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EMERGENCE OF MULTIDRUG-RESISTANT *SALMONELLA ENTERICA* SEROTYPE TYPHIMURIUM DT104 INFECTIONS IN THE UNITED STATES

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ABSTRACT

Background Strains of salmonella that are resistant to antimicrobial agents have become a worldwide health problem. A distinct strain of *Salmonella enterica* serotype typhimurium, known as definitive type 104 (DT104), is resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline and has become a major cause of illness in humans and animals in Europe, especially the United Kingdom.

Methods To characterize typhimurium DT104 infections in the United States, we analyzed data collected by local and state health departments and public health laboratories between 1979 and 1996 in national surveys of the antimicrobial-drug resistance of salmonella. Selected typhimurium isolates with the five-drug pattern of resistance were phage typed.

Results The prevalence of typhimurium isolates with the five-drug pattern of resistance increased from 0.6 percent in 1979–1980 to 34 percent in 1996. In 1994–1995, such isolates were identified in samples from 36 of the 46 surveillance sites (78 percent). Thirty-nine of 43 typhimurium isolates with the five-drug pattern of resistance identified in 1994–1995 and 1996 were phage type DT104 or a closely related phage type.

Conclusions Multidrug-resistant typhimurium DT104 has become a widespread pathogen in the United States. More prudent use of antimicrobial agents in farm animals and more effective disease prevention on farms are necessary to reduce the dissemination of multidrug-resistant typhimurium DT104 and to slow the emergence of resistance to additional agents in this and other strains of salmonella. (N Engl J Med 1998;338:1333-8.)

EACH year in the United States, there are an estimated 800,000 to 4 million salmonella infections, and approximately 500 are fatal.[1] Approximately 40,000 of these infections are confirmed by culture; isolates are serotyped at state public health laboratories and reported to the Centers for Disease Control and Prevention (CDC).[2] Although most salmonella infections are self-limited, bacteremia occurs in 3 to 10 percent of reported, culture-confirmed cases, particularly in cases involving patients at the extremes of age or those who are immunocompromised.[3-7] For these patients, appropriate antimicrobial-drug therapy can be lifesaving.[1,3]

In recent years, testing of salmonella isolates in the United States[8,9] and abroad[10,11] has shown that an increasing proportion of isolates are resistant to several antimicrobial agents. In the United Kingdom, the marked increase in the incidence of a distinct multidrug-resistant strain of *Salmonella enterica* serotype typhimurium (hereafter referred to as typhimurium), characterized as definitive type 104 (DT104), that is resistant to five agents — ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline — has been of particular concern. A recent report from the United Kingdom suggests that infections caused by this five-drug–resistant typhimurium might be associated with greater morbidity and mortality than other salmonella infections.[12] Of further concern, 14 percent of such isolates that were identified in the United Kingdom in

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1996 were also resistant to ciprofloxacin, and 24 percent were resistant to trimethoprim; in each case the level of resistance was 0 percent in 1991.[13] We report on the widespread emergence of typhimurium DT104 in the United States.

METHODS

In the United States, state public health laboratories report culture-confirmed cases of salmonella to the CDC by means of the Public Health Laboratory Information System, a nationwide electronic reporting system. Information on the antimicrobial-drug resistance of salmonella is available from several sources: the National Antimicrobial Resistance Monitoring System established in 1996, the 1995 National Salmonella Antimicrobial Resistance Study, and surveys of antimicrobial-drug resistance that were conducted in sentinel counties in 1979–1980, 1984–1985, 1989–1990, and 1994–1995. We examined data collected by these systems and surveys to identify reports of typhimurium DT104.

Public Health Laboratory Information System

As a part of routine public health surveillance, most clinical laboratories in the United States routinely forward salmonella isolates to state or territorial public health laboratories for serotyping, and state public health laboratories report culture-confirmed salmonella infections, usually after serotyping, to epidemiologists in their state and to the CDC.[2,14]

National Antimicrobial Resistance Monitoring System

Salmonella isolates are not usually forwarded to the CDC; the exceptions are atypical or rare isolates sent for confirmatory serotyping and those included in special surveys of antimicrobial-drug resistance. One such survey, the recently established National Antimicrobial Resistance Monitoring System, was begun in January 1996 in collaboration with 12 state health departments (California, Colorado, Connecticut, Florida, Georgia, Kansas, Massachusetts, Minnesota, New Jersey, Oregon, Washington, and West Virginia) and 2 local health departments (Los Angeles County and New York City) to monitor prospectively the patterns of antimicrobial-drug resistance of human salmonella isolates received at participating public health laboratories.[15] Participants forward every 10th salmonella isolate to the CDC for testing for susceptibility to antimicrobial agents. Isolates are tested with a Sensititre system (Accumed International, Westlake, Ohio), which determines the minimal inhibitory concentration for 15 antimicrobial agents: ampicillin, amoxicillin–clavulanic acid, apramycin, ceftiofur, ceftriaxone, cephalothin, chloramphenicol, ciprofloxacin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfamethoxazole, tetracycline, and trimethoprim–sulfamethoxazole. After testing, a random sample of typhimurium isolates that are resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline are phage typed at the CDC,[16] and strains are classified as DT104, DT104 complex (other closely related definitive types or closely related untypable strains), or unrelated to DT104.

National Salmonella Antimicrobial Resistance Study

The second source of data on the resistance of salmonella to antimicrobial agents was the National Salmonella Antimicrobial Resistance Study conducted between July 1, 1994, and June 30, 1995. All state and territorial public health laboratories were asked to forward every 10th salmonella isolate to the CDC for antimicrobial-drug–susceptibility testing. Isolates were tested by the disk–diffusion method for resistance to 12 antimicrobial agents: ampicillin, amoxicillin–clavulanic acid, ceftriaxone, chloramphenicol, ciprofloxacin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfisoxazole, tetracycline, and trimethoprim–sulfamethoxazole.[17] A random sample of typhimurium isolates with resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline was sent to the Danish Veterinary Laboratory (Copenhagen, Denmark) and the World Health Organization International Center for Enteric Phage Typing (Collindale, United Kingdom) for phage typing[16]; strains were classified as DT104, DT104 complex, or unrelated to DT104.

Periodic Surveys of Antimicrobial-Drug Resistance in Sentinel Counties

The third source of data was a series of surveys conducted in selected counties in the United States. These surveys were conducted every five years in a volunteer panel of counties, initially chosen in 1979.[18] Trends in antimicrobial-drug resistance over time were examined with the use of data from the 23 counties that participated in each of the surveys, conducted over one-year periods from July 1 to June 30 in 1979–1980,[18] 1984–1985,[9] 1989–1990,[8] and 1994–1995. The participating counties were in California, Massachusetts, New Jersey, New Mexico, New York, North Carolina, Ohio, Pennsylvania, Rhode Island, Texas, and Vermont. These health departments were asked to send all salmonella isolates collected in their counties during the survey periods to the CDC, except those associated with an outbreak. In each of the surveys, the isolates were tested with the disk-diffusion method for resistance to nine antimicrobial agents: ampicillin, chloramphenicol, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfisoxazole, tetracycline, and trimethoprim–sulfamethoxazole.[17] After testing, typhimurium isolates with the five-drug pattern of resistance from the 1979–1980, 1984–1985, and 1989–1990 surveys were phage typed at the CDC[16]; strains were classified as DT104, DT104 complex, or unrelated to DT104.

RESULTS

Public Health Laboratory Information System

In 1996, a total of 39,032 culture-confirmed salmonella infections were reported to the CDC by state public health laboratories. Of the 38,218 isolates that were serotyped, 9566 (25 percent) were classified as *S. enterica* serotype enteritidis, the most commonly identified serotype, and 9501 (25 percent) as typhimurium. Although the percentage of serotyped salmonella isolates that are identified as *S. enterica* serotype enteritidis increased from 16 percent in 1987 to 25 percent in 1996, reflecting a decade-long problem associated with contamination of eggs, the percentage of typhimurium isolates identified during that period increased only slightly, from 24 percent to 25 percent.[19]

National Antimicrobial Resistance Monitoring System

In 1996, 1326 salmonella isolates were received at the CDC through the National Antimicrobial Resistance Monitoring System, and 1239 (93 percent) were serotyped (Table 1). Three hundred six (25 percent) of the serotyped isolates were classified as typhimurium; 103 of the 306 (34 percent) were resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. Of 13 isolates with the five-drug pattern of resistance that were phage typed at the CDC, 9 (69 percent) were identified as DT104, 2 as DT104 complex, and 2 as having unrelated phage types. The five-drug pattern of resistance was identified in isolates from 12 of 13 sites that submitted typhimurium isolates; more than 50 percent of the typhimurium isolates from California

TABLE 1. CHARACTERISTICS OF TYPHIMURIUM ISOLATES REPORTED IN THREE SURVEYS OF ANTIMICROBIAL-DRUG RESISTANCE IN SALMONELLA IN THE UNITED STATES, 1979 TO 1996.*

CHARACTERISTIC	NARMS, 1996		NSARS, 1994–1995		SENTINEL COUNTIES, 1994–1995		SENTINEL COUNTIES, 1989–1990		SENTINEL COUNTIES, 1984–1985		SENTINEL COUNTIES, 1979–1980	
	5-DRUG RESISTANCE (N=103)	RESISTANCE TO OTHER OR NO DRUGS (N=203)	5-DRUG RESISTANCE (N=275)	RESISTANCE TO OTHER OR NO DRUGS (N=701)	5-DRUG RESISTANCE (N=31)	RESISTANCE TO OTHER OR NO DRUGS (N=135)	5-DRUG RESISTANCE (N=8)	RESISTANCE TO OTHER OR NO DRUGS (N=100)	5-DRUG RESISTANCE (N=7)	RESISTANCE TO OTHER OR NO DRUGS (N=128)	5-DRUG RESISTANCE (N=1)	RESISTANCE TO OTHER OR NO DRUGS (N=161)
No. of salmonella isolates serotyped	1239		3903		655		468		328		369	
Resistance to chloramphenicol — no. (%)	103 (100)	19 (9)	275 (100)	10 (1)	31 (100)	2 (1)	8 (100)	1 (1)	7 (100)	0	1 (100)	0
Resistance to nalidixic acid — no. (%)	0	1 (0.5)	2 (0.7)	3 (0.4)	0	0	0	0	0	1 (1)	0	0
Disk-diffusion zone — mm												
Median			22	22	23	22	21	21	21	20	21	19
Range			6–27	6–28	18–26	18–30	19–22	18–24	20–24	6–24		14–22
MIC — μg/ml†												
Median	4	4										
Range	≤4 to 8	2 to >64										

*NARMS denotes the National Antimicrobial Resistance Monitoring System; NSARS, the National Salmonella Antimicrobial Resistance Study; and 5-drug resistance, resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline.

†The minimal inhibitory concentration (MIC) was determined as a measure of the susceptibility of the isolates to antimicrobial agents.

and Connecticut had this pattern. Among the five antimicrobial drugs, the most specific marker for this pattern of resistance was resistance to chloramphenicol: 103 of the 122 chloramphenicol-resistant typhimurium isolates (84 percent) were also resistant to ampicillin, streptomycin, sulfonamides, and tetracycline. None of the 306 typhimurium isolates were resistant to ciprofloxacin. One isolate was resistant to nalidixic acid, but it did not have the five-drug pattern of resistance.

National Salmonella Antimicrobial Resistance Study

Patterns of resistance to antimicrobial agents were also determined for 4008 salmonella isolates received from 51 states or territories from July 1, 1994, through June 30, 1995, through the National Salmonella Antimicrobial Resistance Study, and 3903 (97 percent) were serotyped (Table 1). Of these 3903 isolates, 976 (25 percent) were identified as typhimurium, 275 (28 percent) of which were resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. Isolates resistant to these five drugs were identified at 36 of the 46 sites (78 percent) that submitted typhimurium isolates, with the highest proportional prevalence in the western United States. The states in which more than 40 percent of typhimurium isolates had this pattern of resistance were California, Kentucky, Nevada, Oregon, Utah, and Washington. Thirty of the 275 isolates with the five-drug pattern of resistance that were submitted to the CDC were phage typed: 25 (83 percent) were identified as DT104, 3 as DT104 complex, and 2 as unrelated definitive types.

In this series of isolates, resistance to chloramphenicol was again the most specific marker for the five-drug pattern of resistance: 275 of the 285 chloramphenicol-resistant isolates (96 percent) had this pattern of resistance. None of the 701 typhimurium isolates were resistant to ciprofloxacin. Two of the 275 isolates with the five-drug pattern of resistance (0.7 percent) were also resistant to nalidixic acid, as compared with 3 of the 701 isolates (0.4 percent) with other patterns of resistance or no resistance; the median diameters and distributions of the disk-diffusion zone for nalidixic acid were similar in the two groups.

Periodic Surveys of Antimicrobial-Drug Resistance in Sentinel Counties

The periodic surveys conducted in the 23 selected counties further demonstrated the emergence of a pattern of resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline among typhimurium isolates in the United States. The prev-

alence of this pattern was 0.6 percent (1 of 162 isolates) in 1979–1980, 5 percent (7 of 135) in 1984–1985, 7 percent (8 of 108) in 1989–1990, and 19 percent (31 of 166) in 1994–1995 (Fig. 1). Among the 16 such isolates identified between 1979 and 1990, 1 (14 percent) in 1984–1985 and 3 (38 percent) in 1989–1990 were typed as DT104 or DT104 complex.

DISCUSSION

In the past five years in the United States there has been widespread emergence of a strain of typhimurium that is resistant to five major antibiotics: ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. Although the number of cases of typhimurium infection reported to the CDC by means of the Public Health Laboratory Information System has remained relatively constant over the past 15 years (excluding a large outbreak in 1985), the proportion of isolates with the five-drug pattern of resistance has increased from less than 1 percent in 1979–1980 to 34 percent in 1996. The great majority of these isolates are probably DT104; since 1995, 91 percent of such isolates that were phage typed were identified as DT104 or as closely related phage types included in the DT104 complex. Using data from these surveys, we estimate that of the 40,000 salmonella isolates reported annually, 3400 are typhimurium with the five-drug pattern of resistance. Since previous studies have shown that the number of reported cases of salmonella infection represents only 1 to 5 percent of the total number of cases,[20] we estimate that between 68,000 and 340,000 cases of infection with typhimurium with the five-drug pattern of resistance, most of which are probably DT104, occur annually in the United States.

The sources of typhimurium DT104 with the five-drug pattern of resistance remain to be determined. As early as 1985 and coincident with its appearance in the United Kingdom, five-drug–resistant typhimurium DT104 emerged in the United States, particularly in western states. In contrast to the emergence of *S. enterica* serotype enteritidis, which was heralded by a dramatic increase in the number of related foodborne outbreaks,[21] few outbreaks of typhimurium DT104 have been recognized in the United States since the first in 1996.[22] In the United Kingdom, DT104 now appears to be widely distributed in food animals, particularly cattle, and investigations have associated infections in humans with eating pork sausages, chicken, and meat paste and with contact with sick animals.[12,23] Investigations in the United States have found associations between typhimurium DT104 infections in humans and the consumption of unpasteurized dairy products and direct contact with livestock.[24-26]

The emergence of antimicrobial-drug resistance in salmonella isolates is associated with the therapeutic and nontherapeutic use of antimicrobial agents in food animals.[27-29] In the face of the rapid emergence of DT104 and other resistant strains of salmonella, in 1997 a World Health Organization group of experts reaffirmed recommendations to minimize the further emergence of resistance to antimicrobial agents by, among other things, promoting the prudent use of antimicrobial agents in food animals and ending the use as growth-promoting agents in food animals of agents used in human medicine, such as penicillin and tetracycline, to which five-drug–resistant typhimurium DT104 is resistant.[30] Although 14 percent of the five-drug–resistant typhimurium DT104 isolates in the United Kingdom in 1996 were also resistant to ciprofloxacin,[13] we did not identify any ciprofloxacin-resistant DT104 isolates in the United States. This difference may be related to the fact that veterinary use of fluoroquinolones, approved in the United States in late 1995, is allowed only in poultry, and typhimurium DT104 might not yet be present in poultry in the United States.

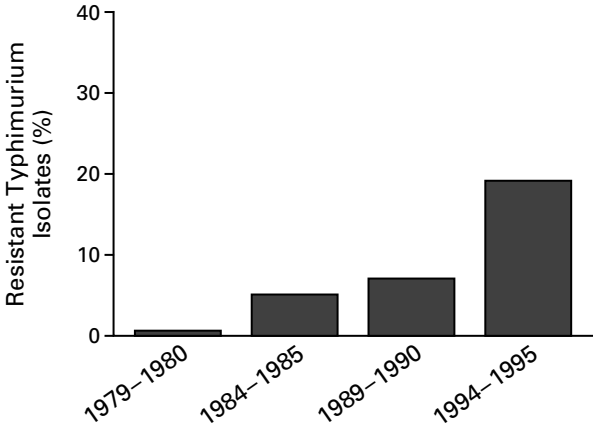

Figure 1. Prevalence of Resistance to Ampicillin, Chloramphenicol, Streptomycin, Sulfonamides, and Tetracycline among Typhimurium Isolates Identified by Surveys of Antimicrobial-Drug Resistance in Sentinel Counties.

Each survey was conducted from July 1 to June 30.

This study has some limitations. Data in the National Antimicrobial Resistance Monitoring System and the periodic surveys of antimicrobial-drug resistance were collected from populations that may not be geographically representative. Since these data were not, however, collected specifically for the study of typhimurium and since the isolates forwarded to the CDC were randomly selected, any major bias is unlikely from this approach. Also, the appropriateness of including multiple phage lysis patterns as a part of a larger DT104 complex and the epidemiologic importance of the DT104 complex are not entirely clear.

Since data on clinical illness were not collected in

the antimicrobial surveys, there remains much to be learned about the spectrum of illness caused by typhimurium DT104. As with most salmonella infections, treatment of these infections depends on the severity of illness. Antimicrobial-drug therapy is usually not essential in cases of uncomplicated salmonella gastroenteritis; a fluoroquinolone, such as ciprofloxacin, or an extended-spectrum cephalosporin, such as ceftriaxone, remains the recommended treatment for invasive typhimurium infections with the five-drug pattern of resistance.[30]

Typhimurium infections are common in the United States; it is the second most commonly identified salmonella serotype and accounted for 25 percent of culture-confirmed, serotyped cases of salmonella in 1996. Because typhimurium is common and few laboratories routinely subtype isolates, it is difficult to detect increases in specific strains. Continued and specific surveillance, including a uniform method of subtyping isolates, is necessary to identify the extent to which DT104 might be contributing to the incidence of typhimurium infection in the United States. Currently used methods of subtyping typhimurium isolates include phage typing, pulsed-field gel electrophoresis, and testing for susceptibility to antimicrobial agents; no one method, however, is capable of identifying five-drug–resistant typhimurium DT104. Phage typing, which requires maintenance of phage stocks and careful quality control, is available in only a few public health laboratories in the world and provides no information about the antimicrobial-drug resistance of the organism. The most common five-drug–resistant DT104 strain in the United States can be identified on the basis of its unique pattern on pulsed-field gel electrophoresis, but other patterns have been reported, and the various patterns identified in different laboratories cannot be compared unless the technique has been carefully standardized (Barrett T, CDC: personal communication). Testing for susceptibility to antimicrobial agents, particularly screening for resistance to chloramphenicol, appears to be a good screening procedure for identifying isolates with the five-drug pattern of resistance, but it is not routinely performed and may not always be done according to the approved methods of the National Committee for Clinical Laboratory Standards.

Further epidemiologic studies are essential to devise a means of preventing the transmission of five-drug–resistant typhimurium DT104, a rapidly emerging pathogen in the United States. Until standardized laboratory procedures have been developed, state and local health departments and other interested persons can use resistance to chloramphenicol as a highly specific marker for DT104 in order to prioritize the investigation of clusters of typhimurium infections. The sources of typhimurium with a five-drug pattern of resistance and the risk factors for infection with the organism must be identified, and the association between the use of antimicrobial agents in food animals and the incidence and continued emergence of these infections must be addressed. Prudent use of antimicrobial agents in farm animals and more effective disease prevention on farms are necessary to reduce the dissemination of five-drug–resistant typhimurium DT104 and to slow the evolution of resistance to additional agents in this and other strains of salmonella.

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