chickens that were fed tetracycline-supplemented feed and were housed with chickens inoculated with tetracycline-resistant *E. coli*. Additionally, those researchers isolated bacteria with the resistance plasmid from animal handlers. A 1977 study showed that antibiotic-resistant bacteria from animals can be transferred to people who handle raw meat.[37]

Salmonella, a food-borne pathogen that sickens an estimated 1.4 million and kills 500 Americans each year,[38] is readily transmissible from animals to humans. In the developed world, the majority of *Salmonella* infections in humans come from food, with additional cases arising from direct contact with animals. If *Salmonella* bacteria carried by animals developed resistance to antibiotics, those resistant bacteria could be transferred to humans.

A study in 1980 showed that an outbreak of antibiotic-resistant *Salmonella* in infants in a hospital nursery originated from farm animals.[39] A farmer's daughter who was pregnant worked with calves up until four days before she delivered her baby. The pregnant woman fed sick calves from her hand in an effort to teach them to drink from a bucket. After the woman gave birth, she had diarrhea. In addition, her baby developed diarrhea three days after he was born, as did two other babies in the nursery. Culturing the patients and calves revealed that all were infected with *Salmonella heidelberg* that was resistant to chloramphenicol, sulfamethoxazole,

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[37] Linton, A.H., Animal to man transmission of Enterobacteriaceae. *Royal Society of Health Journal* 1977; 97: 115-118.

[38] Center for Disease Control and Prevention, National Center for Infectious Disease Branch, *FoodNet*, 1998.

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

and tetracycline. All three of those antibiotics are, or were previously, used in agriculture. Those cases suggest that antibiotic-resistant *Salmonella* spread to a woman through direct contact with sick farm animals. The bacteria also spread from baby to baby in the hospital setting.

An outbreak of multiple-antibiotic-resistant *Salmonella typhimurium* (resistant to ampicillin, chloramphenicol, kanamycin, streptomycin, sufadiazine, and tetracycline) occurred among newborns in a Canadian hospital in 1983.[40] That outbreak was traced back to local dairy cattle which were infected with the same strain of antibiotic-resistant bacterium. The mother of the first infant to become sick lived on the farm with the infected cattle and drank unpasteurized milk. (The other babies became ill three to four days later, probably from cross-contamination by nurses who cared for them.)

A study by Holmberg, published in 1984, demonstrated animal-to-human transmission of antibiotic-resistant *Salmonella newport* (resistant to ampicillin, carbenicillin, and tetracycline).[41] The genes for resistance were located on a plasmid. Eighteen patients had consumed hamburger meat from a herd of cattle that had been fed subtherapeutic amounts of tetracycline to promote growth. Although the suspect meat was not available for testing, all of the patients came from Minnesota, South Dakota, and Iowa, states where the suspect meat was distributed. In addition, the only isolation of that particular antibiotic-resistant strain in the previous year occurred in dairy cows on a farm adjacent to the beef herd.

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[40] Bezanson, G.S., Khakhria, R., Bollegraaf, E., Nosocomial outbreak caused by antibiotic-resistant strain of *Salmonella typhimurium* acquired from dairy cattle. *Canadian Medical Association Journal* 1983; 128: 426-427.

[41] Holmberg, 1984.

4. Antibiotic-resistant bacteria may transfer resistance genes to other bacteria.

Using antibiotics subtherapeutically increases the prevalence of antibiotic-resistant bacteria. Those bacteria could colonize people and pass their resistant genes to human pathogens by a process called horizontal gene transfer.[42] For example, a person might consume meat that is contaminated with nonpathogenic bacteria. If those benign bacteria contained genes that confer antibiotic resistance, the resistance genes could be transferred in a person's gut from the harmless bacteria to pathogenic bacteria.

One example of horizontal gene transfer was observed in Germany.[43] In 1983, farmers in certain parts of Germany began using a new antibiotic, nourseothricin, for growth promotion in swine. That use quickly led to the development of nourseothricin resistance among *E. coli* isolated from swine and from pork products. By 1990, nourseothricin-resistant *E. coli* had been passed to farm workers, farmers' families, citizens in the community in which nourseothricin was used, and patients suffering from urinary tract infections. A few years later, the nourseothricin-resistance gene was found in *Shigella*, a bacterium found in primates (including humans) but not in swine.[44] No nourseothricin-resistant bacteria were isolated from people or animals in other parts of Germany where the antibiotic was not being used. The appearance of nourseothricin-

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[42] Levy, *The Antibiotic Paradox*, 1992 pp. 78-89.

[43] Hummel, 1986.

[44] Tschäpe, H., The spread of plasmids as a function of bacterial adaptability. *FEMS Microbiology Ecology* 1994; 15: 23-31.

resistant *Shigella* indicated that the resistance moved from bacteria exposed to antibiotics on the farm to a human pathogen.

Another example of horizontal transfer was demonstrated in the laboratory. Scientists facilitated the transfer of an unusual tetracycline-resistance gene, tet (Q), from *Prevotella rumincola* isolated from sheep to *Bacteriodies fragilis*, a human pathogen.[45] *P. rumincola* is found in high numbers in the normal gut bacteria of sheep and cattle. Although that experiment does not prove that horizontal transfer of resistance occurs in nature, it shows that transfer is biologically possible. Further research suggested that such transfer likely does occur in nature. The identical tet (Q) gene was found in *B. fragilis* in humans and in *P. rumincola* isolated from animals.[46] A 1992 study showed that *Staphylococcus aureus* and enterococci can transfer antibiotic-resistance genes in the laboratory setting.[47] Presumably, that transfer also could happen in nature.

A fourth example that suggests that transfer of antibiotic-resistant genes can occur between different species of bacteria comes from the U.K.[48] The use of apramycin, an

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[45] Shoemaker, N.B., Salyers, A.A., unpublished data, cited in Speer, B.S., Shoemaker, N.B., Salyers, A.A., Bacterial resistance to tetracycline: mechanisms, transfer, and clinical significance. *Clinical Microbiology Reviews* October 1992: 387-399.

[46] Shoemaker, N.B., Wang, G., Salyers, A.A., Evidence for natural transfer of a tetracycline resistance gene between bacteria from the human colon and bacteria from the bovine rumen. *Applied Environmental Microbiology* 1992; 58: 1313-1320.

[47] Noble, W.C., Virani, Z., Cree, R.G., Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. *FEMS Microbiology Letters* 1992; 72: 195-198 [hereinafter Noble, 1992].

[48] Johnson, A.P., Burns, L., Woodford, N., Threlfall, E.J., Naidoo, J., Cooke, E.M., George, R.C., Gentamicin resistance in clinical isolates of *Escherichia coli* encoded by genes of veterinary origin. *Journal of Medical Microbiology* 1994; 40: 221-226.

aminoglycoside, caused the emergence of resistance in *E. coli* found in feces of treated animals. The resistant bacteria had a unique plasmid profile and were resistant to apramycin, gentamicin (another aminoglycoside), and hygromycin B (an antiparasitic agent used in agriculture). Resistant *E. coli* with the identical pattern of resistance were subsequently found in hospital patients. One of those patients also was infected with *Klebsiella pneumonia* (a human pathogen) that had the same resistance pattern. The resistance gene apparently was horizontally transferred between *E. coli* and *Klebsiella pneumoniae*.

5. Subtherapeutic antibiotic use may select for multi-drug-resistant bacteria that can cause infections that are difficult to treat.

Subtherapeutic use of one antibiotic can select for bacteria that are resistant to several antibiotics. That is because several resistance genes may be grouped together on bacterial DNA. Use of any of the antibiotics to which the bacteria are resistant could select for resistance to all of the antibiotics. Because they are resistant to multiple antibiotics, multi-drug-resistant infections may be particularly difficult to treat.

Multi-drug-resistant *Salmonella typhimurium,* which accounts for about 10 percent of all *Salmonella* infections, poses a major health concern.[49] Most of those infections are caused by *Salmonella typhimurium* DT104, which usually is resistant to ampicillin (a penicillin), chloramphenicol, streptomycin, sulfonamides, and tetracycline. Since 1979, the prevalence of human *Salmonella typhimurium* isolates that are resistant to those antibiotics increased from 0.6 percent to 34 percent.

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[49] Glynn, 1998.

Multi-drug-resistant DT104 caused an outbreak at a dairy farm in Vermont that sickened and killed cattle and sickened nine people (one almost died) who cared for the cattle or who drank unpasteurized milk.[50] Because the infections were multi-drug resistant, physicians had difficulty finding an antibiotic that was effective against those infections. After several failed attempts, physicians finally were able to treat the one hospitalized victim with the one class of drug to which the DT104 strain was not resistant (and to which the patient was not allergic): fluoroquinolones.

Salmonella typhimurium DT104 also may be a particularly virulent strain of *Salmonella*. Infections may be associated with greater morbidity and mortality than other *Salmonella* infections.[51,52] In the U.K., where DT104 is the predominant strain of *Salmonella* isolated from people, a 1994 study reported that 41 percent of people who became ill with that strain required

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[50] Friedman, C.R., Epidemic Intelligence Service Officer, Center for Disease Control and Prevention, memo to Epidemiology Program Office, Centers for Disease Control and Prevention, June 27, 1997.

[51] Wall, P.G., Morgan, D., Lamden, K., A case control study of infection with an epidemic strain of multiresistant *Salmonella typhimurium* DT104 in England and Wales. *Communicable Disease Report CDR Review* 1994; 4: R130-R135 [hereinafter Wall, 1994].

[52] A recent study suggests that DT104 may not be more virulent than other subtypes of *Salmonella typhimurium*. (Threlfall, E.J., Ward, L.R., Rowe, B., Multiresistant *Salmonella typhimurium* DT104 and salmonella bacteraemia. *The Lancet* 1998; 352: 287-288.) This issue has yet to be resolved.

hospitalization, and three percent died.[53] In addition, in some DT104 outbreaks in the U.K., the mortality rate among DT104-infected cattle ranges from 40 to 60 percent.[54]

In 1998, an outbreak in Denmark of multi-drug-resistant DT104 that also was resistant to fluoroquinolones was traced to a herd of pigs. Among the 22 victims were several people who did not respond to fluoroquinolone therapy. One death was indirectly attributable to treatment failure.[55]

6. Subtherapeutic antibiotic use jeopardizes therapeutic options in veterinary and human medicine.

Subtherapeutic use of older antibiotics such as penicillin and tetracycline has rendered them less effective in treating animal disease. Consequently, veterinarians and farmers have had to use newer antibiotics to treat animal disease, which in turn accelerates the development of antibiotic resistance to those newer antibiotics.

In the U.K., the use of antibiotics has fostered the emergence of multi-drug-resistant *Salmonella typhimurium* DT104 that often is lethal to cattle. Because of the agricultural use of antibiotics, multi-drug-resistant-DT104 infections are resistant to the antibiotics typically used to treat *Salmonella* in cattle. As a result, to treat those infections, farmers must resort to the same antibiotics that are used for treating human cases of invasive *Salmonella*: Bactrim (trimethoprim-sulfamethoxazole) and fluoroquinolones. Not surprisingly, the use of Bactrim and

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[53] Wall, 1994.

[54] U.S. Department of Agriculture, Food Safety and Inspection Service, *Situation Assessment: Salmonella typhimurium* DT104. December 1997 [hereinafter *Situation Assessment: Salmonella typhimurium* DT104, December 1997].

[55] Anonymous, Outbreak of quinolone-resistant, multiresistant *Salmonella typhimurium* DT104, Denmark. *Weekly Epidemiological Record* 1998; 42 :327-328.

fluoroquinolones to treat DT104 infections in cattle is leading to the development of resistance to those drugs. In 1995, only two years after fluoroquinolones commonly were used in cattle, 16 percent of multi-drug-resistant DT104 isolated from cattle were resistant to fluoroquinolones.[56] From 1993 to 1996, the proportion of DT104 isolates from cattle resistant to trimethoprim, one of the active ingredients in Bactrim, rose from less than two percent to 24 percent in the U.K.[57] If DT104 bacteria resistant to fluoroquinolones and Bactrim were to cause bloodstream infections in humans, those infections would be difficult to treat.

In the U.S., where tetracycline is used subtherapeutically in livestock, tetracycline-resistance among animal isolates of *Salmonella* ranges from 24 percent in cattle to 50 percent in swine.[58] Because tetracycline is ineffective against many cases of *Salmonella* infections in livestock, other antibiotics, such as ceftiofur (a third-generation cephalosporin), must be used. However, in children, third-generation cephalosporins are the drugs of choice for treating invasive *Salmonella* infections.[59] As ceftiofur is used more in animals, resistance is likely to develop, potentially leaving no therapeutic options for those infected children.

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[56] Hughes, J.M., Assistant Surgeon General and Director, National Center for Infectious Diseases, letter to Stephen Sundlof, Center for Veterinary Medicine, Food and Drug Administration, May 14, 1997.

[57] *Situation Assessment: Salmonella typhimurium* DT104, December 1997.

[58] Tollefson, L., Angulo, F.J., Fedorka-Cray, P.J. National surveillance for antibiotic resistance in zoonotic enteric pathogens. *Veterinary Clinics of North America: Food Animal Practice* 1998; 14: 141-150.

[59] Fluoroquinolones can be used to treat invasive *Salmonella* infections in adults, but are not approved for use in children under 18 years of age.