Drug-Resistant *Salmonella* in the United States: An Epidemiologic Perspective

MITCHELL L. COHEN AND ROBERT V. TAUXE

Salmonellosis poses a health problem of large proportions in the United States. Annually, it accounts for more than 40,000 reported cases, 500 deaths, and financial costs well in excess of $50 million. Antimicrobial resistance is increasing in *Salmonella* strains, a finding that has important public health implications. Although the chain of transmission of the bacteria is often complex, combined epidemiologic and laboratory studies with the use of new methods in molecular biology make it possible to trace antimicrobial-resistant salmonellae to their primary source—foods of animal origin. These studies suggest that the antimicrobial drugs to which food animals are exposed provide selective pressure that leads to the appearance and persistence of resistant strains.

ANTIBIOTICS ARE USED TO TREAT MICROBIAL INFECTIONS in humans and animals, and they are given prophylactically to healthy humans to prevent infections. Antibiotics are also given in low doses to food animals to improve their growth rate and feed conversion. However, the use of an antimicrobial in humans or animals is often followed by the appearance of resistant microorganisms; this effect leads to treatment failures and the need for newer, often costlier, antimicrobials. Many investigators have concluded that the phenomenon of resistance is related to the amount and patterns of use of antimicrobials, and they have recommended more prudent use in both humans and animals. Animal growth promotion accounts for a substantial portion of all antimicrobials used in the United States, and this use has become particularly controversial (*1, 2*).

Critical to this controversy are data that define the public health significance of antimicrobial resistance as well as the source of resistant organisms that infect humans. Such data have not been easily obtained. Only in recent years, with the application of molecular biology techniques for subtyping bacteria or identifying specific genes, has the epidemiology of antimicrobial-resistant organisms become better understood. For one organism, *Salmonella*, the molecular epidemiology of resistant strains has been extensively studied. In this article we review a series of studies, many conducted by the Centers for Disease Control (CDC), that have led to a better understanding of the significance and sources of infections with antimicrobial-resistant *Salmonella*.

Epidemiologic Background

Salmonellae are Gram-negative bacteria that can infect both humans and animals. The organisms most frequently cause a self-limited gastroenteritis, but the spectrum of disease ranges from asymptomatic colonization to major extraintestinal illness such as meningitis or osteomyelitis. Salmonellae can be serotyped by means of somatic and flagellar antigens and can be further subtyped by antibiotic-sensitivity testing, biochemical reactions, phage-typing, and analysis of the plasmids they carry. All of these methods have been useful in defining the epidemiology of salmonellosis. Although more than 1500 *Salmonella* serotypes exist, ten account for more than 70% of the isolates reported from humans each year in the United States. The most frequently isolated serotype is *S. typhimurium*, which accounted for 35% of reported human isolates in 1984. Other common serotypes include *S. enteritidis* (10.0%), *S. newport* (4.5%), *S. infantis* (3.0%), and *S. heidelberg* (1.0%). Some serotypes are highly host-specific and rarely cause disease in other species. For example, *S. typhi*, which causes typhoid fever, only infects humans; there are no known animal reservoirs. *Salmonella gallinarum* and *S. pullorum* are almost exclusively pathogens of poultry. Other *Salmonella* serotypes, such as *S. typhimurium*, have a broad host range and cause disease in many species. Some serotypes currently have specific animal reservoirs but frequently cause human infections. For example, human pathogens *S. heidelberg* and *S. litchfield* have primarily avian and reptilian reservoirs, respectively.

Cases of typhoid fever and of nontyphoidal salmonellosis have been reported by clinicians to public health authorities for many years. In 1963, after several large outbreaks of salmonellosis were traced to commercial egg products, CDC established a *Salmonella* Surveillance System, which provided more detailed and serotype-specific data (*3*). Since then, *Salmonella* isolates submitted to state health department laboratories for serotyping have been reported to CDC along with patient information, including age, sex, county of residence, and source of the clinical specimens. Data on isolates from nonhuman sources, that is, food and animals, are also reported. In addition, CDC has other sources of information on salmonellosis. Outbreak investigations by state, local, and federal agencies identify routes and vehicles of transmission, the reservoirs of causative organisms, and risk factors that determine why some exposed individuals become ill and others do not. Other sources of data are special epidemiologic and laboratory studies, designed to answer specific questions about salmonellosis. CDC conducted prospective studies of reported salmonellosis in 1979 (*4*) and in 1984 (*5*). In these studies, a random sample of stratified urban and rural counties in the United States were asked to submit all *Salmonella* isolates and complete detailed questionnaires on the patients from whom the salmonellae were isolated. These isolates were tested for antimicrobial sensitivity and, in some instances, plasmid DNA content, and the laboratory and epidemiologic data were compared. These studies provided data on the frequency, significance, and origin of antimicrobial resistance in *Salmonella*.

M. L. Cohen is assistant director for medical science, and R. V. Tauxe is assistant chief, Enteric Diseases Branch, Division of Bacterial Diseases, Center for Infectious Diseases, Centers for Disease Control, Atlanta, GA 30333.

Since the early part of this century, the incidence of salmonellosis has changed dramatically. *Salmonella typhi* has become uncommon (Fig. 1), with only 500 isolates reported annually, whereas the isolation rates for the nontyphoid salmonellae have markedly increased (*6*). *Salmonella typhi* has no animal reservoir, and the incidence of typhoid fever tends to decrease as sanitation in a community improves. The increase in the nontyphoid salmonellae may be related to changes in animal husbandry practices that may encourage the spread of *Salmonella* among animal populations, as well as to the industrialization of food processing that facilitates swift and broad distribution of contaminated food items. In the developing world, *S. typhi*, with its well-recognized association with unsanitary conditions, is still the primary *Salmonella* that causes human disease.

Salmonellosis in the United States results in considerable morbidity. Over 40,000 isolates of *Salmonella* are reported each year. However, these reports represent only a small fraction of the number of cases that actually occur. Infection may not be suspected, cultured, diagnosed, or reported for a variety of reasons. Community surveys during outbreaks suggest that the proportion of actual infections reported are between 1 in 10 and 1 in 100 (*7, 8*). Thus, between 400,000 and 4,000,000 cases may occur annually.

The CDC prospective studies provide another measure of the public health impact of salmonellosis. In the 1979 study, 228 (45%) of the 503 patients were hospitalized for salmonellosis, and seven deaths (1.4%) occurred (*4*). Rates for 1984 were similar. Extrapolation from this sample to all reported cases indicates that more than 18,000 hospitalizations and 500 deaths are associated with salmonellosis annually. These numbers may be conservative estimates of the morbidity and mortality since, as previously mentioned, only 1 to 10% of actual cases are reported.

Salmonellosis is also associated with considerable financial cost. Animal producers face costs from illness and death of animals, restaurants and industry incur costs from lost business and lawsuits, and patients experience direct and indirect costs. In a 1976 study in Colorado it was determined that the average case of salmonellosis costs $645 (*9*). Extrapolated to just the reported cases, direct and indirect patient costs for salmonellosis in the United States exceed $50 million (in 1985 dollars) a year. When the total costs of the unreported cases and the costs to industry and business are included, salmonellosis may cost billions of dollars each year (*10*).

Significance of Antimicrobial-Resistant Salmonellae

The significance of antimicrobial resistance is most obvious in its impact on treatment of human infections, but there are other less obvious and perhaps more important effects. Most *Salmonella* infections do not require treatment. Antimicrobials are not indicated for uncomplicated gastroenteritis since treatment does not reduce the duration or severity of symptoms, may prolong convalescence and the carrier state, and may result in the emergence of resistant organisms (*11*). Some physicians treat infants and elderly persons who have uncomplicated gastroenteritis, attempting to prevent complications such as local infections or bacteremia, which occur most frequently in these age groups. In the CDC prospective studies, 40% of patients with salmonellosis were treated with antimicrobial drugs.

Patients with bacteremia, meningitis, or other extraintestinal infections require effective antimicrobial treatment. Chloramphenicol has been the drug of choice for decades because it is effective in treating typhoid fever and because the frequency of chloramphenicol resistance in *Salmonella* has been low. Other effective drugs include ampicillin and trimethoprim-sulfamethoxazole. Proven efficacy is vital since the bactericidal effect of an antimicrobial agent in vitro may not correlate with its ability to cure patients (*12*). This difference may be related to the agent's ability to penetrate mononuclear cells and kill salmonellae within them. If the frequency of resistance to these three antimicrobials rises, the choice of agents that can be used to treat patients becomes more limited, and the likelihood increases that initial therapy, chosen before sensitivity data on the infecting organism are available, will fail in very sick patients. Such a fatal case in a patient infected with a chloramphenicol-resistant *Salmonella* was recently reported (*13*). Newer antimicrobials that have in vitro activity against *Salmonella* are currently being evaluated for in vivo efficacy.

Another impact of antimicrobial resistance is through the recently recognized association between drug-resistant salmonellae and the routine clinical use of antimicrobials for infections other than salmonellosis. There are three facets of this association. (i) Antimicrobial-resistant *Salmonella* infections can complicate antimicrobial treatment of other infections. (ii) Prior antimicrobial therapy allows fewer numbers of antimicrobial-resistant *Salmonella* to cause symp-

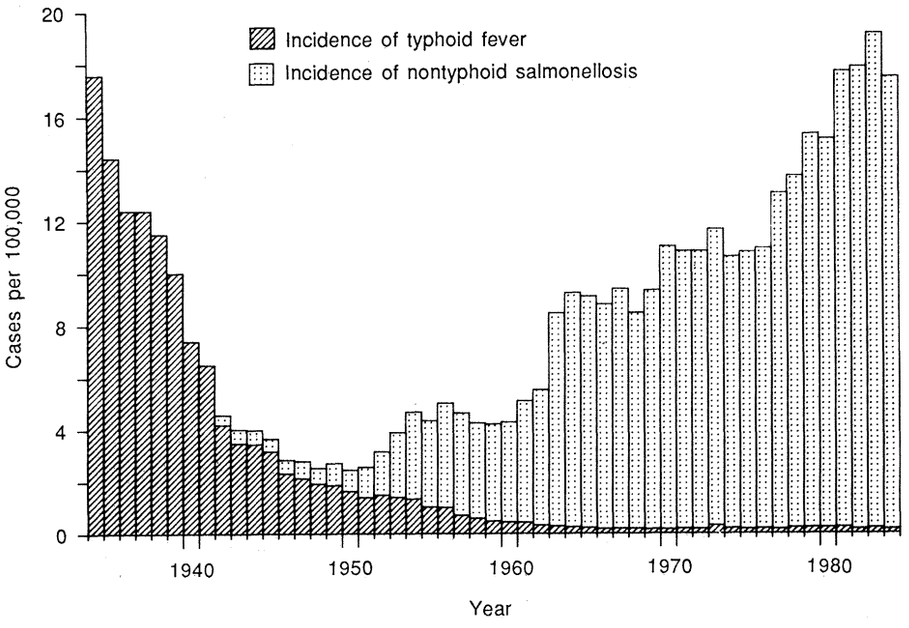

Fig. 1. Reported incidence of typhoid fever and nontyphoid salmonellosis in the United States from 1934 to 1984 (*6*).

Table 1. Etiologic fractions attributed to prior antimicrobial exposure in human salmonellosis outbreaks.

Salmonella serotype	Source	Etiologic fraction (%)	Excess cases*	Reference
S. newport	Beef	30	202	(*15*)
S. typhimurium	Milk	16	2600	(*6*)
S. newport	Beef	64	12	(*14*)
S. indiana	Hospital	53	24	(*34*)

*Cases of salmonellosis that would not have occurred if the ill persons had not been previously exposed to antimicrobials.

tomatic infections. (iii) An increase in the proportion of salmonellae that are antimicrobial-resistant will increase the overall frequency of salmonellosis.

Salmonellosis caused by resistant organisms has been recognized as a complication of antimicrobial therapy for other infections (*4, 7, 14, 15*). In one outbreak, persons treated with penicillin derivatives for streptococcal pharyngitis, bronchitis, or otitis developed severe illness with a penicillinase-producing *S. newport* within 24 to 48 hours after beginning treatment with antimicrobials. The association was so striking that health officials initially feared that an antimicrobial might have been contaminated. It was soon determined that all of the ill persons had taken different penicillin preparations and the source of the resistant *S. newport* strain was subsequently shown to be ground beef. The short interval between the first therapeutic antimicrobial dose and the onset of symptoms suggested that these patients had already consumed the contaminated ground beef and were asymptomatically colonized with the resistant strain; the penicillin derivative provided the selective advantage for the organism to cause disease. Persons ill with the outbreak strain were estimated to be 51 times as likely to have recently taken an antimicrobial as other persons ill at the same time with antimicrobial-sensitive strains of *S. newport* (*14*). This promotion of antimicrobial-resistant *Salmonella* infections by antimicrobial therapy is not seen in antimicrobial-sensitive *Salmonella* infections.

Not only do antimicrobials appear to convert asymptomatic colonization with resistant organisms to symptomatic infection, but these drugs also appear to facilitate infection with antimicrobial-resistant salmonellae by lowering the infectious dose needed to cause disease. In an outbreak of drug-resistant *S. typhimurium* infections transmitted by contaminated milk in 1985 in Illinois, ill persons who were taking antimicrobials to which the organism was resistant had consumed significantly less milk than other ill persons, suggesting that a lower inoculum was sufficient to cause disease in persons already taking an antimicrobial (*7*).

Promotion of antimicrobial-resistant *Salmonella* infections by antimicrobial therapy has a third public health consequence. An outbreak caused by a resistant strain affects a larger number of people than if the outbreak had been caused by a sensitive strain. For example, in the 1985 Illinois outbreak, many persons who drank the contaminated milk would not have become ill if they had not been taking antimicrobials or if the strain had been sensitive. This group of excess cases, attributable to the effect of taking antimicrobials, constitutes an "etiologic fraction," an epidemiologic term used in chronic disease studies. For example, the etiologic fraction of cases of lung cancer associated with smoking cigarettes is about 85%, for if cigarette smoking were eliminated, 85% of lung cancers would be prevented (*16*).

The etiologic fraction can be calculated by using the relative risk, which is a measure of the strength of association of illness with the risk factor, and the proportion of the population exposed to the risk factor. Such analysis for several antimicrobial-resistant *Salmonella* outbreaks demonstrates that an excess of cases occurred that were attributable to the risk factor, that is, taking antimicrobials (Table 1). This type of analysis also predicts that the overall incidence of human salmonellosis will increase if the exposure of humans to antimicrobials increases or if the proportion of *Salmonella* that are resistant increases.

Other public health consequences of prior antimicrobial therapy are more difficult to quantify. Because the infectious dose of resistant *Salmonella* may be lower in humans receiving antimicrobials, the need to detect and prevent even minimal contamination of foods becomes more important. In addition, previous antimicrobial therapy may increase the difficulty of epidemiologic investigations. Because use of an antimicrobial may convert an asymptomatic colonization to an overt infection, the incubation period can be considerably longer than the usual 12 to 72 hours. Consequently, the relevant exposure is more difficult for the infected individual to remember and hence for the epidemiologist to detect.

Frequency of Antimicrobial Resistance

Most published data on the frequency of antimicrobial resistance in *Salmonella* are derived from isolates routinely submitted to laboratories, with little information about the patient provided. Two national reference laboratory-based studies, conducted in 1967 and 1975, showed a significant increase in resistance of *S. typhimurium* and other serotypes in these years (*17, 18*). Such studies are valuable, but investigators may be handicapped by incomplete patient information when they interpret the data. In other studies, the occurrence of multiple isolates from the same patients or from multiple persons in a common-source outbreak may have unpredictable effects on the frequency of resistance. Since salmonellae that cause human illness appear to be clonal in origin, studies based on small geographic areas are more susceptible to wide swings in the frequency of resistance as successive clones circulate (*19*). To address these issues, CDC conducted the two county-based prospective studies in 1979 and 1984. All isolates from a random sample of urban and rural counties in the United States were submitted to CDC with detailed questionnaires. Multiple isolates in the same outbreak or from the same patient were excluded.

The frequency of resistance to one or more antimicrobials by serotype in the 1979 study is shown in Table 2. By 1984, the overall frequency of resistance had increased to 24%. However, not all serotypes have become more resistant. *Salmonella heidelberg* has had significant decreases in resistance to most antimicrobials, whereas the frequency of resistance of *S. typhimurium* has increased, particularly to tetracycline and chloramphenicol (*5*).

Different serotypes have different frequencies of resistance. Certain serotypes are associated with specific animal reservoirs that may be under different antimicrobial pressures. Changes in frequency of

Table 2. Antimicrobial resistance of *Salmonella* by serotype in 1979 CDC study (*4*).

Salmonella serotype (number of isolates)	Resistance (%)
S. heidelberg (37)	65
S. saint-paul (9)	33
S. newport (40)	22
S. enteritidis (30)	17
S. typhimurium (239)	15
S. infantis (17)	12
Other (170)	5
Total (542)	16

resistance, as seen in *S. heidelberg* and *S. typhimurium*, may reflect changes in specific antimicrobial use within their reservoirs. From 1979 through 1983, 69% of nonhuman isolates of *S. heidelberg* reported to CDC came from poultry, whereas 39% of *S. typhimurium* were from bovine sources. By the late 1970's the majority of poultry producers were no longer using penicillin and tetracycline as growth enhancers, whereas the use of tetracycline in calves and beef cattle had continued. In a national survey of animal husbandry that was conducted over 4 years (1979–1982), the proportion of cattle raisers using low doses of tetracycline was 61%, compared with 4% for broiler chicken producers (*20*). The changes in resistance in specific serotypes associated with certain food animal species may reflect patterns of antimicrobial use and suggest that decreased use may reduce antimicrobial resistance.

The increase in resistance to chloramphenicol, particularly in *S. typhimurium*, is also of interest (*5*). Chloramphenicol is not often used in human medicine because of the idiosyncratic and dose-independent development of irreversible aplastic anemia in a small number of persons taking the drug. Only about 2% of the patients included in the 1984 CDC prospective study of salmonellosis had been treated with chloramphenicol. The antimicrobial is not licensed for food animals in the United States because of concern that drug residues in meat might also cause aplastic anemia in the consumer. However, chloramphenicol has been used illegally by livestock producers and residues of the drug were detected in food products in 1985 (*21*). The increase in chloramphenicol resistance in *S. typhimurium* suggests that the use of this drug in animals may be leading to increased resistance in human *Salmonella* infections. Another recent investigation also supports this observation (*15*).

Antimicrobial Therapy in Humans

During antimicrobial therapy in humans, *Salmonella* may acquire transferable resistance factors from other enteric flora. In a community outbreak of sensitive *S. typhimurium* infections, approximately 15% of persons receiving ampicillin for their *Salmonella* infection had ampicillin-resistant isolates identified subsequently in their stool specimens (*11*). Data from the 1979 prospective CDC study showed that 40% of persons with salmonellosis were treated with antimicrobials, and 8.5% used an antimicrobial in the month before onset of their salmonellosis. These data suggest that some portion of resistance in *Salmonella* arises from treatment of human salmonellosis. However, in the 1984 study the drugs to which the resistant *Salmonella* were likely to be resistant (Table 3) were those to which humans with salmonellosis are infrequently exposed (Table 4). Although genes for tetracycline or streptomycin resistance may be on plasmids selected by other more frequently used agents such as ampicillins, the frequency of organisms with single resistance to agents such as tetracycline has increased. These data make it difficult to attribute most antimicrobial resistance in *Salmonella* to the use of these antimicrobials in treatment of human disease. In contrast, tetracycline is widely used in both ill and well animals in a diverse range of doses and preparations in order to promote increased growth rate and feed conversion (Table 5), for disease prevention, and for treatment of illness. Resistance to streptomycin is particularly difficult to attribute to human use of streptomycin or related aminoglycoside antibiotics, but this antimicrobial was used at low doses on 12% of the pig farms and 31% of the chicken farms surveyed (*20*).

The developing world has attracted considerable attention as a potential source for antimicrobial resistance of various human pathogens since these countries have well-recognized problems with antimicrobial-resistant bacteria. Although there are specific examples of importation of *Salmonella* infections, such as *S. typhi* from Mexico in 1972 (*22*) or *S. mbandaka* in adopted children from India (*23*), these importations do not appear to account for any substantial part of the resistant *Salmonella* infections in the United States. The 1984 CDC prospective study indicates that only 4% of multiresistant strains can be attributed to exposures during foreign travel. Also, despite recognition of antimicrobial-resistant *S. typhi* in various parts of the world, the proportion of *S. typhi* strains that are chloramphenicol-resistant has been about 3.0%, and it is not increasing (*24*). The stability of chloramphenicol resistance is remarkable, given that *S. typhi* is a species that is largely imported, has no animal reservoir, and causes an infection for which chloramphenicol is one of the drugs of choice. In contrast, the frequency of chloramphenicol resistance is increasing in *S. typhimurium*, a serotype that is acquired domestically, has large animal reservoirs, and for which chloramphenicol is infrequently used in human infections.

Several authors have suggested that antimicrobial resistance in *Salmonella* is the result of antimicrobial use within the hospital (*25*). Although the hospital may be an important source for resistant *Salmonella* in the developing world (*26*), there is little evidence that this is true in the developed world. In the 1979 CDC prospective study, 9.3 and 7.2% of persons infected with sensitive and resistant strains, respectively, had been hospitalized for other reasons in the month before onset of salmonellosis.

Table 3. Specific antimicrobial resistance of 117 drug-resistant *Salmonella* strains in humans, in 1984 CDC study (*5*).

Antimicrobial drug	Resistant strains (%)
Tetracycline	55
Streptomycin	50
Ampicillin	38
Sulfisoxazole	29
Nitrofurantoin	15
Kanamycin	14
Chloramphenicol	9
Nalidixic acid	5
Cephalothin	3
Trimethoprim-sulfamethoxazole	3
Gentamicin	3
Colistin	2

Table 4. Antimicrobial exposure of persons infected with drug-resistant *Salmonella*, either in the month before onset of salmonellosis (n = 58) or as therapy after onset (n = 142), in 1984 CDC study (*5*).

Antimicrobial drug	Persons receiving antimicrobials	
	Before onset (%)	After onset (%)
Ampicillin	52	50
Trimethoprim-sulfamethoxazole	6	28
Erythromycin	26	8
Penicillin	14	2
Cephalosporin	10	8
Chloramphenicol	2	6
Sulfa	5	0
Tetracycline	5	2
Gentamicin	3	0
Clindamycin	2	0
Metronidazole	0	2
Furoxone	0	2
Streptomycin	0	0

Antimicrobial Use in Food Animals

Animals are fed antimicrobials to prevent and to treat diseases and to enhance growth. The use of low doses of antimicrobials is frequently referred to as subtherapeutic use because the amount of antimicrobial administered is less than that used to treat specific illnesses. The use of subtherapeutic doses as growth enhancers, which accounts for much of the antimicrobial usage, produces effects on animals that are similar to the effects seen in humans who receive antimicrobials for salmonellosis. Animals fed subtherapeutic doses of antimicrobials develop resistant organisms. In contrast to control animals, animals fed subtherapeutic doses of tetracycline excrete resistant organisms in their feces in larger numbers for longer periods and also transmit the organisms to other animals (*27*). Because large numbers of animals have longer and more constant exposure to subtherapeutic antimicrobials than to therapeutic ones, such use may have a greater impact than therapeutic use on the rate at which resistant strains of bacteria develop and persist in the environment. Antimicrobial use in animals also has other effects similar to those observed in humans. For example, previous exposure to therapeutic antimicrobials is a major risk factor in equine salmonellosis in a veterinary hospital (*28*).

In 475 outbreaks of salmonellosis reported to CDC in the 1970's, major sources of the bacteria were foods of animal origin—meats, poultry, and dairy products (*29*). In outbreaks investigated by CDC, data were obtained on the association between resistant and sensitive *Salmonella* and the implicated source (*30*). In 69% of resistant and 46% of sensitive *Salmonella* outbreaks, the most commonly implicated vehicles were foods of animal origin; only a small proportion of either sensitive or resistant *Salmonella* outbreaks were attributed to transmission from other humans. Studies of sporadic cases also suggested that only 10% of human infections are attributable to person-to-person contact (*31*), and in some instances of this type of transmission the ultimate source of the infecting organism was food of animal origin.

Salmonella strains isolated from healthy food animals show considerable antimicrobial resistance (Table 6), and the spectrum of resistance is similar to that in humans (Table 3) and to the spectrum of agents used in food animals (Table 5). Furthermore, analysis of restriction digests of plasmid DNA from *Salmonella* isolated from humans and food animals shows that they share identical strains of *Salmonella* (*32*).

Investigation of outbreaks, combining epidemiologic fieldwork with laboratory subtyping techniques, provides considerable insight into the complexity of *Salmonella* transmission. It has become clear how a single strain may cause illnesses and outbreaks in various settings. For example, two outbreaks began with animal illness on farms and progressed first to animal-to-human transmission and then to limited person-to-person transmission in hospitals. In one outbreak, a resistant *S. heidelberg* strain was traced from ill dairy calves to a farmer's pregnant daughter, who subsequently transmitted the organism to her newborn infant. The organism was then transmitted to two other infants in the hospital nursery, perhaps by direct contact with the hands of nursing personnel (*33*). In the second instance, a multiply resistant *S. newport* organism was traced from ill cattle to an ill member of a farm family, who was hospitalized and underwent colonoscopy. The organism was then transmitted to another hospital patient who was taking antimicrobials for another reason and who underwent colonoscopy after the first patient (*14*).

Table 5. Percentage of 235 farms where antimicrobials were used in low doses in feeds of healthy chickens, beef cattle, and swine, from 1978 through 1981 (*20*).

Antimicrobial drug	Farms* (%)
Tetracycline	48
Sulfa	34
Penicillin	23
Bacitracin	21
Neomycin	17
Lincomycin	14
Streptomycin	13
Flavomycin	10
Tylosin	7
Nitrofuran	3
Virginiamycin	2
Spectinomycin	1
None	11

*More than one antimicrobial is often used on an individual farm.

Table 6. Resistance in *Salmonella* (n = 199) isolated from national sample of healthy chickens, beef cattle, and swine, from 1978 through 1981 [adapted from (*35*)].

Antimicrobial drug	Resistance (%)
Sulfadiazine	61
Streptomycin	56
Tetracycline	33
Kanamycin	5
Carbenicillin	5
Ampicillin	3
Amikacin	0
Gentamicin	0
Nalidixic acid	0
Trimethoprim-sulfamethoxazole	0
None	18

The investigation of this second outbreak demonstrated the complete chain of foodborne transmission from animals to humans. Hamburger contaminated with an antimicrobial-resistant *Salmonella* was traced from well beef cattle, which had been fed subtherapeutic doses of antimicrobials, through meat processing, to supermarkets in another state where ill persons (who were part of the outbreak) had shopped. Tracing this complex chain of transmission depended on a unique plasmid profile and on computerized meat shipping records (*14*). A third investigation further emphasized food animals as a source of antimicrobial-resistant *Salmonella*. Approximately 1000 persons were infected with multiple antimicrobial–resistant *S. newport* in California in 1985 (*15*). This strain was characterized by an unusual marker—chloramphenicol resistance. A combined epidemiologic and laboratory investigation incriminated ground beef from dairy cows as the vehicle of infection. Isolates of chloramphenicol-resistant *S. newport* were obtained through the entire route of transmission—from ill persons, the hamburger they had eaten, beef from meat packers, carcasses in slaughterhouses, and cows and calves on farms where chloramphenicol had been used. This outbreak demonstrated how antimicrobial use in animals may impact on human health.

Approximately 80% of *Salmonella* isolates reported in the United States appear to be sporadic or unrelated to outbreaks. Molecular strain typing used to compare sporadic cases to a known outbreak strain suggests that some sporadic cases of salmonellosis are related to known outbreaks or represent unrecognized clusters themselves. In an investigation of a multistate increase in *S. newport* in 1981, several outbreaks caused by the same strain were associated with a precooked roast beef product. *Salmonella newport* with a single plasmid profile was isolated from the meat (*31*). When isolates from the community were examined, 45% of the sporadic cases had the same plasmid profile. These isolates had not been previously recognized as part of the outbreak. Interviews with the affected individ-

uals revealed that their illness was epidemiologically associated with eating the precooked roast beef product. Many of the so-called sporadic cases during that period had an unrecognized association with the epidemic that was identified only by plasmid profile analysis and further epidemiologic investigation. As part of the investigation, we examined a collection of *S. newport* organisms that had been isolated in this geographic area over several years. Strains with distinctive plasmid profiles sequentially appeared, predominated, and disappeared, demonstrating the clonal nature of *Salmonella* strains.

Conclusion

Well-designed prospective studies have shown that infections with antimicrobial-resistant *Salmonella* are increasing, and this increase has considerable public health implications. Data indicate that antimicrobial use by humans in the United States or in other countries does not play a major role in the emergence or persistence of these resistant *Salmonella* strains in the United States. Epidemiologic and laboratory studies have traced antimicrobial-resistant *Salmonella* to foods of animal origin. Efforts to reduce the occurrence of salmonellosis, which have been successful in only a few isolated instances, must be increased. In addition, more prudent selection and use of antimicrobials in animals as therapeutic agents and production enhancers is necessary to combat the increasing frequency of antimicrobial resistance in *Salmonella*.

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