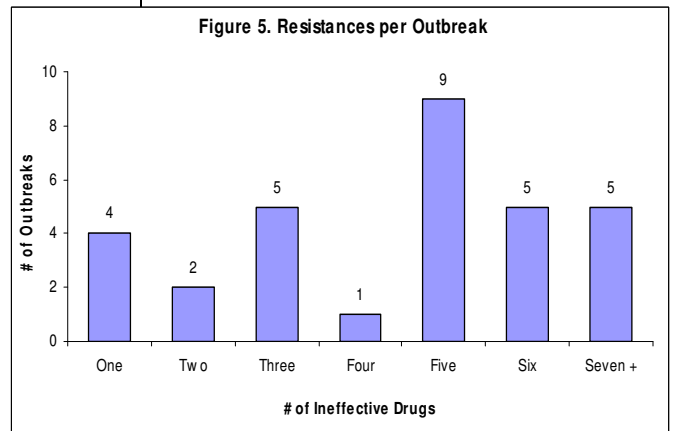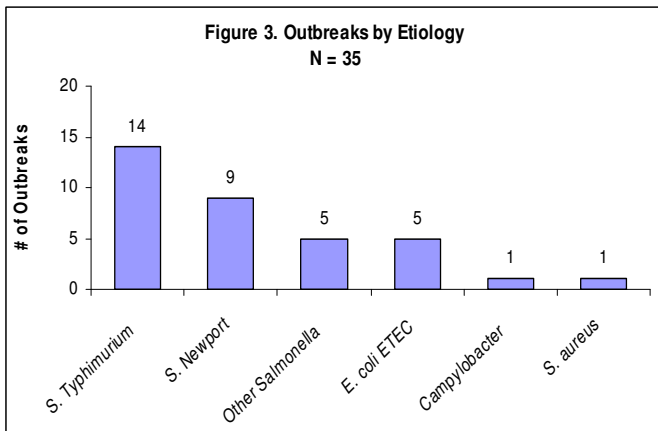
Findings

Reporting of outbreaks due to antibiotic resistant bacteria has increased in each decade since the 1970s, with 40% (14 out of 35) occurring in the last decade (Figure 1). Whether the increase is due to increasing use of antibiotics or to increased testing and reporting could not be determined. Outbreaks were most common in dairy products (34%) and ground beef (26%). Two outbreaks each were linked to poultry, pork, produce, and seafood, and one outbreak each was linked to eggs and multi-ingredient foods. The food vehicle was unknown in four of the outbreaks (Figure 2). A total of 19,894 people were sickened from these 35 outbreaks. This includes one huge *Salmonella* Typhimurium outbreak in milk in 1985 in which 16,659 were sickened, 2,777 were hospitalized, and 18 died.

Figure 1. Outbreak Trends by Year
N = 35

Figure 2. Outbreaks by Food Category
N = 35
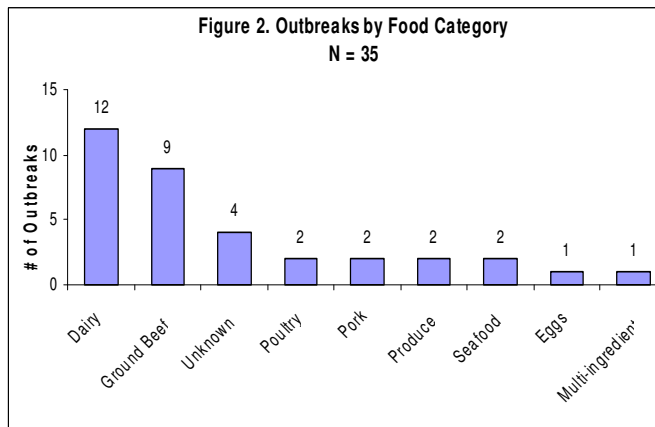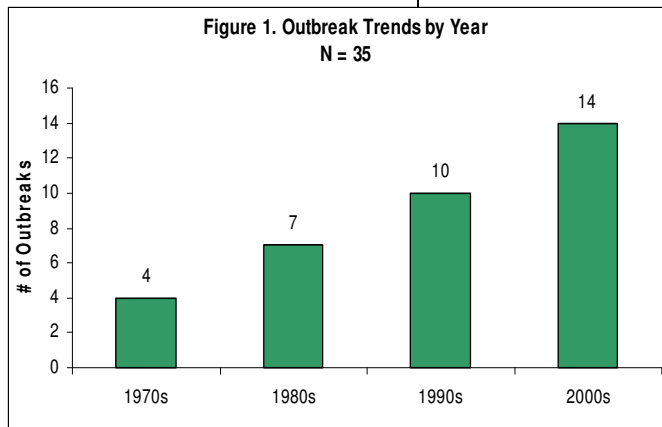
A total of 19,897 people were sickened from these 35 outbreaks. That includes one huge *Salmonella* Typhimurium outbreak caused by milk in 1985 in which 16,659 were sickened, 2,777 were hospitalized, and 18 died.

The most frequently identified bacterial pathogen was *Salmonella* Typhimurium, which was implicated in 14 outbreaks causing 17,808 illnesses (40% of outbreaks, including the one large outbreak) followed by *Salmonella* Newport, which was implicated in nine outbreaks with 586 illnesses (26% of outbreaks). Five other *Salmonella* subspecies were each implicated in one outbreak, with a total of 923 illnesses. Several serotypes of enterotoxigenic *Escherichia coli* (ETEC) were identified in five outbreaks, resulting in 446 illnesses. C*ampylobacter jejuni* and *Staphylococcus aureus* were responsible for one outbreak each, with 128 and 3 illnesses, respectively (Figure 3).

For the 31 outbreaks for which antibiotic-resistance patterns were determined, the responsible bacteria displayed resistance to a total of 14 different antibiotics and to at least one sulfonamide, which is a class of antibiotics. Of those antibiotics, seven are classified by the World Health Organization (WHO) as critically important to human medicine and eight as highly important to human medicine. Bacteria showed resistance to tetracycline in 30 outbreaks. Resistances to streptomycin and ampicillin, both classified as critically important antibiotics, were the next most common (Figure 4). Bacteria associated with 19 outbreaks were resistant to at least five antibiotics (Figure 5). Fifteen of those occurred between 1990 and 2009.

Figure 3. Outbreaks by Etiology
N = 35

Figure 5. Resistances per Outbreak

Figure 4. Drug Resistance Detail
(31 Outbreaks)

* Sulfonamide resistance was listed in five outbreaks. Sulfonamides are a class of drug, not a specific antibiotic. Resistance to sulfamethoxazole, a member of that class, was associated with 17 outbreaks.

**Meat-Related
Outbreaks**

CSPI identified a total of 13 outbreaks related to meat products: nine in ground beef, two in poultry, and two in pork. Of the ground beef-related outbreaks, *S.* Newport was implicated in seven outbreaks and *S.* Typhimurium in two. Meat outbreaks were associated with 1,376 illnesses, 96 hospitalizations, and 5 deaths.

**Dairy-Related
Outbreaks**

Of the 12 outbreaks related to dairy products, seven were associated with milk and five with cheese products. In ten of the outbreaks, the vehicle was described as unpasteurized or raw milk and/or cheese made from unpasteurized milk. Pasteurized milk was responsible for two of the dairy-related outbreaks, including one exceptionally large one. All outbreaks related to dairy products were caused by *Salmonella*—nine by *S.* Typhimurium, two by *S.* Newport, and one by *S.* Dublin. Dairy-related outbreaks sickened at least 17,122, hospitalized 2,860, and killed 19 people (including the outbreak caused by *S.* Typhimuriuim in which 16,659 were sickened, 2,777 were hospitalized, and 18 died).

Background

Development of Antibiotic-Resistant Bacteria in Farm Dwellers

In a study done in the 1970s, isolates from chickens on a farm and from people who lived on the farm were tested and found to have low initial levels of tetracycline-resistant E. coli bacteria. Within two weeks after the chickens were fed tetracycline-supplemented feed, 90 percent of the chickens were excreting bacteria that were resistant to tetracycline. Although the chickens were exposed only to tetracycline, many of the bacteria developed resistance to four antibiotics. Within six months, seven of the 11 people who lived on the farm were excreting antibiotic-resistant E. coli bacteria. When these people were retested six months after the tetracycline-supplemented feed was discontinued, no detectable tetracycline-resistant organisms were found in eight of ten people (Levy et al., 1976).

The discovery of antibacterial agents in the first half of the 20th century radically changed the outcome of common human diseases. Many illnesses that are now readily treatable were often deadly before antibiotics became available. Yet, the ability of bacteria to evolve mechanisms to resist attack by antimicrobials[1] was recognized soon after the widespread deployment of the first antibiotics.

Resistance is an inevitable consequence of antibiotic use; the more antibiotics are used, the more bacteria will develop resistance. In recent years, scientists have begun to understand the sophisticated biochemical mechanisms that allow bacteria to fend off or neutralize antibiotics, and resistance has begun to emerge more rapidly. This poses a major threat to the continued effectiveness of antibiotics used to treat human and veterinary illnesses. Further exacerbating the problem, fewer new antibiotics are being developed to replace those that are no longer effective (Silbergeld et al., 2008).

Numerous studies have documented direct transference of antibiotic-resistant bacteria from animals to humans. After antibiotics were administered to animals to treat infections, the prevalence of antibiotic-resistant E. coli and Campylobacter bacteria also increased in humans. Other studies have confirmed that antibiotic-resistant Campylobacter, Salmonella Typhimurium DT 104, and Salmonella Newport have moved from animals to humans through foods of animal origin (Smith et al., 1999; Ribot et al., 2002; Gahart & Lansburgh, 2004). Reflectin the fact that bacteria can develop resistance to numerous antibiotics at the same time, one group of related antibiotic-resistant Salmonella Newport strains is resistant to most available antimicrobial agents approved for the treatment of salmonellosis, particularly in children (Gupta et al., 2003).

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[1] The term "antimicrobial" is a broad term referring to substances that act against a variety of microorganisms, including bacteria, viruses, parasites and fungi. The term "antibiotic" is a narrower term referring to substances used to treat bacterial infections. Classically, antibiotics were produced by a microorganism, but now both manufactured and naturally occurring substances that kill bacteria are called antibiotics. Most of the concern with antimicrobial use in agriculture is with bacterial resistance, so "antibiotic" will be used in this report.

The human health consequences of these resistant organisms include more serious infections and increased frequency of treatment failures. Patients may experience prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization, and increased mortality (Angulo et al., 2004). Health care costs increase with longer hospital stays and the need for more expensive antibiotics to fight resistant pathogens. The antibiotics used to treat resistant pathogens can be more toxic, with more serious side effects, to the patients.

The reported outbreaks demonstrate the problem of antibiotic resistance in foodborne pathogens, but the risk-management strategy is complicated by the division of authority among several federal agencies and the diverse stakeholders, particularly the drug manufacturers and cattle, hog, and poultry industries. To help determine the cause and identify potential solutions, information is required on the types and quantities of antibiotics sold for use in food-producing animals, the species they are used in, when they are administered, the purpose of their use (disease treatment, disease prevention, or growth promotion), and the method used to administer them. Denmark collects information on the quantities of antibiotics used in animal species by age group and the method of administration. Those data have allowed Danish researchers to determine how changes in the use of antibiotics in animals affect the emergence of antibiotic-resistant bacteria (Gahart & Lansburgh, 2004).

"People infected with drug-resistant organisms are more likely to have longer and more expensive hospital stays, and may be more likely to die as a result of the infection. When the drug of choice for treating their infection doesn't work, they require treatment with second- or third-choice drugs that may be less effective, more toxic, and more expensive" (CDC, 2010).

Many of the antibiotics used for food-producing animals are the same, or belong to the same classes, as those used in human medicine. Resistance to one antibiotic in a class often results in resistance to all drugs in that class, further compounding the problem. In addition, the genes that can render a bacterium resistant are being selected for and can even be shared by different species through horizontal gene transfer. Widespread use of these antibiotics in agriculture can render them ineffective against human illnesses.

The World Health Organization (WHO) has developed criteria for ranking antimicrobials according to their importance in human medicine. The rankings are regularly reviewed by WHO's Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). This ranking of different drugs was developed strictly from a human health perspective for governments and other stakeholders to use when developing risk management strategies concerning the use of antimicrobials in food animals.

The WHO divides 121 antimicrobials into three categories: critically important, highly important, and important, based on their overall importance to human health. Antimicrobial agents are defined as "critically important" if they are the sole or one of few options for treatment of human infections (WHO, 2009).

The WHO lists 77 antibiotics listed as critically important, 36 as highly important, and eight as important. In 2003, the Food and Drug Administration (FDA) also compiled a list ranking 76 antimicrobial drugs according to their importance in human medicine. The FDA ranked 22 drugs as critically important, 36 drugs as highly important, and 18 drugs as important (FDA, 2003).

Antibiotics Important in Human Medicine

"In light of the risk that antimicrobial resistance poses to public health, FDA believes the use of medically important antimicrobial drugs in food-producing animals for production purposes (e.g., to promote growth or improve feed efficiency) represents an injudicious use of these important drugs" (FDA, June 2010).

Antibiotic use in Food-Producing Animals

Antibiotics are used in food-producing animals to treat or prevent
illnesses for example, during the weaning period of young animals.
They may also be used for long periods at low levels to promote
growth, increase feed efficiency, or compensate for unsanitary
growing conditions on concentrated animals feeding operations
(CAFOs) Increased feed efficiency means animals require less
feed per pound of weight gain, which translates to lower costs for
producers. Many animal producers believe the use of antibiotics
for growth promotion also prevents disease (Gahart & Lansburgh,
2004).

In the industrial model of animal husbandry, large numbers of pigs, chickens, or cattle are raised in confined areas. In the pork and chicken industries, large-scale concentrated housing systems reduce costs for labor, feed, and housing. However, the increased stress of crowding and unsanitary conditions makes animals more susceptible to the spread of infectious diseases. Many producers commonly administer an antibiotic to an entire flock or herd via feed or water, but that gives them less control over the dosage consumed by individual animals. This nontherapeutic[2] use of low doses of antibiotics, sometimes administered throughout an animal's life, is among the practices of greatest concern for the development of antibiotic resistance.

Exacerbating the problem is that farmers in the United States can obtain many antibiotics for their animals without a prescription, and can administer those drugs without veterinary advice or oversight. That over-the-counter use has resulted in little reliable historical data regarding the use of antibiotics in food animal production. Beginning in 2008, however, antibiotic drug manufacturers were required to report annually to the FDA the amount of drugs that have been sold or distributed for use in food-producing animals. For 2009, the total quantity of antibiotics distributed for use in all food-producing animal species was slightly over 29 million pounds of active ingredient (FDA, 2010). That amount was not broken down by species, by route of administration, or by purpose of use.

> ### *Quinoline-resistant Camplobacter jejuni in the U.S.*
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> *Emergence of quinoline-resistant Camplobacter jejuni in the U.S. coincided with the approval of fluoroquinolones for use in poultry in 1995. Rates of resistance to fluoroquinolones among human C. jejuni isolates rose sharply during this period as well. Quinolones had been used in human medicine in the U.S. since 1985 with almost no resistance noted. Researchers in Minnesota found an association between molecular subtypes of quinolone-resistant C. jejuni strains found in humans and those found in retail chicken products. Epidemiologic and laboratory data from the Netherlands, Spain, Taiwan, and the United Kingdom also point to the use of flouroquinolones in poultry as a primary factor in the higher rates of quinolone-resistant C. jejuni in humans (Smith 1999).*

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[2] Nontherapeutic refers to use when animals are treated in the absence of bacterial disease or exposure to disease.