Pathogen Biology

Antimicrobial Resistance

A Focus on Antimicrobial Resistance

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This technical review illustrates the following key points about antimicrobial resistance:

- Growing public health concern worldwide.
- Infections caused by antimicrobial-resistant microorganisms increase the risk of morbidity and mortality in serious diseases.
- Use and misuse of antimicrobial drugs in food animal production and human medicine is the main factor accelerating antimicrobial resistance.
- Dairy products and beef are the most commonly implicated sources in foodborne disease outbreaks.
- Research is focused on identifying sources and reservoirs of resistant bacteria, analyzing resistance mechanisms, as well as investigating dissemination routes of resistant bacteria in food animal production.

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Antimicrobial resistance (AMR) or antibiotic resistance (ABR), the ability of bacteria or other microorganisms to resist the effects of antimicrobial drugs or antibiotics, is a growing public health concern worldwide.[21, 22, 44, 7] Infections caused by antimicrobial-resistant microorganisms often fail to respond to standard treatments, thereby reducing the possibilities of effective treatment and increasing the risk of morbidity and mortality in serious diseases. For instance, it is estimated that approximately 440,000 cases of multidrug-resistance tuberculosis (MDR-TB) emerge annually, causing at least 150,000 deaths.[35, 13, 63] The increasing rate of AMR has raised the concern that we may enter the "post antibiotic era" where no effective antibiotics for treating several life-threatening infections would be available.

The extensive use and misuse of antimicrobials have resulted in the development of AMR both in human and animal bacterial pathogens.[44, 35] The persistent circulation of resistant bacterial strains in the environment leads to possible contamination of food and water.[43] In addition, food animals, when exposed to antimicrobials agents, may serve as a significant reservoir of resistant bacteria that can transmit to humans through the food supply.[13] The resistant bacteria, including strains of *Salmonella*, *Campylobacter*, and *Staphylococcus* have been implicated in several foodborne disease outbreaks.[16]

The economic impact of AMR is significant. Insufficient or failed treatment leading to morbidity

and mortality is a huge human cost.[27] AMR not only increases the need of more expensive therapies but also prolong hospital stays.[9] In 2008, a study of attributable medical costs for antibiotic-resistant infections estimated that infections in 188 patients from a single healthcare institution cost between 13.35 and 18.75 million dollars.[23] The National Academies' Institute of Medicine in 1998 estimated that antimicrobial-resistant bacterial infections cost the United States (U.S.) four to five billion dollars annually.[38] Prudent use of antimicrobials in food animals and human medicine, as well as effective monitoring and surveillance is required to control the spread of antimicrobial-resistant bacteria, control the risks of AMR to human health, and to reduce the economic burden.[13]

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Natural Reservoirs and Transmission

AMR has been recognized in several foodborne pathogens, including *Salmonella*, *Campylobacter jejuni*, *Staphylococcus aureus*, *Escherichia coli* and *Yersinia enterocolitica*.[60, 13] Reservoirs of these pathogens include humans as well as several animals. Food animals which may be asymptomatic carrier of these pathogens, when exposed to antimicrobial agents in the animal production environment, may serve as a reservoir of resistant pathogens. Main animal reservoirs include:[60, 13, 47, 19, 20]

- *Salmonella* -- Multiple animal species, including poultry, cattle, pigs, sheep, horses, and wild birds.
- *Campylobacter jejuni* and *Campylobacter coli* -- Food animals, including cattle, poultry, and swine.
- *Staphylococcus aureus* -- Food animals, including poultry, pigs, and cattle, and companion animals, including cats and dogs.
- Shiga toxin-producing *E. coli* -- Food animals, including cattle and swine.
- *Yersinia enterocolitica* -- Multiple animal species, including pigs, rodents, livestock, and rabbits.

In addition, resistant bacteria have been isolated from the environment, including air, water, soils and animal wastes. Soil microbes provide a large reservoir of resistance genes that can quickly move to other microbial communities, including enteric bacteria and pathogens, upon selection from antibiotic use.[36]

Four Modes of Transmission

1. **Food Animals** -- Antimicrobials are used for therapeutic purposes and growth promotion in food animal production.[50] This exerts selection pressure and leads to the potential development of AMR in commensal bacteria in the intestinal tract of food animals. During slaughtering of these animals, carcass contamination may occur that subsequently lead to contamination of meat from these animals.[15] The resistant bacteria are then transmitted to humans through the consumption of contaminated meat.[60, 47, 37] These bacteria can then colonize humans and cause antimicrobial-resistant infections. For example, food animals contribute a significant proportion of *E. coli* in the human gastrointestinal tract through the consumption of contaminated food. Drug-resistant *E. coli* strains of animal origin (e.g. fluoroquinolone-resistant *E. coli* from chickens) can cause infections in humans.[13] Human infection with *Salmonella enterica* serovar Typhimurium (e.g. definitive phage type (DT) 104) has been associated with the consumption of chicken, beef, pork, sausages, and meat paste.[51] In addition, the resistant bacteria can transfer their resistance genes to other endogenous human bacteria and pathogens, including *Campylobacter*, *Salmonella*, and pathogenic *E. coli* O157.[18, 37, 47]

2. **Animal-to-Human Contact** -- Resistant bacteria from animals can transmit to humans by direct contact.[18] Farmers and farm workers may get exposed to resistant bacteria by handling animals, feed, and manure. These exposures are of significant concern to public health, as they can transfer the resistant bacteria to family and community members, particularly through person-to-person contacts. For instance, a study showed that poultry farmers were at a greater risk of carrying drug-resistant enterococci than the urban residents. Another study reported that poultry house workers were 32 times more susceptible to harbor gentamicin-resistant *E. coli* as compared with community counterparts.[48] In addition, companion animals can also transmit the resistant bacteria to humans. For instance, *Salmonella* Typhimurium DT104 and methicillin-resistant *S. aureus* (MRSA) isolates have been reported to spread from companion animals, such as dogs, horses, and cats to humans.[19, 13, 2]

3. **Animal-to-Animal Contact** -- Resistant bacteria can also spread from intensive food animal production area to outside boundaries through contact between food animals and animals in the external environment. Insects, flies, houseflies, rodents, and wild birds play an important role in this mode of transmission. They are particularly attracted to animal wastes and feed sources from where they carry the resistant

bacteria to several locations outside the animal production facility.[48]

4. **Environment** -- Resistant bacteria enter the environment mainly through waste disposal. Resistant bacteria in the environment (soil, water, air) can transmit to humans via food chain and other human exposure pathways. This occurs in the following ways:[48]
    - Contamination of crops fertilized with animal waste
    - Irrigation of crops contaminated by animal waste
    - Emission of waste aerosols from animal houses or waste storage facilities, field fertilized with untreated manure, or trucks transporting animals for processing
    - Waste runoff into groundwater and surface water
    - Contamination of other food animals

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Mechanisms of Acquiring Antimicrobial Resistance

Microbial populations acquire AMR through two main mechanisms. These include:

1. **Mutation** -- Exposure of bacteria to sublethal concentrations of antimicrobial agents results in the selection of resistant strains (survivor bacteria) by the process of natural selection. Under continuous antimicrobial pressure, the survivor bacteria, which have low intrinsic resistance to antimicrobials, reproduce, spread, rapidly dominate, or can even displace the antimicrobial-susceptible population.[48, 41, 37] Over time, the survivor bacteria undergo mutations which may further enhance their resistance to antimicrobials. Spontaneous mutations may lead to the development of AMR in bacteria and favor survival under antimicrobial pressure.[14, 48] For example, resistance to fluoroquinolones (FQs) in *Campylobacter* occurs spontaneously due to mutations, particularly point mutations, in drug target genes. A single point mutation which occurs in the quinolone resistance-determining region (QRDR) of DNA gyrase A (GyrA), substantially develops resistance towards FQs in *Campylobacter*, while in other enteric organisms (e.g. *Salmonella* and *E. coli*), stepwise accumulation of point mutations is required to acquire high-level FQ resistance.[34, 26]
2. **Gene Transfer** -- The resistance genes may also be acquired by horizontal gene transfer (HGT) which requires a donor of the resistance genes.[35] In bacteria, HGT is mediated by three mechanisms:[36, 34]
    - **Transformation** -- Incorporation of foreign (exogenous) DNA from the surroundings into the genome of a bacterial cell. Transformation may be a main mechanism for acquiring chromosomally encoded resistance (e.g. FQ and macrolide resistance in *Campylobacter*).[36, 34]
    - **Conjugation** -- Transfer of extra-chromosomal DNA segments, known as plasmids, between related or unrelated bacteria through physical contact. Conjugation plays a main role in acquiring plasmid-mediated resistance (e.g. tet (O), tetracycline resistance in *Campylobacter*).[37, 36, 34] Plasmids also possess mobile DNA elements, known as transposons and integrons. These DNA elements possess multiple antimicrobial-resistant genes and are responsible for rapid spread of these genes among different bacteria. For example, the ABR pattern of *S. Typhimurium* DT104 constitutes an integron coding for resistance to sulfonamides, ampicillin, and streptomycin. Resistance can also be transferred from commensal (non-pathogenic) to pathogenic bacteria through conjugation.[37, 14]
    - **Transduction** -- Injection of bacteriophage (viral) DNA into the bacterial genome. Bacterial DNA, which may contain resistant genes, may get incorporated into the viral DNA and may disperse with new bacteriophages. These new bacteriophages may then inject into new hosts and disseminate resistance genes into a new population.[36]

It is estimated that mobile genetic elements, including plasmids, transposons, integrons, gene cassettes, and bacteriophages account for more than 95 percent of AMR acquired by gene transfer.[48] These mobile elements have been shown to transmit genetic determinants for several different AMR mechanisms and may result in rapid dissemination of resistant genes among different bacteria.[37]

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Factors Accelerating Antimicrobial Resistance

There are two main factors which accelerate AMR. These factors include:

1. **Use and Misuse of Antimicrobials** -- Antimicrobials are commonly used to treat infections in humans and animals. However, their use and misuse exerts selection pressure and accelerate selection of resistant bacterial populations. The use and misuse

of antimicrobials in animal production and human medicine is summarized below.

- **Antimicrobials in Animal Production** -- Antimicrobials are used in animal production systems to treat and control bacterial infections as well as for growth promotion.[37, 14] The prolonged use of antimicrobials, particularly at low levels, promotes the selection of AMR among commensal bacteria in the gastrointestinal tract of food animals. For example, FQ-resistant *Campylobacter* have emerged as a result of FQ use in chickens.[1] When contaminated food is consumed, the resistance genes from commensal bacteria can be transferred to other bacteria, including foodborne pathogens, in the intestinal tract of humans. Several studies conducted by the Centers for Disease Control and Prevention (CDC) on antimicrobial-resistant *Salmonella* showed that AMR in *Salmonella* strains was most likely due to the antimicrobial use in food animals, and that most infections caused by resistant strains are acquired from the consumption of contaminated food.[24, 37]

- **Antimicrobials in Human Medicine** -- Antimicrobials are commonly used in human medicine to treat bacterial infections. They are not meant to be used against viral infections like common cold, most sore throats, and flu.[22, 7] Both overuse, such as over-prescribing of antimicrobials for critically ill patients, and underuse, such as taking inadequate dose for an inappropriate length of time, are the main cause of selection of antimicrobial-resistant bacterial populations.[62, 9] The inappropriate use of antimicrobials in the hospitals and close contact among sick patients creates an environment for the dissemination of antimicrobial-resistant bacteria.[41] For example, methicillin-resistant *Staphylococccus aureus* (MRSA) and vanomycin-resistant enterococci (VRE) are mainly associated with hospital environments or those who have had prolonged stays in the hospital.[27]

2. **Environmental Stresses** -- Several environmental stresses, which are frequently applied in food preservation processes, have been linked to the increase in bacterial resistance towards antimicrobials. For example, a study reported an increase in AMR in foodborne pathogens, including *S. aureus*, *E. coli*, and *S. enterica* serovar Typhimurium, under sublethal low pH or high sodium chloride stress. Another study showed that high osmolarity and starvation regulates the expression of bacterial lipocalin, a protein which helps bacterial adaptation to environmental stress and is responsible for the dissemination of AMR genes. Environmental stress can enhance plasmid transfer and plasmid numbers, thereby increasing resistance.[39]

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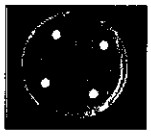
Detection Methods (Antimicrobial Susceptibility Testing)



There are three main purposes of antimicrobial susceptibility testing. These include:[30, 31, 57]

- Detect clinically relevant AMR in common pathogens
- Confirm susceptibility to chosen antimicrobial agents
- Administer appropriate antimicrobial therapy

The methods to determine antimicrobial susceptibility are based on the analysis of bacterial growth on solid or liquid medium containing a specified concentration of a single drug.[25] Several methods are used by clinical laboratories to test antimicrobial susceptibility. These methods are categorized into three main types:

1. **Quantitative Methods** -- In these methods, minimum inhibitory concentration (MIC) i.e. the lowest concentration of antibiotic that inhibits bacterial growth is determined. These methods are performed on a liquid medium (broth) or on a solid medium (agar), and take approximately three days to complete. There are four main types of quantitative methods:[31, 61]

   - **Macrobroth or Tube Dilution Method** -- The procedure involves preparing two-fold dilution of antibiotics in test tubes containing a liquid growth medium. Then, these test tubes are inoculated, incubated, and examined for visible bacterial growth as observed by turbidity. The lowest concentration of antibiotic that completely inhibits visual growth of bacteria (no turbidity) is recorded as MIC. This method is tedious and requires large amount of reagents and space.[31]

   - **Microbroth Dilution Method** -- The procedure involves inoculation of a standard amount of bacteria into the wells of a microtiter plate containing different dilutions of antibiotic. After incubation, the plates are either examined visually or with an analytical instrument for bacterial growth to determine MIC. This method is fast, convenient, reproducible, and requires less space and reagents.[49, 31]

   - **Agar Dilution Method** -- The procedure involves inoculation of a standard

amount of bacteria onto the nutrient agar plates containing different concentrations of antibiotic. After incubation, the plates are examined for bacterial colonies that indicate bacterial growth. The lowest concentration of antibiotic that inhibits colony formation on agar surface is recorded as MIC.[61]

- **Antimicrobial Gradient Method** – The procedure involves the use of commercially available strips containing an exponential gradient of antibiotic. The strips are placed in a radial fashion on the agar plate that has been inoculated with a standard bacterial suspension. After incubation, MIC is read at the point of intersection of an elliptical growth inhibition zone with the strip that has an MIC scale printed on it. The Etest (AB BIODISK) is a commercial version of this method available in the U.S. The test is rapid and easy to use, but is expensive and best suited for MIC determination of one or two drugs.[61, 31, 5]

2. **Qualitative Methods** -- In these methods, susceptibility or resistance of bacteria to a particular antibiotic is determined. MIC is not determined in these methods. The main qualitative method is disk diffusion method.

   - **Disk Diffusion Method** -- The procedure involves the use of paper disks that are impregnated with a single concentration of different antibiotics. The disks are placed onto the agar plate that has been the inoculated with standard number of bacteria. After incubation, zone diameter (zone of inhibition around each antibiotic disk) is measured to the nearest millimeter and reference tables published by the Clinical and Laboratory Standards Institute (CLSI) are used to determine if the bacteria are Susceptible (S), Intermediate (I) or Resistant (R). The test is simple, does not require any special equipment, flexible in terms of disk selection, and is least expensive of all susceptibility methods.[31, 49]

3. **Rapid Methods** -- Several molecular methods that are rapid, and highly sensitive and specific have been developed or are underway research for direct detection of resistance genes. Some of these methods include:[30, 31, 25, 42, 19]

   - Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP)
   - Polymerase Chain Reaction-Single Stranded Conformational Polymorphism (PCR-SSPC)
   - Amplified Fragment Length Polymorphism (AFLP)
   - Pulsed-field Gel Electrophoresis (PFGE)
   - Multilocus Enzyme Electrophoresis
   - DNA Fingerprinting

   Rapid methods have limited application because only a few resistance genes are strongly associated with phenotypic resistance. There are several other mutations and expression mechanisms responsible for AMR which are difficult to detect by current molecular techniques. Therefore, there is considerable need for development of rapid and accurate methods to detect AMRin microorganisms.[30, 31]

For additional information on antimicrobial susceptibility testing, please visit CDC -- Laboratory Testing and Training Resources – Antibiotic/Antimicrobial Resistance.

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Prevention and Control of Antimicrobial Resistance

Limiting the inappropriate use of antimicrobials both in humans and animals, and controlling the transmission of resistant bacteria is a key to control AMR. This can be achieved through the following ways in human medicine and animal agriculture.[4, 37, 13, 16]

In Human Medicine:

- Reducing inappropriate prescriptions and informing consumers about the appropriate uses and limitations of antimicrobial drugs.
- Discouraging the inappropriate use of antimicrobials, such as for viral infections without bacterial complications.
- Using rapid and accurate diagnostic methods to facilitate appropriate drug prescriptions.
- Developing vaccines and adapting hygienic practices, such as hand washing and safe food handling to reduce the spread of AMR.

For additional information on prevention of antibiotic-resistant infections through appropriate use of antimicrobials, please visit CDC -- How can I Prevent Antibiotic-resistant Infections.

In Animal Agriculture:

- Understanding the risks and benefits of antimicrobial use in food animals.
- Development and implementation of principles guiding appropriate antimicrobial use in the food animal production.
- Improvement in animal husbandry and food production practices to reduce the dissemination of AMR.

- Development of regulations for prudent use of antimicrobials in food animals.
- Development of testing and reporting protocols for drug-resistant foodborne pathogens by regulatory agencies.
- Reduction in the usage of antimicrobials that are "critically important" for human medicine in food animals.

In addition, several surveillance programs, and educational and health campaigns have been initiated by national and international agencies to monitor, control, and prevent AMR. Some examples include:[36, 37, 8, 22]

- The National Antimicrobial Resistance Monitoring System (NARMS) established by the Food and Drug Administration (FDA), U.S. Department of Agriculutue (USDA), and CDC monitors trends in antimicrobial resistance of zoonotic bacterial pathogens and facilitate identification of AMR.
- The Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP) monitors antibiotic use, resistance prevalence, and associations between antimicrobial use and resistance prevalence among bacteria associated with humans and animals.
- CDC, in partnership with other agencies, such as FDA, has initiated several National education campaigns to provide both technical and general information on AMR and appropriate use of antimicrobials in different settings.
- The World Health Organization Global Strategy for Containment of Antimicrobial Resistance recommends several interventions that can be used to slow the emergence and reduce the spread of AMR in diverse range of settings.
- The World Health Organization (WHO) has published a report on Critically Important Antimicrobials for Human Medicine to facilitate risk management strategies for non-human antimicrobial use, such as in food animal production.

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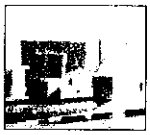
Foodborne Disease Outbreaks



Antimicrobial-resistant strains of foodborne pathogens are widespread throughout the world. Most of these resistant pathogens are zoonotic in origin and acquire their resistance in food animal host before they transmit and infect human beings via the consumption of contaminated food.[51] Therefore, foods of animal origin are frequently associated with antimicrobial-resistant foodborne disease outbreaks. Some foods that have been associated with antimicrobial-resistant infections and outbreaks include:[45, 51, 16]

- Chicken
- Beef
- Pork
- Dairy products
- Salad vegetables

There is limited information available on these outbreaks because reporting of AMR in foodborne pathogens, such as *Salmonella* and *E. coli*, is not required by the CDC. Between 1973 and 2009, 35 outbreaks resulting in 19,897 illnesses, 3,061 hospitalizations, and 26 deaths have been reported by the Center for Science in the Public Interest. Dairy products (34 percent) and ground beef (26 percent) were most commonly implicated foods in these outbreaks. *Salmonella* Typhimurium was the main causative microorganism responsible for 14 of 35 outbreaks.[16]

The lists of national and international outbreaks summarized below, demonstrate that most antimicrobial-resistant outbreaks are associated with *Salmonella* Typhimurium DT104 which is usually resistant to five drugs – ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline.

Selected Foodborne Outbreaks in North America

The following list of national outbreaks indicates that dairy products are the most frequently implicated foods in antimicrobial-resistant outbreaks.

2011 Multistate Turkey Burger Outbreak[10]

- Contaminated turkey burgers
- Resulted in 12 cases
- Contamination was possibly due to improper food handling
- Implicated microorganism was *Salmonella* Hadar with multidrug resistance

2009 Multistate Beef Outbreak[11]

- Contaminated beef and ground beef
- Resulted in 40 cases

- Contamination source was not reported
- Implicated microorganism was *Salmonella* Newport with multidrug resistance

2006-2007 Illinois Cheese Outbreak[6]

- Contaminated Mexican-style aged cheese
- Resulted in 85 cases
- Contamination was due to inadequately pasteurized milk used to prepare cheese
- Implicated microorganism was *Salmonella* Newport with multidrug resistance

2001 Tennessee Barbeque and Coleslaw Outbreak[29]

- Contaminated pork barbeque and coleslaw
- Resulted in three cases
- Contamination was due to handling of barbeque and coleslaw by an infected food handler
- Implicated microorganism was methicillin-resistant *Staphylococcus aureus*

1997 Northern California Cheese Outbreak[12]

- Contaminated Mexican-style cheese
- Resulted in 31 cases
- Contamination was due to unpasteurized raw milk used to prepare cheese
- Implicated microorganism was *Salmonella* Typhimurium DT104 with 5-drug resistance

1997 Northern California Milk-Cheese Outbreak[12]

- Contaminated Mexican-style cheese and raw milk
- Resulted in 79 cases
- Contamination was due to unpasteurized raw milk and cheese prepared from it
- Implicated microorganism was *Salmonella* Typhimurium DT104b with 5-drug resistance

1997 Washington State Cheese outbreak[58]

- Contaminated Mexican-style soft cheese
- Resulted in 54 cases
- Contamination was due to unpasteurized raw milk used to prepare cheese
- Implicated microorganisms were and *Salmonella* Typhimurium DT104 and *Salmonella* Typhimurium DT104b with 5-drug resistance

1985 Illinois Milk Outbreak[46]

- Contaminated pasteurized milk
- Resulted in 16,659 cases
- Contamination was likely due to mixing of raw milk and pasteurized milk
- Implicated microorganism was *Salmonella*Typhimurium with unusual antimicrobial resistance pattern

For additional information on antimicrobial-resistant bacterial outbreaks in the U.S. , visit OutbreakNet -- Foodborne Outbreak Online Database.

For additional foodborne outbreak information and statistics in the U.S., visit FoodNet -- Foodborne Diseases Active Surveillance Network.

Selected International Foodborne Outbreaks

The following list of international outbreaks indicates that not only meat and dairy products, but also salad vegetables, such as lettuce and potato are also implicated in antimicrobial-resistant outbreaks.

2008 Morocco Chicken Tagine Outbreak[3]

- Contaminated chicken tagine
- Resulted in 45 cases
- Contamination was due to poorly cooked broiler chicken used to prepare tagine
- Implicated microorganism was *Salmonella* Typhimurium with multidrug resistance

2005 Denmark Carpaccio (Beef) Outbreak[17]

- Contaminated carpaccio (thinly sliced raw fillet of beef)
- Resulted in five cases
- Contamination was due to contaminated imported beef used to prepare Carpaccio
- Implicated microorganism was *Salmonella* Typhimurium DT104 with 6-drug resistance

2000 England and Wales Lettuce Outbreak[28]

- Contaminated lettuce
- Resulted in 361 cases
- Contamination was likely due to inadequate washing of lettuce at food outlets
- Implicated microorganism was *Salmonella* Typhimurium DT104 with 6-drug resistance

1998 England Raw Milk Outbreak[59]

- Contaminated raw milk
- Resulted in 86 cases
- Contamination was due to failure of on-farm pasteurization of milk
- Implicated microorganism was *Salmonella* Typhimurium DT104 with multidrug resistance

1998 Denmark Pork Outbreak[40]

- Contaminated pork and pork products
- Resulted in 25 cases, including two deaths
- Contamination was due to contaminated pork and products prepared from it
- Implicated microorganism was *Salmonella* Typhimurium DT104 with 5-drug and quinolone resistance

1995 Netherlands Food Outbreak[32]

- Contaminated food
- Resulted in 41 cases, including five deaths
- Contamination was due to infected dietary worker who prepared food for patients
- Implicated microorganism was methicillin-resistant *Staphylococcus aureus*

1989 Caribbean Potato Salad Outbreak[33]

- Contaminated potato salad served at a cruise ship
- Resulted in 21 cases
- Contamination was due to infected food handler who prepared and handled salad
- Implicated microorganism was *Shigella flexneri* with with multidrug resistance

For additional international foodborne outbreak information, visit the Program for Monitoring Emerging Diseases of the International Society of Infectious Disease.

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Research at the USDA Agricultural Research Service

The USDA Agricultural Research Service (ARS) is actively involved in food safety research related to AMR in foodborne pathogens under the National Food Safety Program 108. This research program provides the means to ensure that the food supply is safe and secure for consumers and that food and feed meet foreign and domestic regulatory requirements. The following ARS research units conduct research on AMR in foodborne pathogens:

- Bacterial Epidemiology and Antimicrobial Resistance Research Unit
- Food and Feed Safety Research Unit
- Food Safety and Enteric Pathogens Research Unit
- Livestock Behavior Research Unit

Some research projects on AMR being conducted at these ARS units are:

Epidemiology, Ecology, and Molecular Genetics of Antimicrobial Resistance in Pathogenic and Commensal Bacteria from Food Animals

Location: Bacterial Epidemiology and Antimicrobial Resistance Research Unit

Project Objectives[54]

1. Use ABR data obtained from the Collaboration on Animal Health and Food Safety Epidemiology (CAHFSE) and the NARMS programs and poultry studies to identify sources, reservoirs and amplifiers of resistant food borne and commensal bacteria, as well as the path of dissemination of these resistant bacteria in food producing animals and poultry.
2. Map the spread of antimicrobial resistance throughout the U.S. using molecular epidemiology and population genetic studies of antimicrobial-resistant bacterial isolates, including participation in USDA VetNet.
3. Analyze and differentiate antimicrobial resistance mechanisms, both phenotypically and genotypically, and rapidly identify resistant strains.

Accomplishments[54]

1. Conducted antimicrobial susceptibility testing and speciation of *Campylobacter* isolates from the Food Safety Inspection Service (FSIS) chicken parts shakedown and baseline studies on raw chicken parts.
2. Characterized multidrug-resistant *E. coli* by plasmid replicon typing and Pulsed-Field Gel Electrophoresis. Observed a high degree of genotypic diversity, with 34 different PFGE types found among the 35 isolates examined.
3. Analyzed AMR genes in bacteria co-isolated from swine fecal samples and indicated

that *Salmonella* and *E. coli* may have a common source for acquiring AMR genes or may exchange resistance genes in the swine environment.
4. Suggested that the common genetic elements in different bacteria may serve as a reservoir for resistance in important pathogens such as *Salmonella*.
5. Developed microarrays for detection of multi-drug resistant plasmids in *Salmonella* and *E. coli*.
6. Conducted sequence analysis of multidrug-resistant plasmids from *Salmonella* and *E. coli* and indicated that plasmids encode metal and sanitizer resistance genes that may give bacteria that possess them a survival advantage in the animal environment or in the meat processing plant environment.
7. Determined prevalence of ColE1-like plasmids and kanamycin resistance genes in *Salmonella enterica* serovars.
8. Determined prevalence of antimicrobial-resistant *E. coli* from companion animals and indicated that healthy dogs and cats are a source of antimicrobial-resistant *E. coli* and may act as a reservoir of AMR that can be transferred to the human host.
9. Characterized MRSA from companion animals and humans and reported that all isolates from companion animals exhibited the same resistance pattern among the 18 antimicrobials tested.
10. Detected a new multi-locus sequence type (MLST) among the MRSA isolates.
11. Conducted antimicrobial susceptibility testing of foodborne pathogens by the animal arm of NARMS on *Salmonella*, *Campylobacter*, *E. coli* and *Enterococcus* from animal and environmental sources.
12. Determined prevalence, species distribution, and antimicrobial resistance of enterococci isolated from U.S. dairy cattle and found that *Enterococcus hirae, E. faecalis, and E. faecium* were the most prevalent enterococcal species in dairy cattle fecal samples. The highest levels of resistance were to lincomycin, flavomycin, and tetracycline17.
13. Conducted Pulsed-Field Gel Electrophoresis (PFGE) to evaluate AMR patterns of *Salmonella* serotypes isolated from broiler external carcass rinses and found that *S. Kentucky* isolates exhibited the greatest heterogeneity with six different AMR patterns within 13 different PFGE patterns.
14. Determined prevalence of antimicrobial-resistant bacteria from dairy cattle in the northeast U.S. and found that *Campylobacter* isolates recovered from dairy cattle were resistant to tetracycline.

Development of Resistance to 4th Generation Cephalosporin

Location: Bacterial Epidemiology and Antimicrobial Resistance Research Unit

Project Objectives[53]

1. Assess resistance among *Salmonella* and *E. coli* originating from bovine sources to 4th generation cephalosporins over time.
2. Assess resistance among *Campylobacter jejuni, Campylobacter coli, Enterococcus faecalis and Enterococcus faecium* originating from bovine and porcine sources to macrolides over time.

Accomplishments[53]

1. Collected *Salmonella* and generic *E. coli* isolates originating from cattle as part of the animal arm of NARMS originating from cattle specimens which are being tested on antimicrobials cefquinome sulfate and cefepime. These antimicrobials belong to a class of drugs called cephalosporins.
2. Planned to perform molecular analysis of isolates to determine which gene may be responsible for any decreased susceptibilities which are observed as well as detection of extended spectrum Beta-lactamases, enzymes which confer resistance to cephalosporin antimicrobials.

Novel Pre-Harvest Intervention to Protect Antimicrobials of Critical Importance in Human and Veterinary Medicine

Location: Food and Feed Safety Research Unit

Project Objectives[56]

1. Determine the AMR of *E. coli* from cattle reared with various antibiotic usage regimens.

Accomplishments[56]

1. Developed new information on the genetic aspects of how *E. coli* develops resistance to a member (ceftiofur) of an important class of antibiotics used both in agriculture and in human medicine.
2. Developed new insights on the bacterial/chemical interactions as related to practical antibiotic treatment protocols.

Molecular Analysis of Salmonella Virulence, Antibiotic Resistance, and Host Response

Location: Food Safety and Enteric Pathogens Research Unit

Project Objectives[55]

1. Investigate the molecular mechanisms that coordinate virulence and ABR in *Salmonella* obtained from cattle (DT104 and *S. dublin*) and swine (DT104 and *S. choleraesuis*).
2. Investigate the molecular basis for swine resistance to *Salmonella* colonization by characterizing the immunological aspects of infection.

Accomplishments[55]

1. Searched sequence databases for genetic variations in greater than 3,000 porcine genes identified by the research team as differentially-expressed during exposure to *Salmonella*.
2. Identified thirty DNA sequence variations in the pig genome, referred to as single nucleotide polymorphisms (SNPs).
3. Showed that three of the SNPs associated with fecal shedding or tissue colonization of *Salmonella* in pigs by genotype analysis of four independent pig populations.

An Integrated Systems Approach to Reduce Salmonella in Organic and All Natural Poultry Handling

Location: Livestock Behavior Research Unit

Project Objectives[52]

1. Conduct on-farm surveys in organic and all natural poultry production practices to determine the prevalence and diversity of *Salmonella* serovars in these production systems as compared to more intensive commercial systems.
2. Develop and evaluate intervention strategies targeting control of *Salmonella* during the feed withdrawal and transportation processes prior to slaughter of broiler chickens to minimize cross contamination during transport and slaughter.
3. Evaluate post-harvest interventions to control *Salmonella* using novel antimicrobials in pre- and post-chiller applications, for both water and air chilling, and for finished raw products.
4. Develop risk assessment models that can be adapted to organic and all natural production and processing systems.

Accomplishments[52]

1. Completed on-farm surveys.
2. Isolated large collection of *Salmonella* with serovar Kentucky being the most commonly recovered.
3. Conducted studies on addition of prebiotics to diets as a means to mitigate *Salmonella* colonization.

FSRIO Research Projects Database

For additional USDA Antimicrobial Resistance Projects, please visit the FSRIO Research Projects Database.

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