White paper: Public Health Impact of Multi-Drug Resistant Pathogens

M. Ellin Doyle, Food Research Institute, University of Wisconsin

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INTRODUCTION

Antibiotic resistance, including multi-drug resistance (MDR), is an increasing problem globally. A recent publication by CDC on antibiotic resistance threats in the U.S. listed carbapenem-resistant enterobacteriaceae (CRE), drug-resistant gonorrhea, and *Clostridium difficile* infections as urgent threats (46). Drug-resistant foodborne bacteria, including *Campylobacter*, *S.* Typhi, non-typhoidal salmonellae, and *Shigella,* were ranked as serious threats. Salmonellae carrying genes coding for resistance to many antibiotics are the most frequent causes of foodborne MDR outbreaks. One foodborne outbreak in a hospital was attributed to an MDR strain of *Klebsiella pneumonia*. (41) CRE are also considered a serious threat in Europe since CRE have been detected in pigs, poultry, cattle, and horses as well as humans. (85)

Multidrug resistant bacteria are frequently detected in humans and animals from many countries, with MDR bacteria that cause tuberculosis and typhoid fever of particular concern in Africa, Asia, and South America. (207; 315) The World Health Organization released a 2014 report on global surveillance of antimicrobial resistance pointing out the increasingly serious threat this poses to human health. Very high rates of resistance have been reported in many common bacteria causing common infections in all regions of the world. Better coordination of surveillance programs and strategies for preventing and reducing antimicrobial resistance are needed. (223)

Infections caused by MDR microbes can be difficult to treat because so few antibiotics are still effective and these infections may result in increased costs for treatment due to use of more expensive drugs, more complications, higher mortality, and prolonged hospital stays. (56) A recent analysis of the cost of treating tuberculosis in the U.S. in 2010 USD found that non-MDR TB cost about $17,000 per patient, MDR TB cost about $134,000 per patient and extensively drug resistant (XDR) TB cost $430,000 per patient. Median number of antibiotics that MDR and XDR strains were resistant to was 5 (range 2 – 16). (188)

Some MDR bacteria may be less virulent than comparable susceptible strains but in other cases there appears to be no effect of MDR on virulence. Some studies in the 1950s showed that *Mycobacterium tuberculosis*, resistant to isoniazid, was less pathogenic in guinea pigs than drug-sensitive strains (207) and acquisition of ceftriaxone resistance in *Salmonella* Typhimurium was correlated with a diminished growth rate and reduced invasion into cultured epithelial cells. (169) However, presence or absence of multidrug resistance in *Yersinia pestis* did not affect virulence of plague in a mouse model. (172)

Food processors and retailers may consider themselves removed from the issue of antibiotic resistance but articles in the popular press warning of "superbugs" in food raise questions in consumers' minds about safety of foods containing antibiotic-resistant bacteria. Consumer Reports recently reported that testing of packages of chicken breasts, purchased nationwide, revealed that nearly 50% contained at least one strain of multi-drug resistant bacteria. (58) Multidrug resistance has also been detected in enterobacteriaceae on fresh produce in supermarkets. (29) Three excellent review articles summarize much useful information on antibiotic resistance and the challenges it presents for the food industry. (42; 83; 136)

Surveillance reports

In the U. S., NARMS (National Antimicrobial Resistance Monitoring System) monitors changes in antibiotic resistance in bacteria isolated from humans, animals, and foods. Surveillance data from 2011 on multidrug resistance in human and meat isolates of some enteric bacteria are listed in Table 1 (209). EFSA (European Food Safety Authority) and ECDC (European Centre for Disease Prevention and Control) also publish a yearly report on antibiotic resistance in bacterial isolates from humans, livestock, and food. Data on 2012 isolates are summarized in Table 2. (90). Multidrug resistance was found to be relatively high in *E. coli* and *Salmonella* isolates from poultry in the U.S. and from poultry and swine in Europe. It should be noted that there is sometimes wide variation in antibiotic resistance levels among different countries in Europe.

Table 1. Multi-drug resistance detected by NARMS in 2011 (209; 210; 272)

Bacteria	Human isolates	Animal isolates	Meat isolates
Campylobacter spp.	3%	Chickens (1.3%)	1.4%
Enterococcus spp.		Chickens (61.6%)	
E. coli	4.3%	Chickens (38.3%)	Chicken (37.5%), ground turkey (64.4%), ground beef (6%), pork chop (8.9%)
Shigella spp.	51%		
S. ser. Typhi	12.3%		
S. ser. Heidelberg	30%		
S. ser.I4,[5],12:i:-	27%		
S. ser. Typhimurium	26%		
Salmonella spp.	9.1%	Chickens (15.2%); turkeys (37.1%); swine (27.9%); cattle (28.7%)	Chicken (44.9%), ground turkey (50%), ground beef (11.1%), pork chop (28.6%)

Table 2. Multidrug resistance detected in the European Union in 2012. (90) (Note: In some cases, surveillance data were reported by only one or a few countries in the EU. Prevalence of MDR also varies significantly among reporting countries.)

Bacteria	Human isolates	Animal isolates	Meat isolates
Campylobacter coli	24.8%	22.5% (broilers); 34.6% (pigs)	
Campylobacter jejuni	35.1%	1.6% (broilers); 12.3% (cattle)	
E. coli		31.1% (broilers); 30.9% (pigs)	
Salmonella spp.	28.9%	46.4% (broilers); 21.1% (laying hens); 68.9% (turkeys); 73.5% (pigs); 34.2% (cattle)	64.2% (chicken); 50.9% (pork);
MRSA		12% (turkeys); 27.5% (pigs); 33.4% (cattle)	12.4% (chicken); 47% (turkey); 7.6% (pork); 19% (beef)

In addition to these large annual surveillance reports, there have been numerous journal articles documenting the presence of MDR bacteria in different foods.

- **Dairy**: Multidrug resistant *Salmonella* serotypes Dublin, Infantis, Newport, Typhimurium have been detected in bulk tank milk in the U.S. (288) and MDR *Enterococcus* spp. were detected in French cheese (142).
- **Turkey**:
  - Of drug resistant enterobacteriaceae isolated from retail turkey in Tennessee, 90% were MDR. The most common MDR contaminants were *Salmonella* spp. (154)
  - MDR *S.* Saintpaul was detected in turkey meat products in Germany (25).
  - Multidrug resistance was present in *C. jejuni*, *C. coli*, *E. coli*, and 7 serovars of *Salmonella* isolated from retail turkey meat in Canada. High levels of resistance to 5 or more antibiotics were detected in *E. coli* (20%) and *Salmonella* (13%) isolates. (19; 59)
- **Chicken:**
  - Of drug resistant enterobacteriaceae isolated from retail chicken in Tennessee, 71% were MDR. The most common species identified were: *Salmonella* spp. and *Morganella* spp. (154) Of *Salmonella* isolated from chicken meat in PA, 31% were MDR. (181)
  - Multidrug resistance was also detected in *C. jejuni* and *C. coli* from chicken livers and gizzards from retail stores in the U. S. (214)
  - Multidrug resistance was detected in retail chicken in Canada (*Salmonella* spp.) (19); Italy (*Campylobacter* spp.) (246) and *Salmonella* (21); and retail chicken (*S. enterica* and *E. coli*) in Bangkok (51) Vietnam (273), and Japan (6).

- **Beef:**
  - Analyses of 4136 commercial ground beef samples in the U.S. indicated that 4.2% contained detectable salmonellae and 11.5% of those salmonellae were MDR. (36) Testing of 238 samples of ground beef from butcher shops in Mexico found that 27.4% of salmonellae isolated were MDR. (40)
  - Canadian retail samples of milk-fed veal were found to frequently harbor *E. coli* and at least 36.6% of the tested *E. coli* isolates were MDR. (60)
  - Antimicrobial testing of *Salmonella* isolates from cattle carcasses at 6 U.S. processing plants demonstrated that 11.7% of the salmonellae from preevisceration carcasses and 0.33% of salmonellae from postintervention carcasses were MDR. (37)
  - Of drug resistant enterobacteriaceae isolated from retail beef in Tennessee, 92% were MDR. The most common species identified were: *Salmonella* spp., *E. coli* O157:H7, and *Yersinia* spp. (154) About 46% of *Salmonella* isolates from retail beef in Hanoi markets were multidrug resistant. (283). Retail beef in Iran contained MDR *Salmonella* spp., *Campylobacter* spp., and *Yersinia* spp. (68)
- **Pork**: Surveys at two large commercial pork processing plants in the U. S. revealed that multidrug resistance was present in 71.2%, 47.8%, and 77.5% of the tested *Salmonella* isolates from prescald, preevisceration, and chilled final carcasses, respectively. MDR *Salmonella* was also detected in 3.2% of the final carcasses sampled. (252) In Germany, MDR *Salmonella* serovar 4,[5],12:i:- has been isolated from pork (123). MDR *Salmonella* Oranienberg, resistant to fluoroquinolines, was detected in pork in China. (305)
- **RTE meat**: Of listeriae detected in RTE meat in Spain, 2.9% of *L. monocytogenes* and 13.9% of *L. innocua* exhibited multidrug resistance. (110)
- **Sausage:** A survey of raw meat sausages for retail sale in Botswana revealed that 22% contained *Salmonella* and all the *Salmonella* isolates were resistant to 4 or more antimicrobials. (245)
- **Produce:** A Dutch survey of fresh vegetables, commonly eaten raw, revealed the presence of several environmental species of MDR enterobacteriaceae. These bacteria were similar to MDR bacteria isolated from the agricultural environments where the plants were grown. (29) A European outbreak of foodborne illness in 2000 was attributed to *S*. Typhimurium DT104 on lettuce. (132; 277)
- **Pet food:** Multidrug resistant salmonellae have been detected in dog foods and have been associated with some human illness.(97; 228; 300)

Multidrug resistance has also been reported in bacteria from other foods from many countries in the world. Examples include:, imported horse meat in France (*S*. Newport) (87), quail in Italy (*Salmonella* spp.)(21), fish in India (*S*. Oslo) (147), shrimp in Bangladesh (134), eggs in Grenada (*E. coli*) (17), and meat in Turkey (*Klebsiella* spp.) (116), (*Salmonella* spp.) Algeria (194), and Brazil (*Salmonella* spp.) (61).

Outbreaks

Although many genera of bacteria contain MDR strains, *Salmonella* spp. are the most common type of MDR bacteria associated with outbreaks of foodborne illness. (Table 3 lists outbreaks attributed to MDR salmonellae.) Widespread reports, in the mid-1990s, of *S.* Typhimurium DT104 in meats and livestock, were the first indication of this emerging problem. DT104 is resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline – a resistance pattern designated as ACSSuT. (54; 133; 269; 285) This pattern of resistance has spread and was identified in 26% of *S*. Typhimurium, 27% of *Salmonella* I,4,[5],12:i:-, and 30% of *S*. Heidelberg isolates tested by NARMS in 2011. (209)

Recently, a highly drug-resistant strain of *Salmonella enterica* serotype Kentucky, ST198-X1, has been identified as a potential foodborne pathogen that may seriously impact human health. This strain has developed resistance to ciprofloxacin, a drug of choice for treating severe salmonellosis. Some strains have also become resistant to extended spectrum cephalosporins (ESCs), carbapenems, sulfonamides, most aminoglycosides, and azithromycin. ST198-X1 has now been detected in humans in Europe and in Canada and in poultry flocks and turkey meat in Europe. (166; 208) Since *S*. Kentucky is one of the most common *Salmonella* strains detected in chickens and ground chicken, there is concern that it may become a problem in the U.S.

A multidrug resistant, extended-spectrum β-lactamase (ESBL) producing strain of *Klebsiella pneumonia* was identified as the cause of a foodborne outbreak affecting 156 hospital patients in Spain. The outbreak strain was isolated from some kitchen surfaces and food handlers. (41) ESBL-producing enterobacteriaceae were detected 92% of raw chicken samples from supermarkets and from hospital kitchens in Switzerland. These bacteria were not detected in eggs, beef or cooked chicken. (268) Examination of vinyl gloves, after use by hospital kitchen staff for handling raw chicken, and of cutting boards, used in hospital and community kitchens for cutting raw chicken, in Switzerland revealed that 12% of boards and 50% of gloves contained EBSL-producing *E. coli*. (284)

MECHANISMS AND EVOLUTION OF DRUG RESISTANCE

Origin and Selection for Resistance

Many antibiotics currently used in in human and veterinary medicine are derived from chemicals produced by microbes for the purpose of inhibiting or killing competitors, predators, or parasites in their environment. Examples are penicillin made by the fungus *Penicillium* and tetracycline produced by bacteria in the genus *Streptomyces*. Since these antibiotics were manufactured long before humans discovered and made use of them, there are, in caves and permafrost environments isolated for thousands or millions of years from any human contact, bacterial genomes that contain antibiotic resistance genes. There is evidence that some β-lactamases even predate the existence of humans. (98)

Some non-pathogenic bacteria that live in soil and other environments today, with no significant exposure to antibiotics used in human and veterinary medicine, have developed mechanisms to protect themselves from antibiotics and other toxins present in their environments. (296) There are multiple ways in which genetic information encoding resistance can be passed from one bacterial cell to others in the same and different species and genera. Widespread use of antibiotics in human and veterinary medicine and as growth promoters for intensive livestock production is believed to be the primary force driving rapid sharing and selection of genes conferring antimicrobial resistance in recent years. Human and veterinary

health care facilities commonly harbor drug resistant bacteria. Low concentrations of antibiotics added to some animal feeds may be excreted in animal wastes and bedding, some of which may then be spread on agricultural fields and remain in the terrestrial environment or they may be washed into surface waters.

Antibiotics are also used prophylactically in the aquaculture industry and have selected for antibiotic resistance among bacteria in ponds. (212) Wastes from pharmaceutical manufacturing contain antimicrobial compounds and their derivatives that exert selective pressure for antibiotic resistance in bacteria at water treatment plants. (186) Urban wastewater treatment plants also receive an inflow of antibiotics from health care facilities and individual residences. It used to be common practice to dispose of excess or outdated antimicrobials down the sink or toilet. Although pharmaceutical take-back programs are available in many locations, it is probable that many antibiotics are still disposed of in this fashion. (196)

In addition to direct selection for specific antibiotic resistance by a particular antimicrobial compound, selection may be indirect because some genes encoding resistance to antibiotics maybe located close to other types of resistance genes. Some bacterial plasmids contain genes for both antibiotic resistance and heavy metal resistance. (73; 159) Therefore, under some conditions, exposure to heavy metals may co-select for heavy metal and antibiotic resistance. In-feed antibiotics containing chlortetracycline, sulfamethazine, and penicillin that were fed to pigs selected for resistance to unrelated aminoglycoside antibiotics, presumably because different antibiotic resistance genes were closely located on a mobile genetic element. (179) Use of disinfectants, perhaps at sublethal concentrations, may also spur selection of antibiotic resistance. As bacteria develop resistance to certain disinfectants, they also become resistant to some antimicrobials. (278) (39; 125)

A retrospective study that examined antibiotic resistance in 1729 *E. coli* isolates from 1952 to 2002 in the U.S. documented an increasing trend of resistance in bacteria from humans, cattle, pigs, and chickens. Only 7.2% of *E. coli* were MDR during the 1950s as compared to 63.6% in the 2000s. (275) Another example of a pathogen that has become progressively more resistant to antibiotics over the past 75 years is *Neisseria gonorrhoeae*. The first antibiotics used to treat gonorrhea were sulfonamides in the 1930s. However, by the 1940s, resistance to sulfa drugs was common in this bacterium. Penicillin was used next and was effective for several decades although increasing doses of the drug were needed to control this disease. By the 1980s, *Neisseria* was commonly resistant to both penicillin and tetracycline. So fluoroquinolines became the next drug of choice. Fluoroquinoline resistance was observed in Asia in the 1990s and was subsequently detected in the U.S. in the early 2000s. By 2007, resistance to fluoroquinolines was common enough that CDC recommended that cephalosporins be used to treat gonorrhea. Cephalosporin resistance was observed in Asia during the 2000s and in Europe in the past few years. There are also some reports of the isolation of cephalosporin-resistant *Neisseria* in the U.S. It has become very difficult to stay ahead of the rapid acquisition of antibiotic resistance by some important pathogens. (131)

Some bacterial strains are now resistant to three or more classes of antimicrobial substances – the currently accepted definition of multi-drug resistance (MDR). (Some earlier papers considered resistance to 2 or more antimicrobials to be MDR.) Other bacteria are called extensively drug resistant (XDR) and are susceptible to drugs in only one or two antimicrobial categories. Pandrug resistance (PDR) is defined as resistance to all agents in all currently available antimicrobial categories. (183) Multidrug resistance in *Mycobacterium tuberculosis* is defined as resistance to the two most potent anti-TB drugs, isoniazid and rifampicin. However,

mycobacteria are naturally resistant to many other antibiotics. *M. tuberculosis* that are also resistant to one or more of the secondary drugs used to treat TB are XDR. (207)

Many other species of bacteria, including important human and foodborne pathogens in which MDR has been identified, are listed in Table 3. This is not a comprehensive list of all of the MDR genera of bacteria reported in the literature nor are all the reported countries or food/animal/environmental samples containing these bacteria included in the table. Rather this table is meant to illustrate the widespread occurrence of multidrug resistance, both geographically and in numerous types of bacteria.

Numerous serovars of *Salmonella* contain MDR strains, some of which have been implicated in outbreaks of foodborne disease (Table 4). CDC reported that while multi-drug resistance declined in *Salmonella* isolates in recent years, this was due to a reduction in numbers of *S*. Typhimurium isolated. However multidrug resistance has increased in other *Salmonella* serovars , including *S*. Newport and *S*. Heidelberg. Resistance to the important drugs, ceftriaxone and ciprofloxacin, has also increased during this time. (193) Several highly drug-resistant S. Kentucky ST198-X1 strains, apparently originating in North Africa, the Middle East and India, have been detected in recent years in France and other European countries. Approximately 40% of *S*. Kentucky strains examined during 2000-2008 in France were resistant to ciprofloxacin; in 2009-2011, 83% of *S*. Kentucky were resistant to this drug. Some of these strains also produce several enzymes (carbapenemases, cephamycinase, or extended spectrum β-lactamases) in addition to being resistant to fluoroquinolines, trimethoprim-sulfamethoxazole, and azithromycin. (166)

Fitness Costs

It was originally thought that antibiotic resistance would exact a "fitness cost" on resistant organisms because they would need to manufacture new enzymes or structures to catabolize or exclude antimicrobial compounds. Since this would require energy, cells would have less energy available for ordinary metabolic activities necessary for growth and survival. Therefore, in the absence of antimicrobial compounds, it was believed that resistant organisms would be at a competitive disadvantage compared to their susceptible counterparts. In vitro experiments have demonstrated that *Salmonella* Enteritidis resistant to fluoroquinoline does incur a fitness costs when grown in media without the antibiotic. (216) But resistance to fluoroquinolines does not decrease fitness of *Neisseria gonorrhoeae* grown in the absence of this antibiotic. (163)

Other in vitro experiments with MDR *E. coli* demonstrated no significant difference in growth rates between susceptible and MDR strains and, for the most part, MDR strains retained plasmids encoding resistance and remained resistant to multiple antibiotics, even after 36 days of continuous culture without antibiotics. (231) An extended discussion on the evolution of MDR *Mycobacterium tuberculosis* discussed the development of MDR in different genetic backgrounds and pointed out that predicting retention of MDR genes in environments with no selective pressure is a complex process. Some antibiotic resistance genes apparently have a low fitness cost and cells may use compensatory mechanisms to thrive in spite of "wasting energy" manufacturing antibiotic resistance proteins that are no longer required. In addition, environmental conditions outside the laboratory may be significantly different from those encountered in in vitro experiments, thereby affecting any fitness cost of retaining antibiotic

resistance. Some resistance mechanisms may perform other useful functions for bacterial cells in their natural environment. (207)

Mechanisms

Bacterial cells can survive exposure to antibiotics, without undergoing genetic changes, by drastically decreasing their metabolic activity and entering a dormant state. Since they are not growing, these cells are not significantly affected by antibiotics that interfere with cell wall synthesis, protein synthesis, or other metabolic processes. These "persister" cells usually comprise about 1% of cells in biofilms and stationary cultures. Although they do not grow in the presence of antibiotics, they can resume growth when drug levels fall. (306)

Other bacteria, including *Mycobacterium tuberculosis*, are intrinsically resistant to some antibiotics because of their thick, lipid-rich cell walls that many antibiotics cannot penetrate. (207) In addition, many bacteria have acquired genes coding for altered proteins that do not bind to antibiotics or for enzymes that break down antibiotics, prevent their entry into cells, or actively expel antimicrobial compounds that have entered the cells. Multiple resistance is often associated with ATP powered efflux systems. A recent review describes genetic mechanisms, present in bacteria from U.S. livestock, that protect them from several important antibiotics. (104)

Structural changes.

Antibiotics bind to proteins or other macromolecules in order to gain entry into cells and interfere with normal metabolic processes. Therefore, one way to prevent damage by antimicrobial compounds is to produce molecules with altered structures so that antibiotics can no longer bind to them. Methicillin-resistant *Staphylococcus aureus* (MRSA) synthesizes altered cell wall proteins with low affinity for binding methicillin, thereby diminishing its uptake into cells. (242) Fluoroquinolones target bacterial gyrases and topoisomerases that help bacteria maintain their chromosome in a supercoiled state. Mutations in these enzymes prevent fluoroquinolones from attaching to and inhibiting them. These mutations may also protect against other antimicrobials by inducing stress responses in cells.(297)

Inactivation enzymes.

Bacteria also use enzymes to break down or make changes in antibiotic molecules to render them less effective or completely eliminate their toxic effects. Aminoglycoside resistance is often mediated by enzymes that modify the antibiotic molecules, thereby inactivating them. (136)

Resistance to penicillin-type drugs is generally mediated by β-lactamase enzymes. There are many β-lactamases, some capable of degrading only a few members of the penicillin family of drugs while others, called extended spectrum β-lactamases (ESBL), can attack a wide variety of second and third generation β-lactams, including cephalosporins. Examination of >5700 isolates of *E. coli*, *Klebsiella* spp., and *Proteus mirabilis* collected at U.S. hospitals in 2012 found that 12.2% carried ESBL genes. (43)

Carbapenems are more recently developed β-lactam type antibiotics whose use has been jeopardized by the evolution and spread of carbapenemases. (307) A zinc-containing enzyme, New Delhi metallo-β-lactamase (NDM), was first described in 2008 in bacteria from clinical specimens from a person infected in India. NDM genes encode enzymes that can inactivate all penicillins, cephalosporins, and carbapenems. These genes have spread to several genera of enterobacteriaceae and to other bacteria such as *Acinetobacter* and *Pseudomonas* and to

countries all over the world. (161) (34; 75; 108; 260) The gene encoding NDM-1 has also been detected in *E. coli* isolates from companion animals in the U.S. and in bacteria from livestock (258; 307)

Efflux systems.

Numerous efflux systems have been characterized in both Gram positive and Gram negative bacteria. Some systems are specific for certain molecules such as the tetracycline pump which is encoded on a mobile genetic element. However, most efflux systems can interact with many molecules including dyes and detergents as well as antibiotics used in human and veterinary medicine. Genes for these pumps are usually located on the chromosome. *Salmonella* Typhimurium cells may have as many as 10 types of efflux pumps. (310) A recent review describes efflux systems present in many species of bacteria. (96)

Efflux systems also aid cells in adapting to acidic conditions (72) and oxidative stress (31; 239) that they may encounter in the environment or during the infection process. Some data indicate that efflux pumps contribute to biofilm production by *E. coli* and other bacteria and to the enhanced antibiotic resistance of biofilms. (189; 266)

Efflux systems also operate in cells of higher organisms. Some opportunistic pathogenic fungi, including yeasts (*Candida* spp. and *Cryptococcus*) and molds (*Aspergillus fumigatus)* can cause serious infections in immunocompromised persons. Efflux proteins known as ABC (ATP-binding cassette) proteins are found in all fungi and confer resistance to a variety of antimicrobials, thereby increasing the morbidity and mortality of these infections. (158; 203; 234) Similar ABC efflux systems and multi-drug resistance have also been identified in the protozoan parasites *Toxoplasma* and *Cryptosporidium* (249), in parasitic round worms (nematodes) (18) and flatworms (*Schistosoma*) (115), and in human cancer cells (162).

Transfer to other genera

Genes encoding antibiotic resistance may be located on mobile genetic elements including plasmid DNA, transposons, integrons, and genomic islands. All of these mobile elements were present in bacteria prior to human use of antibiotics but, as far as we can determine, they were rarely associated with antibiotic resistance. Plasmids are circular pieces of DNA that are separate from the bacterial chromosome. They vary greatly in size and may carry a variety of genes. Transposons are small pieces of DNA forming part of a chromosome or plasmid that can spontaneously move to a different location on the plasmid or chromosome. This is accomplished by means of an enzyme, transposase, that cuts DNA strands releasing the transposon and opening DNA at another location to allow reintegration of the transposon. Ancient bacteria, isolated from permafrost, contained transposons encoding resistance to mercury and some of transposons have more recently acquired antibiotic resistance genes. Integrons are genetic elements encoding genes that allow them to integrate into chromosomes at specific sites. They are not mobile on their own but their association with transposons or plasmids permits dissemination among many bacterial cells. Integrons can include gene cassettes that confer antibiotic resistance and some include genes encoding resistance to 9 antibiotics. Genomic islands are relatively large sections of DNA that differ from the rest of the chromosome in their nucleotide characteristics, indicating that they may have originated in another cell. They are usually flanked by a repeated series of nucleotides. (146; 269) Multidrug resistance in

salmonellae is often encoded by *Salmonella* genomic island 1 which confers resistance to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline. (26) Genetic elements that encode antibiotic resistance, including ESBLs, in modern bacteria are often complex structures that include transposons, integrons, and genomic islands.

Bacteria have three major mechanisms for transferring genes from one cell to another: (1) Conjugation in which a donor cell forms an attachment (pilus) to a related recipient cell and transfers a copy of plasmid DNA through the pilus. (2) Transduction in which a dormant bacterial virus (prophage), located in the DNA of a bacterium. is induced to become active and form viral particles (phages) that may contain pieces of bacterial DNA that were near the viral DNA in the chromosome. These phages can then infect other bacteria and carry along DNA from the first bacterium. (3) Transformation in which pieces of DNA from one bacterium are extruded into the environment and taken up directly by other bacteria. All of these processes can transfer antibiotic resistance genes from one cell to another. Conjugation and transduction tend to occur between related bacterial cells but transformation allows horizontal transfer of DNA among many species. (79; 151; 269)

Numerous examples of transfer of antibiotic resistance have been reported:

- Certain aspects of the environment or lifestyles of pathogens may enhance horizontal gene transfer. *Vibrio cholerae* cells have a strong association with the chitinous exoskeletons of zooplankton, often forming biofilms that may contain as many as 10^6 cells per individual in the zooplankton. Attachment to chitin increases the ability of cells to transfer genetic information by transformation. There is evidence that genes for both virulence and antibiotic resistance have been shared among *Vibrio* cells by transformation and phage induction. (30)
- Antibiotics in the environment induce the spread of resistance genes among bacteria. A prominent example of this is the generation of multiresistant bacteria in wastewater treatment plants receiving industrial wastewater from pharmaceutical plants. Genetic elements responsible for antimicrobial resistance have spread to many different species of bacteria living in these treatment plants. Genome sequencing of some of these bacteria shows that they acquired resistance genes from several sources. (143)
- Sublethal doses of antibiotics mixed in animal feed also appear to encourage transfer of resistance genes among bacteria, in part by inducing replication of prophages. (11) Antimicrobial resistance in bacteria living in feed was increased, even to some compounds that were not added to the feed (179).
- Streptomycin is sprayed on some fruit trees to control fire blight. Examination of nasal and fecal flora from sheep that grazed on grass sprayed with streptomycin found that exposure to the antibiotic increased numbers of MDR *E. coli* and *Staphylococcus*. (251)
- Genes conferring methicillin resistance in *Staphylococcus aureus* reside on a large mobile genetic element called the staphylococcal cassette chromosome (SCC*mec*). These genes have been transferred to multiple methicillin-susceptible *S. aureus* strains on several occasions. (242)
- Analyses of over 450 *S.* Typhi cultures isolated worldwide since 1958 revealed that earlier strains (prior to 1995) contained variety of plasmids of the IncHI1 type that are known to be the primary carriers of antibiotic resistance in this species. Since that time 98% of isolates were found to contain one specific version of this plasmid, indicating that one multidrug resistance plasmid has spread among *S.* Typhi globally. (130)
- The *Salmonella* genomic island 1, encoding multidrug resistance is mobilized by the IncA/C plasmid for dissemination to other cells. (81) IncA/C plasmids also spread MDR in *E. coli*

and other enteric bacteria. (94; 103) In some salmonellae, including *S*. Typhimurium, multidrug resistance genes have been transferred to the chromosome with subsequent loss of the plasmid. (170)

- Experiments with laboratory cultures (233) and animals including meal worms (232) and poultry (286) have demonstrated that horizontal gene transfer occurs in vivo. In experiments with mice, sequencing of fecal bacteriophage populations before and after antibiotic treatment, demonstrated that drug treatment increased numbers of genes conferring resistance to the antibiotic used as well as to other antibiotics. (199)

RESERVOIRS OF MDR IN ANIMALS AND THE ENVIRONMENT

In some cases, multidrug resistant bacteria apparently originated in human health care facilities while others developed in animals either in veterinary facilities or on farms. Research has documented their presence in livestock, companion animals, wild animals, insects, and the natural environment, including soil and surface waters. Even if these bacteria are not known human pathogens, they may constitute a health risk because of their ability to transfer genetic information to pathogenic microbes.

MDR bacteria can be transmitted from person to person (289), among animals (250), and between animals and humans (7). Insects may also be vectors dispersing antibiotic resistant bacteria to animals and humans (5).

Livestock

Cattle

Prevalences of MRSA and MDR *Salmonella* in cattle in Europe were reported to be 33.4% and 34.2%, respectively (2012 data). MDR *Salmonella* in U.S. cattle was reported to be 28.7% in 2010. (See Table 2.) *Salmonella* serotypes, isolated from humans and cattle, are similar but generally a greater proportion of isolates from cattle are MDR as compared to similar human isolates. (129; 220)

A longitudinal study of the acquisition of new MDR *Salmonella* strains by dairy herds in the U.S. found that this was a fairly common event. Rates of introduction were 1.2/herd-year for *S*. Newport, 0.4/herd-year for *S*. Typhimurium, and 0.1/herd-year for *S*. Dublin, the 3 most common MDR serovars. Herd size and off-farm heifer raising were significantly correlated with the introduction of new MDR salmonellae. (2; 3) A median prevalence of 11.8% was observed for *Salmonella* contamination of lymph nodes from feedlot cattle and 8.3% of those were determined to be multidrug resistant. (113)

Bacterial infections can cause diarrhea in calves and some of the implicated strains are multidrug resistant. An MDR strain of *Salmonella* Oranienburg was identified during an outbreak of dairy calves in Michigan. (149) A high percentage (>81%) of E. coli isolated from calves with diarrhea tested in one study in the U.S. were multidrug resistant. (22) In Australia, by contrast, 72.4% of *Salmonella* isolates associated with diarrhea in calves were susceptible to all drugs tested. Only 2.3% of nearly 600 strains tested were resistant to 3 or more antibiotics. (140)

MDR *Salmonella* Stanley and *E. coli* have been described from Japanese cattle. (66; 219) Very high levels of antibiotic resistance were detected in *E. coli* from cattle in Nigeria (13; 218) and in STECs from cattle in India (240). Other MDR bacteria have been detected in cattle

including: *Arcobacter butzleri* isolated from cattle in Malaysia (255), *Klebsiella* spp. and *S. aureus* from dairy cattle in Canada (244), and enterococci in dairy cattle in the U.S. (141).

Swine

Prevalences of MRSA, MDR *Campylobacter coli*, MDR *E. coli*, and MDR *Salmonella* in swine in Europe were reported to be 27.5%, 34.6%, 30.9%, and 73.5%, respectively (2012 data). MDR *Salmonella* in U.S. swine was reported to be 27.9% in 2010. (See Table 2.)

Numerous reports of MDR salmonellae in swine emphasize how widespread this problem is in many countries. These bacteria are detected in lymph nodes, feces, housing and environments where swine are raised (farrowing, weaning and finishing pens), in lairage pens, and on carcasses in slaughterhouses. *S*. Typhimurium is often identified as the dominant MDR serovar but *S*. Infantis and other serovars also express resistance to multiple antibiotics. From one fourth to three fourths of *Salmonella* spp. isolates from swine that were tested were positive for multidrug resistance. (32; 67; 109; 118; 150; 152; 197; 252)

As many as 98% of *E. coli* isolated from pigs in Thailand were multidrug resistant. (165) MDR *E. coli* were also isolated from Australian pigs with post-weaning diarrhea. (264) Examination of *E. coli* and *Salmonella* spp. from the same fecal samples, collected from Canadian swine finishing farms, revealed that about twice as many *E. coli* displayed resistance to at least 1 antibiotic and that multidrug resistance was also more common in *E. coli* than in *Salmonella*. (290)

MDR *Campylobacter* have also been reported from swine in Brazil (27), China (236), and Australia (217) Over 90% of *Enterococcus* isolates from pigs in China were MDR. (177)

Several studies provided evidence for the spread of drug-resistant bacteria from swine and their environments to humans working in those areas. (9; 215; 222)

Chickens

Prevalences of MDR *Campylobacter coli*, MDR *E. coli*, and MDR *Salmonella* in broilers in Europe were reported to be 22.5%, 31.1%, 30.9%, and 46.4%, respectively (2012 data). MDR *Campylobacter*, *Enterococcus*, *E. coli*, and *Salmonella* in U.S. swine were reported to be 1.3%, 61.6%, 38.3%, and 15.2%, respectively, in 2010. (See Table 2.)

Analyses of antimicrobial resistance in *Salmonella* isolates from chicken fecal pellets revealed that nearly 40% of those originating from conventional farms in the U.S. were resistant to 6 antibiotics while none of the *Salmonella* from birds on organic farms had this type of MDR. (10) Of salmonellae isolated from broilers in Japan, 90% were MDR. (247) *S*. Infantis has recently become one of the most important MDR serovars in poultry in Europe (211) and Japan (256). Another important MDR serovar in poultry in some European countries is *S*. Paratyphi B. (82)

All *C. coli* and *C. jejuni* isolates from Italian broiler farms were multi drug resistant in a recent survey. (106) High levels of MDR were also detected in *Campylobacter* spp. from broilers in Turkey (55), and chickens in Malaysia (185)

Of 600 *E. coli* isolates from poultry flocks in Alberta Canada in 2005, 54.3% were resistant to 3 or more antibiotics. (184) *E. coli* from poultry in the U.S. are more likely than human isolates to be multi-drug resistant and pathogenic strains were more often MDR. (145)

Multidrug resistance in *L. monocytogenes* in poultry in Spain increased dramatically between 1993 and 2006: from 18.6% to 84%. (12) Multidrug resistance has also been detected in *Enterococcus* spp. in Canada (78), *Enterococcus* spp. in China (177), and *C. perfringens* in Egypt (224).

Turkeys

MDR *Salmonella* in U.S. turkeys was reported to be 37.1% in 2010. (See Table 2.) Prevalences of MRSA, and MDR *Salmonella* in turkeys in Europe were reported to be 12%, and 69%, respectively (2012 data). A clonal multi-drug resistant strain of *Salmonella* Saintpaul is widespread in German turkeys and has also been isolated from Dutch poultry. This strain has also been detected in some samples of turkey products and in some people. (25)

A clonal multidrug strain of *Campylobacter coli* was identified in turkeys in the U.S. (64) *C. coli* and *C. jejuni* from turkeys raised on commercial farms in Italy had a very high rate of multidrug resistance (98%) in one recent study. (106) Other reports of multidrug resistant bacteria in turkeys include: enterococci in Canada (281), *Campylobacter jejuni* in Germany (86), *Salmonella* and *E. coli* in Greece (137), and *Salmonella* and *E. coli* in the UK (206).

Other Animals

MDR bacteria have also been isolated from farmed rabbits in Italy (*Salmonella* Typhimurium DT104) (35), feedlot lambs in the U.S. (*E. coli* O157:H7) (84), and farmed ducks in Tanzania (*Campylobacter* spp.) (213)

Companion animals

Several types of MDR bacteria have been isolated from pets and other companion animals. These include *E. coli*, *Klebsiella pneumoniae*, *Staphylococcus* spp., *Enterobacter* spp., and *Salmonella* spp. In recent years, many pet owners have sought more advanced veterinary care for their animals with the result that more animals are treated with a variety of antibiotics and may be hospitalized for periods of time. Some studies have shown that more MDR bacteria are isolated from dogs, cats, and horses after two or more days in a veterinary hospital than were present at admission and treatment with certain antibiotics was correlated with carriage of MDR bacteria. (107; 119; 182; 250; 303) Such MDR bacteria in companion animals may complicate treatment of sick animals and potentially increase health risks for pet owners and those caring for sick animals. (301) The European Medicines Agency published online a draft of a paper discussing the risk of transfer of antimicrobial resistance, including MDR, from companion animals to humans. (4)

Dogs and Cats.

Dogs and cats are generally close companions of their human caretakers thereby providing opportunities for exchange of antibiotic resistant bacteria. Outbreaks of MDR *S.* Typhimurium have occurred among employees and clients of veterinary facilities that were caring for cats with diarrhea. (235) In the U.S., MDR *E. coli* have been isolated from 29% of 376 clinical specimens from sick dogs and cats in 2005 (257) and MDR was identified in 11% of isolates from healthy dogs and 7.6% of isolates from healthy cats. (69) MDR *E. coli* were even present in feces of pups in commercial breeding kennels in Japan. Specific patterns of resistance differed somewhat between kennels, but MDR and ESBL *E. coli* were isolated from both kennels surveyed. (120) Surveys in England reported MDR *E. coli* in 15 % of healthy dogs (298). Analyses of multidrug resistant *E. coli* ST131 from people and companion animals in Australia revealed significant similarities indicating that these bacteria had been passed from one species to the other. (229)

MDR staphylococci were detected in 31% of healthy dogs in the U.K. (253) and in 27.5% of healthy dogs in the U.S. in 2006-2011 (76). Some *Klebsiella pneumonia* isolates from dogs

and cats in Spain are similar to the human MDR sequence type 11 and may be a source of infection for pet owners or caregivers. (128)

Horses. In a cohort study of 103 horses admitted to an equine referral hospital in England**,** nearly half of the *E. coli* isolated from feces were multidrug resistant. (182) Sixty-one large animals (54 horses) at a Pennsylvania large animal hospital were infected during an outbreak of MDR *Salmonella* Newport with 36% of animals dying. Although the hospital had an infection control program, the outbreak strain persisted in the environment necessitating hospital closure and extensive decontamination, costing >$4 million. (250)

Rodents. In 2003-2004, 28 human cases of MDR *Salmonella* Typhimurium were linked to exposure to pet hamsters, mice or rats. The outbreak strain was also isolated from a mouse and hamsters from a pet store. (271)

Reptiles. Examination of *Salmonella* Kentucky isolates from lizards, snakes, and their indoor environments in Poland revealed that most strains belonged to reptile-associated clones and were susceptible to most drugs tested. However, a few isolates were similar to isolates from poultry and exhibited multidrug resistance (314). It was suggested that the carnivorous reptiles were exposed from their feed. During 2008-2010, over 400 cases of human salmonellosis were attributed to tetracycline-resistant *Salmonella* Typhimurium in feeder mice used as reptile food (121). Since multi-drug resistant salmonellae have been isolated from pet rodents, there is a possibility that pet carnivorous reptiles may also be a source for human infection.

Multidrug resistant *Pseudomonas aeruginosa* has been isolated from 15 species of pet reptiles in Italy. (101)

Wild Animals and Insects

Multi-drug resistant *E. coli* and *Salmonella* spp. have been detected in a variety of wild mammals, including wolves (262), wild boar (173), and mongoose (227). In most cases these bacteria are very similar to MDR bacterial strains isolated from humans or domestic animals and they do not seriously impact the health of wild animals. MDR *Salmonella* were detected in wild reptiles and amphibians living in a produce-growing region of central California. (111) MDR bacteria are also present in birds, including ducks (122; 291), seagulls (127; 230; 291), cranes (156), raptors (201), and pigeons (65). Because birds are very mobile and often migrate over long distances, they may disseminate MDR bacteria widely to many new locations and aquatic birds may deposit MDR bacteria in surface waters.

House flies and blow flies on two Dutch poultry farms were found to harbor ESBL-producing *E. coli*. ESBL-producing *E. coli* are prevalent in poultry on farms in the Netherlands and these flies likely play a role in disseminating these bacteria around the farm environment and potentially to humans as well. (28) MDR enterococci have been isolated from house flies and cockroaches collected at two commercial swine farms in the U.S. (5) Multi-drug resistant bacteria were also detected in flies collected at an airport in China (178) and in cockroaches at a hospital in Ethiopia (280).

Environment

MDR bacteria have been isolated from a variety of natural environmental sources (soil, surface water, etc.) and from environments where humans are active (surfaces in homes and healthcare facilities and agricultural and wastewater facilities). Bacteria and genetic elements encoding multidrug resistance may be transferred from one environment to another and may also be transferred to humans and animals. While environmental MDR bacteria may not be human

pathogens, their pools of genetic resistance may serve as a reservoir enabling pathogens to become multiresistant. The importance of the environment in maintaining antibiotic resistance levels was discussed in a recent review. (98)

Agricultural environments where antibiotics are used may contain many species of resistant bacteria in soil and water, including MDR strains. Analyses of agricultural soils have revealed the presence of antibiotic resistant bacteria. (296) Antibiotic resistant *Salmonella* were detected in soil and irrigation water on tomato farms and may be sources of contamination for tomatoes. (195) MDR bacteria can survive in manure and waste lagoons and may spread from these sources to areas outside of the farms. (16) Compared to reference sites distant from intense agricultural activity, river water downstream from concentrated animal feeding operations in the U.S. contained much higher levels of MDR bacteria. (299) MDR bacteria are also present in water from some aquaculture systems in Japan (212)

Environmental surfaces in locations where antibiotics are frequently used, such as medical and veterinary facilities may also harbor MDR bacteria. Efforts to control a chronic outbreak of MDR *Klebsiella oxytoca* in a Spanish hospital involved more stringent cleaning and sanitation procedures and education of staff which helped temporarily to contain the infection. Further investigation revealed that the causative agent had found a safe niche to survive in sink drains and traps and only when these were thoroughly cleaned was the outbreak finally brought under control. (292)

Examination of 93 bacterial strains from a waste water treatment plant serving an antibiotic producing plant in India found that 86% of strains were resistant to 20 or more antibiotics (186). Treated water from wastewater plants is often discharged into surfaces and there are numerous reports of MDR bacteria in surface waters including: river water in Mexico (*E. coli*) (238), Lake Erie water (*Aeromonas* spp.) (263), coastal marine sediments near Italy (293), Salmon River in British Columbia (308), and surface waters in Turkey (312).

MDR bacteria have been isolated from other environmental surfaces for example, high-touch surfaces on a university campus (MRSA) (241) and domestic kitchen surfaces in Tennessee (*Cronobacter sakazakii*)(153). Not all resistant environmental isolates are known human pathogens but they are reservoirs of resistance and may transmit antibiotic resistance genes to pathogens.

CONTROL STRATEGIES

Preventing the emergence of multi-drug resistant bacteria and protecting food from contamination with these resistant strains are complex problems. Overuse and misuse of antimicrobials occurs in human medicine when antimicrobials are prescribed for viral diseases (not susceptible to antibiotics) or for bacterial infections without testing the sensitivity of the pathogens. Some patients receiving appropriate antibiotic prescriptions do not finish the full course of medicine because they feel better. This may select for and allow survival of resistant strains. In some developing countries, antibiotics can be purchased over the counter and may therefore be used to treat conditions where they are ineffective. Improved control over the use of antibiotics in human medicine would help control the emergence of multi-drug resistance.

Antimicrobial use in agriculture also drives evolution of resistant bacteria. According to a recent FDA report, a greater quantity of antibiotics (in kilograms) are sold for use in animals than in humans. (45) Although some drugs are used to treat sick animals, large amounts are used in feed to promote growth and feed efficiency. These are often available over the counter.

More judicious use of antibiotics in both veterinary and human medicine has been shown to reduce numbers of resistant bacteria. FDA has recently issued new guidance for drug

companies to voluntarily remove the use of antimicrobials for production purposes and to change marketing status from over the counter to prescription by a veterinarian. (99) A new proposed rule, Veterinary Feed Directive, is intended to encourage judicious use of antibiotics in animal agriculture, particularly for drugs that are important in human medicine. (100) However, the prevalence of resistant bacteria does not revert to zero when the use of certain antibiotics is ended. Reservoirs of resistance genes may persist for long periods of time.

Several approaches may be utilized for reducing antibiotic usage in livestock. USDA discusses these on its web page (http://www.ars.usda.gov/alternativestoantibiotics/) These include: proper use of immunomodulators that increase immune function and disease resistance of animals; timely clinical inspections to identify and treat sick animals before disease spreads to others; assessment of animal based welfare parameters to maintain a hygienic and healthy living environment; use of laboratory tests to detect animals at risk of developing disease. Components for such a system were reviewed for dairy cattle. (282)

National surveillance and programs to combat the increasing problem of resistance to antimicrobials, particularly with reference to antibiotic usage in animal agriculture in Denmark have effectively reduced prevalence of antibiotic resistant bacteria in livestock. However, implementation of programs and policies for more prudent use of antimicrobials and better animal husbandry methods to prevent development of resistant microbes was not always easy and various stakeholders need to be involved. (302) Strategies to reduce antibiotic usage in livestock have also been implemented in the Netherlands and other European countries. (164)

Australia has maintained fluoroquinoline resistance at low levels by legislation controlling the use of these drugs in humans and animals. (53)

Efforts to combat multidrug resistant TB and MRSA in health care facilities, including enhanced hygiene measures and testing and isolation of infected patients have aided in containing these infections. (102; 135; 270) The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has published guidelines for reducing transmission of MDR Gram-negative bacteria in hospitals. (274) Some of these practices may also be useful in veterinary clinics, animal husbandry, and food processing. (83)

SUMMARY

Multidrug resistance in microbes has become very widespread geographically with newly evolved MDR strains spreading around the world in a fairly short time. This is not just a problem of developed countries where large quantities of antibiotics are used for human medicine and in animal agriculture. Less developed countries often do not have adequate controls on use, sale and distribution of antibiotics so that drugs may be used to treat illnesses for which they are ineffective and persons using antibiotics may not realize the importance of completing a course of treatment. While there is some level of resistance to antimicrobials in environmental bacteria that have not been exposed to human and veterinary drugs, the widespread use of antibiotics in medicine and agriculture has driven the selection of microbes with greater levels of resistance thereby significantly increasing costs for treatment of some common infections as well as their morbidity and mortality.

Humans may be potentially exposed to MDR pathogens through a variety of routes including: environments at health care facilities, farm environments and animals, companion animals and their food, foods from animals carrying MDR bacteria, fresh produce carrying MDR

pathogens acquired from contaminated soil or water, and exposure to other individuals carrying MDR microbes.

Several reviews have documented the increasing trends of resistance to multiple drugs in diseases such as tuberculosis, gonorrhea, and typhoid fever. Surveillance studies have also documented increasing trends in multidrug resistance in many other pathogens, although there are a few reports of the decline of certain multidrug pathogens. For example, MRSA is still a major health concern, but numbers have declined in some healthcare facilities that have adopted stringent controls on antibiotic usage and screening and treatment of incoming patients to prevent importation of new sources of MRSA into hospitals.

Strategies for controlling use of antimicrobials need to be implemented in both human and animal medicine and agriculture and in countries around the world. Resistant microbes can spread rapidly from where they originated to far distant places and countries.

Table 3. Reported multidrug resistance in bacterial species other than *Salmonella*.

Bacteria	Isolated from	References
Achromobacter xylosidans	Humans (Japan)	(309)
Acinetobacter baumanii	Humans (France)	(33)
Aeromonas	Fish (Thailand, China); salmon aquaculture facilities (Canada)	(73; 191; 311)
Arcobacter	Cattle (Malaysia)	(255)
Bacteroides fragilis	Humans (U.S.)	(148)
Bacills cereus, B. subtilis	Food, humans (India); Lab (Japan)	(14) (261) (155)
Burkholderia	Humans (U. K.)	(248)
Campylobacter jejuni, C. coli	Pigs (Brazil); Pigs (China); farm animals (Europe); chicken liver & gizzards (U.S.); chickens (Turkey)	(27) (236) (205) (214) (55)
Citrobacter freundii	Humans, (India, Italy. China)	(105; 160) (52)
Clostridium difficile	Humans (Europe, North America)	(267; 279)
Clostridium perfringens	Soil, food humans (Costa Rica); chickens (Egypt)deferred comp	(74; 224)
Cronobacter sakazakii	Kitchens	(153)
Enterobacter	Humans (Spain)	(95)
Enterococcus faecium & faecalis	Pigs and farm environment (Portugal); Cheese (France); laying hens (Europe)	(215) (142) (287)
E. coli	Broiler chickens (Canada); laying hens (Europe); gulls (Chile); Humans (U.S.); chicken meat (Japan); cattle (Canada); lambs (STEC; U.S.); Dogs (STEC; Brazil); Humans (U.S.)	(184) (127) (287) (57) (6) (77) (84) (226) (144)
Helicobacter pylori	Humans (Italy)	(44)
Klebsiella pneumoniae	Humans (France); Humans (Guinea-Bissau)	(187) (139)
Legionella pneumophila	Humans (France)	(93)
Listeria	Poultry (Spain); Food (Columbia); Food (Switzerland)	(12) (243) (24)
Mycobacterium leprae	Humans (U.S.)	(304)
Mycobacterium tuberculosis	Humans (U.S. France)	(202) (23)
Neisseria gonorrheae	Humans (Worldwide)	(131)
Photobacterium	Aquaculture site (Japan)	(212)
Proteus mirabilis	Humans (Italy, Europe)	(180) (63)
Pseudomonas aeruginosa	Reptiles (Italy); Humans (U.S.)	(101)
Shigella	Humans (U.S.), (Belgium), (China)	(259; 295; 317)
Staphylococcus	Dogs (U.S.); Housing surfaces (U.S.); pigs and farmers (Switzerland); pigs (China)	(76) (241) (222) (124)
Streptococcus pneumoniae	Humans (Korea)	(265)
Vibrio cholerae	Humans (China); water (Cameroon)	(8; 313)
Vibrio parahaemolyticus	Shrimp (Hong Kong); Humans, environment (Canada)	(176) (175)
Yersinia	Chicken, beef (Iran); Humans (Spain)	(68; 91)

Table 4. Foodborne outbreaks linked to MDR *Salmonella* spp.

Year	Serotype	Food	Cases	Country	Reference
2013	Heidelberg	Chicken	9	USA: TN	(50)
2013	Heidelberg	Chicken	524	USA (25 states + PR)	(48)
2011-2012	Typhimurium	Beef, ground	20	USA (7 states)	(47)
2011	Typhimurium	Pork	51	England	(225)
2011	Heidelberg	Turkey, ground	136	USA (34 states)	(49)
2011	Hadar	Turkey, ground	19	USA (13 states)	(114)
2011	4, 5, 12:i:-	Pork sausage	337	France	(112)
2010	4, 5, 12:i:-	Beef, ground	554	France	(237)
2008	Typhimurium DT104	Pork?	152	Netherlands	(80)
2008	Typhimurium DT104	Beef biltong	16	England	(198)
2007	Newport	Beef, ground	42	USA (4 states)	(254)
2006-07	Newport	Cheese, unpasteurized	85	US: IL	(20)
2006	4,[5],12:i:-	Pork?	21	Luxembourg	(204)
2006	4,[5],12:i:-	Pork?	112	Luxembourg	(204)
2005	Typhimurium DT104	Beef, raw (carpaccio)	31	Denmark	(88)
2005	Typhimurium DT104	Beef	169	Netherlands	(157)
2005	Hadar	Chicken	1983	Spain	(167)
2005	Typhimuriun DT104b	Lettuce	60	Finland	(277)
2005	Typhimurium DT104	Beef, minced	5	Norway	(138)
2003-04	Typhimuriun DT 104	Beef, ground	58	US: 9 states	(71)
2003	Typhimurium	Restaurant buffet	77	Europe	(89)
2003	Newport	Horse meat	14	France	(87)
2003	Typhimurium	Beef burgers	47	US: AK	(192)
2003	Typhimurium DT104	Boxed lunches	358	Japan	(276)
2002	Newport	Beef	47	US: 5 states	(316)
2002	Typhimurium DT120	Turkey, RTE	41	Denmark	(126)
2002	Typhi	Water, city	5963	Nepal	(168)
2001	Typhimurium DT104	Sesame seed candy	203	Australia, Germany, Norway, Sweden	(1; 38; 174)
2001	Newport	Cheese, soft	26	US: CT	(190)
2000	Typhimurium DT104	Lettuce	361	UK	(132)
2000	Typhimurium DT204b	Lettuce	392	Europe: 5 countries	(62)
2000	Typhimurium DT104	Beef burgers	35	France	(117)
2000	Typhimurium DT104L	Anchovy, dried	33	Singapore	(171)
2000	Typhimurium	Milk	93	US: 2 states	(221)
1998	Typhimurium DT104	Milk	86	UK	(15)
1998	Blockley	Smoked eel	13	Germany	(92)
1998	Typhimurium DT104	Pork	25	Denmark	(200)

1997	Typhimurium	Soft cheese	113	France	(70)
1997	Typhimurium DT104	Cheese	31	US: CA	(54)
1997	Typhimurium DT104	Cheese	79	US: CA	(54)
1997	Typhimurium DT104	Cheese, unpasteurized	54	US: WA	(294)

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