

Salmonella: A Postmodern Pathogen¹

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ABSTRACT

The reported incidence of *Salmonella* infections in the United States has increased substantially since reporting began in 1943. These infections cause important morbidity, mortality, and economic burden in this country and are particularly severe in the infant, elderly, or immunocompromised patient. Four recent trends suggest that salmonellosis will present an increasing challenge to public health in the future. Antimicrobial resistance is present in an increasing proportion of *Salmonella* isolates. *Salmonella* bacteremia has emerged as a serious complication of human immunodeficiency virus infection. Infections caused by the egg-associated serotype *Salmonella enteritidis* are steadily increasing in incidence and geographic scope, and these infections are now the most common form of salmonellosis in some parts of the country. Finally, contamination of food produced in centralized facilities has led to extremely large and widespread outbreaks. Better understanding of the biology of specific animal reservoirs and of the microbiologic aspects of food processing is needed to control salmonellosis in the future.

The year 1988 marked the centenary of the identification of nontyphoid *Salmonella* as a human pathogen. An outbreak in Germany in 1888 affected 50 persons who consumed raw ground beef made from a moribund cow (18). All who ate the meat became ill, and one previously healthy 29-year-old man died. An organism subsequently known as *Salmonella typhimurium* was isolated from the victim's blood and spleen and from the leftover meat. The following century of the epidemiology of *Salmonella* infections can be divided into three periods. During the first period, from the late 1800s to 1949, typhoid fever caused by *Salmonella typhi* was the predominant *Salmonella* infection in humans in the United States (Fig. 1). *Salmonella choleraesuis*, identified in 1885 by Dr. Salmon, was an important pathogen of swine; *Salmonella bovismorbificans* was an important cause of severe infections in cattle; and *Salmonella pullorum* and *S. gallinarum* were recognized as major pathogens of chickens. Each of these caused a severe invasive disease in one species and had a reservoir in the same species in which they caused disease. Although foodborne outbreaks such as the one that occurred in 1888 were frequently recognized in Europe in the first half of the

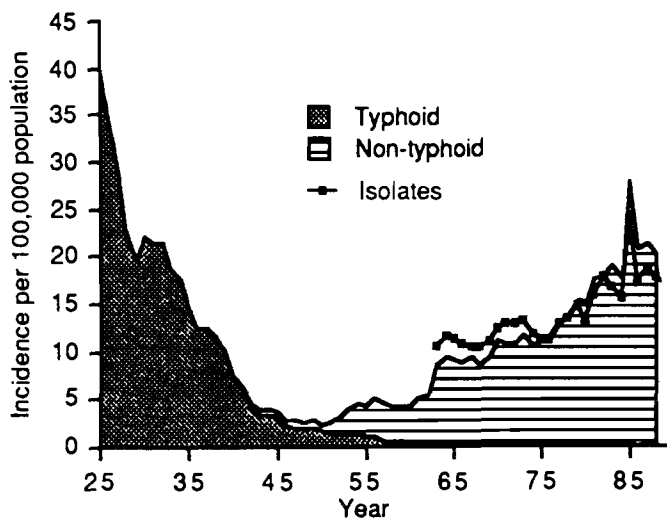


Figure 1. Reported clinical cases of typhoid fever and nontyphoid salmonellosis per 100,000 population, United States, 1930-1987 (7,33). Reported isolates of *Salmonella* per 100,000 population (line with dots), National Salmonella Surveillance System United States, 1963-1987.

20th century, the predominant cycles of transmission of *Salmonella* recognized in the United States appear to have been severe infections by organisms having a reservoir in the affected species.

In the second time period, 1950-69, these severe and species-restricted infections became relatively rare. Typhoid fever was nearly eliminated in many industrialized countries, probably due to improved sewage disposal, drinking water treatment, and other public health measures. Among animal populations, many of the most severe *Salmonella* infections came under control with improved hygiene and disease control measures on the farm. At the same time, other nontyphoid *Salmonella* species began to be identified and reported more frequently as causes of gastroenteritis in humans. The second period was marked by relatively low levels of transmission of the severe species-specific agents and a modest level of transmission of nontyphoid *Salmonella* to humans, probably from a variety of reservoirs. The typical clinical illness produced by *Salmonella* in humans changed from typhoid fever, a systemic bacteremic infection, to gastroenteritis, marked by diarrhea, fever, and abdominal pain with rare systemic

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invasion. The most challenging human salmonellosis outbreaks of that period occurred in hospitals. Nosocomial salmonellosis emerged as a postwar public health problem, particularly in hospital nurseries, where formula feeding had largely replaced breast feeding, and continued to be a challenge in the United States until comprehensive infection control measures were instituted in the 1970s.

The most recent period, since 1970, has been characterized by a steady increase in reported nontyphoid human salmonellosis. Large outbreaks traced to contaminated foods of animal origin have replaced hospital outbreaks as the major public health challenge presented by salmonellosis. Foods of animal origin are now thought to be the cause of the great majority of all *Salmonella* infections in humans. At the same time, a variety of *Salmonella* serotypes, often resistant to antimicrobial agents, has become ubiquitous among food-producing animals, though they rarely cause illness in them. If the relative rarity of *Salmonella* infections in the 1950s and 1960s was the result of modern human and veterinary preventive medicine, newly equipped with antimicrobial agents, the current epidemiologic picture of salmonellosis is a postmodern paradox: large numbers of human beings become ill after consuming food produced from apparently healthy animals that are colonized with *Salmonella*. This new epidemiologic paradigm is also true for other important and emerging foodborne pathogens, such as *Campylobacter* (with a reservoir in healthy poultry) (29), *Escherichia coli* 0157:H7 (dairy cattle) (13), and *Vibrio vulnificus* (oysters) (5). Laws and regulations pertaining to the control of salmonellosis written in the typhoid era may not reflect the current epidemiologic paradigm.

Salmonellosis has been a notifiable disease in the United States since 1943, which means that physicians are instructed to report cases to local health departments, which in turn report them to state health departments, which report the annual totals to the Centers for Disease Control (CDC), which publishes the total number of cases annually (7). Three other sources of data at the CDC describe the epidemiology of *Salmonella* in greater detail. First, the National *Salmonella* Surveillance System was established in 1963 as a collaborative effort by the Council of State and Territorial Epidemiologists, the Association of State and Territorial Public Health Laboratory Directors, CDC, the U.S. Department of Agriculture (USDA), and the Food and Drug Administration (FDA). This laboratory-based surveillance system depends on voluntary reporting by state health departments and federal agencies of *Salmonella* isolates serotyped by reference laboratories. Routine determination and reporting of serotype has been instrumental in detecting outbreaks, determining their source, and in monitoring long-term trends. It has been critical to the many advances in our understanding of the epidemiology of salmonellosis. These data have been computerized since 1967, and surveillance reports are published periodically (15).

Outbreak investigations are a second source of information. Investigations conducted by state or county health departments are voluntarily reported to CDC as part of the Foodborne Disease Outbreak Surveillance System; a much smaller number of investigations is conducted by CDC

directly in collaboration with health departments. These investigations have provided much insight into the epidemiology of salmonellosis and have led to identification of contaminated foods and development of specific control measures. Because of the success of these investigations, much of the public health approach towards *Salmonella* has been to investigate, understand and prevent outbreaks. Isolates reported through the National *Salmonella* Surveillance System and outbreaks reported through the Foodborne Disease Outbreak Surveillance System show parallel trends (Fig. 2). Both demonstrate a substantial increase from the 1970s (20,000-25,000 isolates and 30-40 outbreaks reported each year) to the late 1980s (40,000-45,000 isolates and 60-80 outbreaks reported each year).

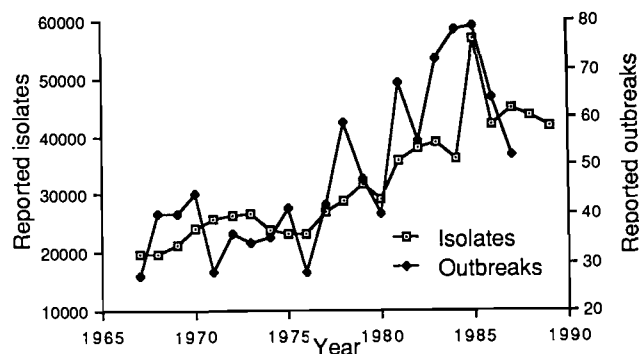


Figure 2. Reported isolates of *Salmonella* and reported foodborne outbreaks of salmonellosis, by year, United States, 1967-1987.

A third source of data is surveys in sentinel counties in which detailed epidemiological information is collected from a sample of reported cases along with the *Salmonella* isolate itself. These sentinel county investigations, central to our understanding of the epidemiology of antibiotic resistance in *Salmonella*, were first done in 1979-80 and have been repeated in 1984-85 and 1989-90 (20,24). The sentinel county data can be used to estimate the health impact of reported cases of salmonellosis. The 1979-80 survey indicated that 45% of those persons from whom *Salmonella* isolates had been reported were hospitalized for their illness and 1.3% of them died in association with that infection. Very similar proportions were found in the 1984-85 study. Using these proportions, we can estimate that in 1988 the 43,785 reported isolates represent a minimum of 19,000 hospitalizations and 500 deaths. Cases of *Salmonella* infection may not be reported to CDC for a number of reasons. They may not be ill enough to visit a physician, they may visit a physician but a culture may not be obtained, or the culture may not yield *Salmonella*. *Salmonella* may be isolated but not reported to the county health department nor referred to state health laboratory for serotyping. The number of infections that go unreported every year has been estimated by various means to be from 20-fold to nearly 100-fold greater than the number of reported infections (8). This means the actual number of infections in 1988 is between 840,000 and 4,000,000. The proportion of unreported cases which are severe illness is unknown, but a conservative estimate of the total number of hospitalizations and deaths in the U.S. due to

salmonellosis would include 500 additional deaths and 19,000 hospitalizations attributable to the much larger number of unreported cases in addition to those associated with reported cases.

The patient-related cost of salmonellosis has been assessed in the outbreak setting (9). In 1988 dollars, this cost is \$1,560 per reported case and \$250 per person for an illness that was not severe enough to bring someone to medical attention and therefore not likely to have been reported. By applying the cost per reported case to the 43,785 isolates reported in 1988, and the mild illness cost to the range of estimates of unreported cases, we can estimate the total patient-related cost of salmonellosis in 1988 to be between \$275 million and \$1.1 billion.

Outbreak investigations have been particularly useful in identifying the sources of infection. Between 1973 and 1987, 790 outbreaks of foodborne salmonellosis were reported to CDC via the foodborne disease outbreak surveillance system (4). A specific food vehicle was identified in 59% of these outbreaks. The great majority of identified food vehicles in the period 1983-1987 were foods of animal origin (Table 1). Recent changes in the epidemiology of foodborne disease in the United States reflect changes in food production and in the eating behavior of the population. The proportion of outbreaks that are associated with food prepared in the home has declined substantially from 36% in the early 1970s to approximately 18% in the late 80s, while the proportion traced to food prepared in a restaurant or other commercial establishment increased from 25% to nearly 50% (Fig. 3). This may reflect an increasing proportion of all meals that are eaten outside of the home, a decline in public health resources available to investigate outbreaks in the home (which are typically smaller than restaurant-associated outbreaks), or even an improvement in foodhandling in the home. Only a small proportion of isolates reported to the national *Salmonella* surveillance system is related to a recognized outbreak; most isolates are sporadic cases. The serotype distribution of outbreaks is similar to the distribution of all reported isolates (Table 2), suggesting that sporadic cases and outbreaks have the same sources. However, it is probable that the proportion of outbreaks caused by a specific food vehicle is not the same as the proportion of sporadic cases caused by that vehicle, as some contaminated food vehicles (such as pasteurized milk or precooked roast beef) may be more likely to cause large outbreaks, while others (such as chicken) may be more likely to cause very small outbreaks or sporadic cases.

New trends for the 1990s

In the 1990s, four recent trends in *Salmonella* infections are likely to present important public health challenges: a) increasing antimicrobial resistance, b) the intersection of salmonellosis and the acquired immunodeficiency syndrome (AIDS) epidemic, c) egg-associated *Salmonella enteritidis* infections, and d) large and dispersed outbreaks.

Increasing antimicrobial resistance

Between the two sentinel county studies of 1979 and 1984, resistance in *Salmonella* isolates to one or more agent

TABLE 1. Foodborne salmonellosis outbreaks and associated cases, distribution by food vehicle for outbreaks with known vehicle, United States, 1983-1987.

Food vehicle	Cases		Percentage of Outbreaks	
	Number	Percent	Number	Percent
Chicken	1800	(16.8)	15	(8.8)
Beef	938	(8.8)	19	(11.2)
Turkey	763	(7.1)	7	(4.1)
Egg*	412	(3.8)	9	(5.3)
Fruits/ Vegetables	234	(2.2)	5	(2.9)
Pork	144	(1.3)	5	(2.9)
Seafood	60	(0.6)	3	(1.8)
Dairy	47**	(0.4)	6	(3.5)
Other	6309	(58.9)	101	(59.4)
(including multiple vehicles)				
Total	10707	(100)	170	(100)

* Thirteen outbreaks and 656 cases associated with egg-containing foods are listed under "other", including french toast, caesar salad, and montecristo sandwiches.

** Excluding 16,661 cases associated with one milk-associated outbreak.

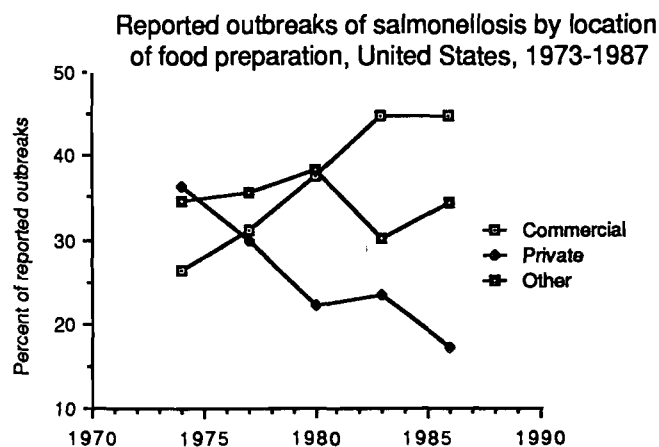


Figure 3. Distribution of reported foodborne salmonellosis outbreaks by location of food preparation, 3-year periods, 1973-1987.

increased from 16 to 24%, resistance to two or more agents increased from 12 to 15% and resistance to tetracycline, chloramphenicol, gentamicin, nalidixic acid, and trimethoprim all increased (Table 3) (10,20,24). This change in resistance did not occur equally in all serotypes. In isolates of *Salmonella heidelberg*, a poultry-associated serotype, resistance actually decreased from 67% in 1979 to 35% in 1984, while resistance among *S. typhimurium*, which is often cattle-associated, increased from 14% to 26%. It is likely that these differences reflect changes in the use of antimicrobial agents in the various food animal reservoirs.

Antimicrobial resistance in *Salmonella* is of public health importance for a number of reasons. Although most *Salmonella* infections are limited to the gastrointestinal tract and do not require antimicrobial therapy, occasionally infections spread to the blood stream, and appropriate

TABLE 2. Distribution by serotype of *Salmonella* isolates (National Salmonella Surveillance System) and of foodborne salmonellosis outbreaks (National foodborne outbreak surveillance system), 1973-1987.

Serotype	Percentage of reported 1973-1987	
	Isolates	Outbreaks
<i>typhimurium</i> *	34.7	20.5
<i>enteritidis</i>	8.9	20.5
<i>heidelberg</i>	8.4	7.5
<i>newport</i>	5.9	3.7
<i>infantis</i>	3.7	3.6
<i>agona</i>	3.4	2.5
<i>saint paul</i>	2.1	2.1
<i>montevideo</i>	1.8	2.1
<i>typhi</i>	1.7	1.7
<i>oranienburg</i>	1.5	1.5
<i>muenchen</i>	1.3	0.7
<i>javiana</i>	1.3	0.7
<i>thompson</i>	1.2	1.7
<i>derby</i>	1.2	0.5
<i>hadar</i>	1.2	1.8
<i>blockley</i>	1.1	1.8

*Including *copenhagen* variant.

TABLE 3. Rates of antimicrobial resistance for *Salmonella* isolated in 1979-1980 and 1984-1985, by antimicrobial agent.

Antimicrobial	Isolates resistant, No. (%)				P
	1979-1980 (n=511)		1984-1985 (n=485)		
Ampicillin	42	(8)	44	(9)	NS*
Cephalexin	7	(1.4)	4	(0.8)	NS
Chloramphenicol	4	(0.8)	10	(2)	NS
Colistin	0	(0)	2	(0.4)	NS
Gentamicin	0	(0)	3	(0.6)	NS
Kanamycin	18	(3.5)	17	(3.5)	NS
Nalidixic acid	0	(0)	6	(1.2)	.05
Nitrofurantoin	6	(1)	18	(3.7)	NS+
Streptomycin	63	(12)	59	(12.2)	NS
Sulfamethoxazole	41	(8)	34	(7.0)	NS
Tetracycline	44	(8.6)	64	(13)	.05
Sulfamethoxazole and trimethoprim	1	(0.2)	3	(0.6)	NS

*NS indicates not significant.

+ Approaches statistical significance at the P=.05 level (p=.055).

antimicrobial therapy can be lifesaving. Antimicrobial resistance to the agents of choice compromises such therapy. Of greater import is the observation that treatment with antimicrobial agents can actually promote *Salmonella* infections in both humans and animals, particularly if the infecting strain is resistant to the agents being used (8,16,20,22,26,28). The complex interplay between the ecology of *Salmonella* and competing microorganisms in the intestinal tract confers a protective "colonization resistance" to the untreated host (34). Antimicrobials that kill competing microorganisms reduce the competition which under ordinary conditions would help prevent salmonellosis after exposure to small inocula of *Salmonella*. This permits a lower dose of *Salmonella* to produce illness in the pre-treated individual; it also means that silent colonization

with a resistant organism can be converted to overt infection by concurrent antimicrobial use. In animals, the likely net effect of increased resistance in *Salmonella* will be more widespread dissemination of this organism in animal populations that are heavily exposed to antimicrobial agents. In humans, the result is likely to be more and bigger outbreaks, and more sporadic cases. In recent years we have traced multiply-resistant strains of *Salmonella* back through the food chain to the source farms and have observed the spread of multiply-resistant *Salmonella* through the food animal reservoir. For instance, multiply-resistant *Salmonella newport*, which emerged as an epidemic problem in the United States in the western states in 1985, has since spread throughout the western bovine reservoir as a result of the transfer of calves from dairy to beef operations (21,28). The emergence of resistance to gentamicin and trimethoprim may increase the challenge to the public health in the 1990s. This problem is not limited to the use of antimicrobials agents in food animals. Small pet turtles were a major source of salmonellosis in the United States until their distribution was halted in 1975 (31). Since then, attempts to eliminate *Salmonella* in turtles via gentamicin treatment have resulted in resistant strains of *Salmonella* in exported turtles (11).

Salmonellosis and the AIDS epidemic

In the person infected with the human immunodeficiency virus (HIV), salmonellosis can be a severe invasive disease, and recurrence of bacteremic infections after appropriate therapy is common. Recurrent *Salmonella* bacteremia has been included as an indicator disease of AIDS since 1987. Among AIDS patients in San Francisco, the annual incidence of salmonellosis is 384 per 100 thousand, 20 times the background rate (6). Widespread use of prophylactic antimicrobials in this population may further increase their risk of salmonellosis. Bacteremia due to *S. typhimurium*, *Salmonella dublin*, and *S. enteritidis* appears to be particularly common in AIDS patients; this may be related to the invasiveness of those serotypes and to their frequent occurrence in raw milk, raw eggs, or raw beef which may be consumed by patients in the mistaken belief that such foods could bolster their defenses (19). As the number of HIV-infected persons increases, greater attention to the prevention of salmonellosis infections among these patients and other immunosuppressed patients at risk of severe illness will be needed. Particular attention to food safety and sanitation is needed to reduce the risk of salmonellosis in this population (3,14).

Egg-associated Salmonella enteritidis

A third major challenge posed by *Salmonella* to the public health has been the recent global increase of one serotype, *S. enteritidis* (27). This serotype represented only 5% of all isolates in the United States in 1970s but increased to 20% in 1989. This increase was particularly prominent in the New England region beginning in 1979; the mid-Atlantic region was first affected in 1984 (Fig. 4). In 1989, *S. enteritidis* was more frequently reported in those regions than any other serotype. In some states it represented more than one half of all *Salmonella* reported. Although this

epidemic was initially confined to the northeastern part of the United States, *S. enteritidis* has emerged as a frequent cause of outbreaks outside of the Northeast. In 1988, 19 of 77 reported outbreaks occurred outside the northeastern United States. As of mid-1990, 241 outbreaks of *S. enteritidis* infections were reported from states through stimulated surveillance in the United States from 1985 to 1989, involving 8,553 cases with 44 deaths (30). Most deaths occurred in outbreaks in a hospital or nursing home. The case-fatality rate was 3.2% for outbreaks in hospitals and nursing homes, compared to 0.05% in other settings.

Investigations of outbreaks of *S. enteritidis* infections have shown repeatedly that the most common source is the grade A shell egg, usually consumed undercooked or raw. The safest control measure is to use pasteurized egg in any recipe calling for pooled eggs. Because of high case-fatality rates in institutional outbreaks, this should be standard practice in those settings. Because the epidemic appears to be spreading to the entire country, it is also time to review foodhandling practices in hospitals and nursing homes and other institutions with high-risk populations in all parts of the country to prevent exposure to raw eggs, to minimize errors in handling bulk pooled eggs, and to eliminate cross-contamination of other foods with raw eggs in blenders or other food processing equipment. Control measures are also needed to prevent restaurant-associated outbreaks, including attention to good food preparation and service, storing and transporting eggs under refrigeration, and using pasteurized egg in recipes calling for pooled egg. In 1990, the FDA defined shell eggs as a potentially hazardous food, requiring refrigeration during storage and particular care during preparation (1).

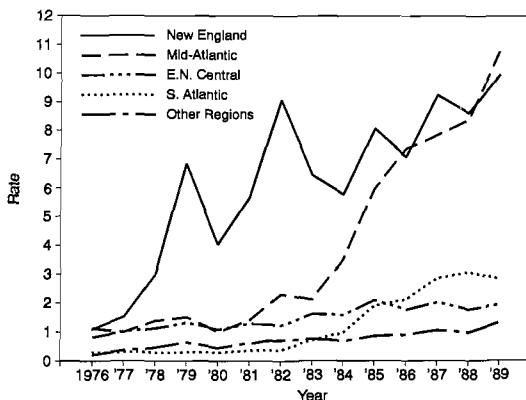


Figure 4. Reported isolation rates of *Salmonella enteritidis* per 100,000 population by region, 1976-1989.

Eggs are contaminated internally with *S. enteritidis*, probably as a result of infection in the hen's ovaries and oviducts (12,17). Efforts on the part of the USDA to control the *S. enteritidis* epidemic by identifying and eliminating infected flocks began in earnest in 1990 (2). If the number of outbreaks and infections caused by *S. enteritidis* continues to increase, the use of pasteurized egg is likely to become more common in the 1990s. As *S. enteritidis* infections are increasing rapidly in many industrialized countries with varied approaches to safe egg-handling, a multinational or global approach to this problem is likely to emerge (25).

Large and dispersed outbreaks

A fourth challenge to the public health by salmonellosis has been its ability to cause enormous widespread and subtle outbreaks, as a result of changes in the structure of the nation's food supply. The trend towards centralized large-scale food processing with wide distribution means that when contamination occurs, it can rapidly affect large numbers of people over a large area. For example, in March 1984, an outbreak of salmonellosis affected passengers who had flown first class on a large European airline (32). Investigation of that outbreak indicated that for 3 days most international flights of that airline leaving one airport to all non-European locations served contaminated food. The number of exposed passengers was approximately 23,500, and the investigators concluded that more than 3,000 passengers were likely to have been affected by this global outbreak. An even larger outbreak occurred in the midwestern United States in 1985, after two brands of pasteurized milk produced at the same dairy were contaminated (26). A multiply-resistant strain of *S. typhimurium* was isolated from over 17,000 persons in the course of that outbreak; the estimated number of cases exceeded 180,000. In 1990, a winter outbreak of *Salmonella chester* infections was traced to cantaloupe imported from Central America (23). This nationwide outbreak was only detected because of routine laboratory-based surveillance with serotyping. Because of the large number of persons served by a centralized food producer, an outbreak with a low attack rate can still be large. This means that even low-level or intermittent contamination of mass-produced foods is of concern. Sophisticated national surveillance and investigation techniques are necessary to detect, investigate, and intervene in such outbreaks.

In addition to the patient-related costs, the economic impact of such outbreaks can be considerable, including plant closures, job losses, legal expenses, and service disruption. These outbreaks suggest that in the future, investigations are more likely to cross state and national boundaries, and to require collaboration of public health authorities in many jurisdictions; they illustrate the need for a global approach to food safety.

Salmonellosis has been increasing steadily as a public health problem over the last 40 years in the United States. Salmonellosis plays a role in at least 1,000 deaths a year in this country and causes up to a billion dollars in patient-related costs annually. In addition to the simple magnitude of the problem, salmonellosis is bringing new challenges to the protection of the public health in the form of increasing antimicrobial resistance, the growing problem of salmonellosis in the immunocompromised population, the growing importance of new food vehicles such as eggs, and in the potential for enormous and widely dispersed outbreaks related to the increasingly centralized production of foods. Consumer education and careful attention to food hygiene have always been important measures for preventing outbreaks of salmonellosis. The new challenges mean that the critical control points of the future also include understanding the biology of the animal reservoirs and the complex food processing which brings *Salmonella* from the colonized animal to our tables.

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