ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2011, p. 1148–1154 Vol. 55, No. 3
0066-4804/11/$12.00 doi:10.1128/AAC.01333-10

Antimicrobial Resistance among Invasive Nontyphoidal *Salmonella enterica* Isolates in the United States: National Antimicrobial Resistance Monitoring System, 1996 to 2007[▽]

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Received 29 September 2010/Returned for modification 29 November 2010/Accepted 25 December 2010

Nontyphoidal salmonellae (NTS) are important causes of community-acquired bloodstream infection. We describe patterns of antimicrobial resistance among invasive NTS in the United States. We compared bloodstream NTS isolates with those from stool submitted to the National Antimicrobial Resistance Monitoring System (NARMS) from 1996 to 2007. We describe antimicrobial resistance among invasive strains by serogroup and serotype. Of the 19,302 NTS isolates, 17,804 (92.2%) were from stool or blood. Of these, 1,050 (5.9%) were bloodstream isolates. The median ages (ranges) of patients with and without bacteremia were 36 (<1 to 97) years and 20 (<1 to 105) years, respectively ($P < 0.001$). Males (odds ratio [OR], 1.21; 95% confidence interval [CI], 1.06 to 1.38) and those ≥65 years of age were at greater risk for invasive disease. *Salmonella enterica* serotypes Enteritidis, Typhimurium, and Heidelberg were the most common serotypes isolated from blood; *S. enterica* serotypes Dublin, Sandiego, and Schwarzengrund were associated with the greatest risk for bloodstream isolation. Of invasive isolates, 208 (19.8%) were resistant to ampicillin, 117 (11.1%) to chloramphenicol, and 26 (2.5%) to trimethoprim-sulfamethoxazole; 28 (2.7%) isolates were resistant to nalidixic acid and 26 (2.5%) to ceftriaxone. Antimicrobial resistance to traditional agents is common. However, the occurrence of nalidixic acid and ceftriaxone resistance among invasive NTS is cause for clinical and public health vigilance.

Nontyphoidal salmonellae (NTS) are important bacterial causes of diarrhea in the United States, where they are estimated to cause ~1.0 million illnesses annually (33a, 35). Globally, NTS gastroenteritis is estimated to cause 93.8 million illnesses and 155,000 deaths each year (27). Invasive NTS infection occurs when the organism spreads beyond the gastrointestinal mucosa to infect normally sterile sites, such as the bloodstream, the meninges, bone, and joint spaces (19). In sub-Saharan Africa, invasive NTS disease incidence appears to be much higher than elsewhere (30, 31), particularly among children and HIV-infected adults with CD4-positive T-lymphocyte counts of <200 cells/mm^3, among whom NTS bacteremia annual incidence has been estimated at 88/100,000 and 7,500/100,000, respectively (2, 13). In Africa, epidemics of multidrug-resistant invasive *Salmonella enterica* serotypes Enteritidis and Typhimurium, sometimes due to strains with distinct genotypes, require the use of antimicrobial agents that are more expensive, less widely available, or inconvenient to use in resource-limited settings (14, 23).

In a study in the United States, the gastrointestinal tract was identified as the source of 16% of community-acquired bloodstream infections among persons ≥65 years of age (5). Analysis of population-based data of the Foodborne Disease Active Surveillance Network (FoodNet) from 1996 to 1999 estimated that annual incidence of invasive salmonellosis in the United States was 0.9 cases/100,000 population and was highest among infants, who had an annual incidence of 7.8/100,000. Of those with invasive disease, 5% died, and 45% of deaths occurred among persons ≥60 years of age (36). Some NTS serotypes appear to be more closely associated with invasive disease and poor outcomes than others (21). Antimicrobial therapy may not be required for healthy adult patients with NTS diarrhea and may prolong *Salmonella* shedding, but appropriate antimicrobial therapy can be lifesaving for those with invasive NTS disease (16). Whereas ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole could traditionally be relied upon for the treatment of invasive *Salmonella* infections, antimicrobial resistance among NTS has increased. Fluoroquinolones or extended-spectrum cephalosporins are now recommended for the management of NTS invasive disease (16).

In the United States, a large proportion of NTS infections are associated with consumption of contaminated food (33a). Evidence suggests that antimicrobial use in food animals contributes to antimicrobial resistance in food-borne NTS (1, 10, 17, 20), and acquisition of antimicrobial-resistant *Salmonella* may be linked to international travel (18). Increases in antimicrobial resistance have been observed among NTS causing human disease in the United States over recent decades (3, 25, 26, 33). Of concern, antimicrobial-resistant NTS infections

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▽ Published ahead of print on 3 January 2011.

have been associated with excess bloodstream infections and hospitalizations (28, 34).

We sought to build on previous work (21, 34, 36) to provide a contemporary picture of invasive NTS infections in the United States to inform clinicians and public health policy makers. We examined patterns of antimicrobial resistance and other microbiologic characteristics of invasive NTS and described the characteristics of patients with invasive NTS in the United States using the National Antimicrobial Resistance Monitoring System (NARMS) for enteric bacteria.

(Part of this research was presented at the 47th Annual Meeting of the Infectious Diseases Society of America, Philadelphia, PA, 29 October to 1 November 2009, abstract no. 831 [8].)

MATERIALS AND METHODS

NARMS for enteric bacteria. The National Antimicrobial Resistance Monitoring System (NARMS) (http://www.cdc.gov/narms) was established in 1996. Since then, state and local public health laboratories in California (Los Angeles and Alameda and San Francisco counties), Colorado, Connecticut, Florida, Georgia, Kansas, Massachusetts, Minnesota, New Jersey, New York City, Oregon, Washington, and West Virginia have forwarded every 10th nontyphoidal *Salmonella* isolate, regardless of specimen source or serotype, to the Centers for Disease Control and Prevention (CDC; Atlanta, GA). Maryland joined in 1997, and New York began statewide participation in 1998. Tennessee joined in 1999, and Arizona, Hawaii, Louisiana, Maine, Michigan, Montana, Nebraska, New Mexico, South Dakota, Texas, and Wisconsin joined in 2002. By 2003, all states were participating, and laboratories forwarded every 20th rather than every 10th isolates to the CDC. In 2005, the population under surveillance was 296 million persons (3). Submitting laboratories are asked to provide patient age and sex and the body site of specimen collection for each isolate. Only one isolate from each patient is reported per year.

Isolates submitted to the CDC are tested by broth microdilution (Sensititre; TREK Diagnostic Systems, Cleveland, OH) to determine the MIC for each of 15 antimicrobial agents: amikacin, amoxicillin-clavulanic acid, ampicillin, cefoxitin, ceftiofur, ceftriaxone, chloramphenicol, ciprofloxacin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfisoxazole, tetracycline, and trimethoprim-sulfamethoxazole. Before 2004, sulfamethoxazole was used instead of sulfisoxazole to represent the sulfonamides. Cephalothin was tested prior to 2003 and cefoxitin testing began in 2000. Interpretive criteria established by the Clinical and Laboratory Standards Institute (CLSI) are used when available (4). For the purposes of this analysis, MIC results were dichotomized; isolates with an intermediate susceptibility result were categorized as susceptible.

Analysis. *Salmonella enterica* serotypes Typhi, Paratyphi A, Paratyphi B [L-(+)-tartrate negative], and Paratyphi C and isolates with unknown serotypes were excluded from the analysis, as were isolates from sources other than blood or stool. Patients with NTS bacteremia were compared by age and gender with patients whose NTS was from stool by using the *t* test and chi-square test. To examine the effect of age on risk for bacteremia, patients were divided into the age groups of <1 year, 1 to 4 years, 5 to 17 years, 18 to 64 years, 65 to 84 years, and ≥85 years. Age group 18 to 64 years was used as the referent. Bloodstream isolates were compared with stool isolates by serotype, using *Salmonella* Typhimurium as the referent, and the pattern of antimicrobial resistance was compared with fully susceptible isolates for those serotypes with ≥10 bloodstream isolates in the database using the chi-square test. Variables were defined for fully susceptible, resistant to one or more antimicrobial agent, clinically important resistance, and resistance type (R-type) ACSSuT (resistance to at least ampicillin, chloramphenicol, streptomycin, sulfonamide, and tetracycline). Clinically important resistance was defined as resistance to one or more of the following agents: ampicillin, ceftriaxone, ciprofloxacin, gentamicin, or trimethoprim-sulfamethoxazole. While gentamicin is not recommended for the management of invasive *Salmonella* infection (22), it is frequently used in the management of Gram-negative sepsis. R-type ACSSuT was selected due to its association with *Salmonella* Typhimurium DT104 and mobile genetic elements (32). The proportion of invasive isolates by serotype stratified by resistance to one or more antimicrobial agent was examined and compared using the chi-square test. Patterns of antimicrobial resistance by NTS serogroup and serotype were described when ≥10 bloodstream isolates for the serotype were available. Consistent with current convention, *Salmonella* serogroups (also known as somatic antigen or O groups) are presented using the contemporary numeric scheme, with the historic letter-based serogroup designation provided in parentheses in each instance (15).

TABLE 1. Proportion of nontyphoidal *Salmonella* isolated from blood from patients of different age groups, among isolates submitted to NARMS, 1996 to 2007

Age group (yr)	No. of total isolates	No. (%) of blood isolates	OR	95% CI
18–64	7,057	450 (6.4)	Referent	
<1	1,825	90 (4.9)	0.76	0.60–0.97
1–4	3,131	115 (3.7)	0.56	0.45–0.69
5–17	2,775	123 (4.4)	0.68	0.55–0.84
65–84	1,303	157 (12.1)	2.01	1.7–2.5
≥85	223	24 (10.8)	1.77	1.1–2.8

RESULTS

Of 19,302 NTS isolates tested by NARMS from 1996 to 2007, 17,804 (92.2%) originated from blood or stool. Of 1,498 isolates not from blood or stool, 676 (45.1%) were from urine, and the remainder were from other sites. Of the 17,804 blood or stool isolates, 1,050 (5.9%) were bloodstream isolates. Of patients with blood or stool NTS isolates, the median (range) age was 22 (<1 to 105) years, and of 16,570 for whom gender was known, 8,396 (50.7%) were female.

Characteristics of patients with NTS bacteremia. The median age (range) of patients with NTS bacteremia was 36 (<1 to 97) years and it was 20 (<1 to 105) years for patients with NTS isolated from stool ($P < 0.001$). The relationship between age group and risk for NTS isolation from blood is shown in Table 1. NTS bacteremia was more common in males (odds ratio [OR], 1.21; 95% confidence interval [CI], 1.06 to 1.38) than in females, and bacteremia was more common in patients who were ≥65 years of age.

Characteristics of bloodstream NTS isolates. The proportion of NTS serotypes isolated from blood is shown in Table 2. *Salmonella enterica* serotypes Dublin, Sandiego, Schwarzengrund, Panama, Heidelberg, Oranienburg, and Enteritidis were associated with bloodstream isolation. Table 3 shows the proportion of various antimicrobial resistance patterns among NTS isolated from blood. Resistance to nalidixic acid, gentamicin, ampicillin, kanamycin, sulfonamide, chloramphenicol, streptomycin, and tetracycline was associated with bloodstream isolation. The proportion of invasive isolates by serotype stratified by resistance to one or more antimicrobial agent showed an association between antimicrobial resistance and bloodstream isolation for *Salmonella* serotypes Typhimurium (OR, 2.1; 95% CI, 1.5 to 2.8) and Enteritidis (OR, 1.5; 95% CI, 1.1 to 2.2) and for the group of all isolates that did not have ≥10 bloodstream isolates for the serotype in the collection (OR, 1.6; 95% CI, 1.1 to 2.3).

Patterns of antimicrobial resistance among bloodstream NTS isolates by serogroup and serotype. Table 4 shows antimicrobial resistance to specific antimicrobial agents among common NTS serogroups and serotypes isolated from the bloodstream. Of all 1,050 NTS bloodstream isolates, 730 (69.5%) were susceptible to all antimicrobial agents tested. Three hundred twenty (30.5%) isolates were resistant to ≥1 antimicrobial agent, 235 (22.4%) were resistant to antimicrobial agents classified as clinically important, and 104 (9.9%)

TABLE 2. Proportion of nontyphoidal *Salmonella* isolated from blood by serotype among isolates submitted to NARMS, 1996 to 2007

Salmonella serotype[a]	Serogroup	No. of total isolates	No. (%) of blood isolates	OR	95% CI
Typhimurium[b]	O:4 (B)	4,125	211 (5.1)	Referent	
Dublin	O:9 (D_1)	45	39 (86.7)	120.6	48.2–320.4
Sandiego	O:4 (B)	74	19 (25.7)	6.4	3.6–11.3
Schwarzengrund	O:4 (B)	91	10 (11.0)	3.3	1.1–4.6
Panama	O:9 (D_1)	81	12 (14.8)	3.2	1.6–6.3
Heidelberg	O:4 (B)	1,027	142 (13.8)	3.0	2.4–3.8
Oranienburg	O:7 (C_1)	333	40 (12.0)	2.5	1.7–3.7
Poona	O:13 (G)	146	13 (8.9)	1.8	0.96–3.4
Enteritidis	O:9 (D_1)	3,547	234 (6.6)	1.3	1.1–1.6
1,4,[5],12:i:−	O:4 (B)	337	18 (5.3)	1.1	0.62–1.8
Other	NA[c]	8,399	413 (4.9)	0.96	0.81–1.1
Saintpaul	O:4 (B)	347	17 (4.9)	0.96	0.56–1.6
Montevideo	O:7 (C_1)	468	22 (4.7)	0.92	0.57–1.5
Agona	O:4 (B)	284	12 (4.2)	0.82	0.43–1.5
Infantis	O:7 (C1)	254	10 (3.9)	0.76	0.37–1.5
Newport	O:8 (C_2-C_3)	1,667	35 (2.1)	0.40	0.27–0.58
Javiana	O:9 (D_1)	704	14 (2.0)	0.38	0.21–0.67

[a] *Salmonella* serotypes isolated from blood on ≥10 occasions are listed individually; serotypes isolated from blood on <10 occasions are grouped in the "Other" category.
[b] Includes *Salmonella* Typhimurium O:5−.
[c] NA, not applicable.

were R-type ACSSuT. Of all invasive isolates, 208 (19.8%) were resistant to ampicillin, 117 (11.1%) were resistant to chloramphenicol, and 26 (2.5%) were resistant to trimethoprim-sulfamethoxazole. While no invasive NTS isolates were resistant to ciprofloxacin, 28 (2.7%) were resistant to nalidixic acid, and 23 (82.1%) of these showed ciprofloxacin MIC values of ≥0.12 μg/ml). Twenty-six (2.5%) isolates were resistant to ceftriaxone.

TABLE 3. Proportion of nontyphoidal *Salmonella* isolated from blood by antimicrobial resistance type among isolates submitted to NARMS, 1996 to 2007

Antimicrobial resistance pattern	No. of total isolates	No. (%) of blood isolates	OR	95% CI
Fully susceptible	13,570	730 (5.4)	Referent	
Nalidixic acid	292	28 (9.6)	1.9	1.2–2.8
Gentamicin	395	34 (8.6)	1.7	1.14–2.4
Ampicillin	2,544	208 (8.2)	1.6	1.3–1.8
Kanamycin	724	56 (7.7)	1.5	1.1–2.0
Sulfonamide[a]	2,804	223 (8.0)	1.5	1.3–1.8
Chloramphenicol	1,593	117 (7.3)	1.4	1.1–1.7
Streptomycin	2,630	197 (7.5)	1.4	1.2–1.7
Trimethoprim-sulfamethoxazole	344	26 (7.6)	1.4	0.94–2.2
Tetracycline	3,068	214 (7.0)	1.3	1.1–1.6
Ceftriaxone	38	2 (5.3)	0.98	Invalid
Cefoxitin[b]	487	25 (5.1)	0.95	0.62–1.5
Cephalothin[b]	420	21 (5.0)	0.93	0.58–1.5
Ceftiofur	535	26 (4.9)	0.90	0.59–1.4
Amoxicillin-clavulanate	616	28 (4.6)	0.84	0.56–1.3
Amikacin	1	0 (0.0)	0.00	0.00–04.7
Ciprofloxacin	14	0 (0.0)	0.00	0.00–6.4
Clinically important[c]	2,893	235 (8.1)	1.6	1.3–1.8
≥1 agent	4,234	320 (7.6)	1.4	1.3–1.7
R-type ACSSuT[d]	1,431	104 (7.3)	1.4	1.1–1.7

[a] For sulfonamide resistance, sulfamethoxazole was tested from 1996 to 2003, and sulfisoxazole was tested from 2004 to 2007.
[b] Cephalothin was tested prior to 2003 and cefoxitin testing began in 2000.
[c] Resistant to one or more of the following: ampicillin, ceftriaxone, ciprofloxacin, gentamicin, or trimethoprim-sulfamethoxazole.
[d] Resistant to at least ampicillin, chloramphenicol, streptomycin, sulfonamide, and tetracycline.

Of NTS bloodstream isolates by serogroup, 256 (56.0%) of 457 isolates belonging to serogroup O:4 (B) were susceptible to all antimicrobial agents tested, compared with 94 (80.3%) of 117 serogroup O:7 (C_1) isolates, 38 (70.4%) of 54 serogroup O:8 (C_2-C_3) isolates, 242 (77.8%) of 311 serogroup O:9 (D_1) isolates, 18 (94.7%) of 19 serogroup O:3,10 (E_1) isolates, 1 (100.0%) of 1 serogroup O:1,3,19 (E_4) isolate, 7 (87.5%) of 8 serogroup O:11 (F) isolates, 30 (90.9%) of 33 O:13 (G) isolates, and 44 (88.0%) of 50 other serogroups. Among the four serogroups accounting for the most NTS bloodstream isolates, *Salmonella* serotype Typhimurium had the lowest proportion of fully susceptible isolates in serogroup O:4 (B), accounting for 77 (36.7%) of 210 isolates; the category "other serotypes" in serogroup O:7 (C_1) accounted for 27 (58.7%) of 46 isolates; the category "other serotypes" in serogroup O:8 (C_2-C_3) accounted for 13 (68.4%) of 19 isolates; and *Salmonella* serotype Dublin in serogroup O:9 (D_1) accounted for 23 (59.0%) of 39 isolates.

DISCUSSION

We have demonstrated that among NTS causing bloodstream infection in the United States, antimicrobial resistance to the traditional first-line antimicrobial agents ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole occurs in a substantial proportion of isolates but that susceptibility to fluoroquinolones and extended-spectrum cephalosporins is largely but not completely preserved. We have confirmed that *Salmonella* serotypes Typhimurium, Enteritidis, and Heidelberg are the most common nontyphoidal *Salmonella* serotypes isolated from blood in the United States, whereas *Salmonella* serotypes Dublin, Enteritidis, Heidelberg, Oranienburg, Panama, Sandiego, and Schwarzengrund are relatively more often isolated from blood compared with *Salmonella* serotype Typhimurium. Furthermore, we have shown that bloodstream iso-

TABLE 4. Antimicrobial resistance by serogroup and serotype of NTS bloodstream isolates submitted to NARMS, 1996 to 2007

Salmonella serogroup	*Salmonella* serotype (no. of isolates)	No. (%) of isolates by antimicrobial resistance pattern[d]															
		AMC	AMP	CEP	CHL	CIP	CRO	FOX[a]	GEN	NAL	SSS[b]	SXT	TET	Fully susceptible	≥1 agent	Clinically important	R-type ACSSuT
O:4 (B)	Agona (12)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (50.0)	0 (0.0)	6 (50.0)	6 (50.0)	6 (50.0)	0 (0.0)	0 (0.0)
	1,4,[5],12:i− (18)	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.6)	17 (94.4)	1 (5.6)	1 (5.6)	1 (5.6)
	Heidelberg (141)	6 (4.3)	24 (17.0)	5 (3.6)	1 (0.7)	0 (0.0)	6 (4.3)	5 (3.6)	16 (11.4)	0 (0.0)	19 (13.5)	0 (0.0)	18 (12.8)	98 (69.5)	43 (30.5)	34 (24.1)	1 (0.7)
	Saintpaul (17)	1 (5.9)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (23.5)	13 (76.5)	4 (23.5)	1 (5.9)	0 (0.0)
	Sandiego (19)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	17 (89.5)	2 (10.5)	0 (0.0)	0 (0.0)
	Schwarzengrund (10)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)	2 (20.0)	8 (80.0)	2 (20.0)	0 (0.0)	0 (0.0)
	Typhimurium (210)	6 (2.9)	116 (55.2)	3 (1.4)	88 (41.9)	0 (0.0)	4 (1.9)	4 (1.9)	4 (1.9)	2 (1.0)	127 (60.5)	11 (5.2)	110 (52.4)	77 (36.7)	133 (63.3)	119 (56.7)	82 (39.1)
	Other (30)	1 (3.3)	5 (16.7)	2 (6.7)	1 (3.3)	0 (0.0)	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	3 (10.0)	1 (3.3)	7 (23.3)	20 (66.7)	10 (33.3)	5 (16.7)	1 (3.3)
	Total (457)	14 (3.1)	147 (32.2)	10 (2.2)	91 (19.9)	0 (0.0)	12 (2.6)	11 (2.4)	21 (4.6)	3 (0.7)	159 (34.8)	12 (2.6)	148 (32.4)	256 (56.0)	201 (44.0)	160 (35.0)	85 (18.6)
O:7 (C_1)	Infantis (10)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Montevideo (22)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.6)	0 (0.0)	1 (4.6)	0 (0.0)	1 (4.6)	21 (95.5)	1 (4.6)	1 (4.6)	0 (0.0)
	Oranienburg (39)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	2 (5.1)	0 (0.0)	0 (0.0)	36 (92.3)	3 (7.7)	1 (2.6)	0 (0.0)
	Other (46)	0 (0.0)	5 (10.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)	8 (17.4)	16 (34.8)	7 (15.2)	12 (26.1)	27 (58.7)	19 (41.3)	10 (21.7)	0 (0.0)
	Total (117)	0 (0.0)	5 (4.3)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.4)	8 (6.8)	20 (16.2)	7 (6.0)	13 (11.1)	94 (80.3)	23 (19.7)	12 (10.3)	0 (0.0)
O:8 (C_2-C_3)	Newport (35)	7 (20.0)	8 (22.9)	6 (17.1)	9 (25.7)	0 (0.0)	7 (20.0)	7 (20.0)	1 (2.9)	0 (0.0)	10 (28.6)	1 (2.9)	10 (28.6)	25 (71.4)	10 (28.6)	8 (22.9)	7 (20.0)
	Other (19)	0 (0.0)	1 (5.3)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	1 (5.3)	5 (26.3)	13 (68.4)	6 (31.6)	2 (10.5)	0 (0.0)
	Total (54)	7 (13.0)	9 (16.7)	7 (13.0)	9 (16.7)	0 (0.0)	7 (13.0)	7 (13.0)	1 (1.9)	0 (0.0)	12 (22.2)	2 (3.7)	15 (27.8)	38 (70.4)	16 (29.6)	10 (18.5)	7 (13.0)
O:9 (D_1)	Dublin (39)	4 (10.3)	13 (33.3)	1 (2.6)	13 (33.3)	0 (0.0)	4 (10.3)	4 (10.3)	1 (2.6)	2 (5.1)	16 (41.0)	0 (0.0)	15 (38.5)	23 (59.0)	16 (41.0)	13 (33.3)	10 (25.6)
	Enteritidis (232)	2 (0.9)	27 (11.6)	2 (0.9)	1 (0.4)	0 (0.0)	2 (0.9)	2 (0.9)	1 (0.4)	13 (5.6)	8 (3.5)	4 (1.7)	14 (6.0)	188 (81.0)	44 (19.0)	29 (12.5)	1 (0.4)
	Javiana (14)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	1 (7.1)	12 (85.7)	2 (14.3)	0 (0.0)	0 (0.0)
	Panama (12)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	11 (91.7)	1 (8.3)	0 (0.0)	0 (0.0)
	Other (14)	0 (0.0)	3 (21.4)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (21.4)	1 (7.1)	4 (28.6)	0 (0.0)	1 (7.1)	8 (57.1)	6 (42.9)	5 (35.7)	1 (7.1)
	Total (311)	6 (1.9)	43 (13.8)	3 (1.0)	16 (5.1)	0 (0.0)	6 (1.9)	6 (1.9)	5 (1.6)	17 (5.5)	28 (9.0)	4 (1.3)	32 (10.3)	242 (77.8)	69 (22.1)	47 (15.1)	12 (5.9)
O:3,10 (E_1)	Total (19)	0 (0.0)	1 (5.3)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (5.3)	0 (0.0)	1 (5.3)	18 (94.7)	1 (5.3)	1 (5.3)	0 (0.0)
O:1,3,19 (E_4)	Total (1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
O:11 (F)	Total (8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	7 (87.5)	1 (12.5)	1 (12.5)	0 (0.0)
O:13 (G)	Poona (13)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	12 (92.3)	1 (7.7)	1 (7.7)	0 (0.0)
	Other (20)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	18 (90.0)	2 (10.0)	0 (0.0)	0 (0.0)
	Total (33)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (9.1)	30 (90.9)	3 (9.1)	1 (3.0)	0 (0.0)
Others[c]	Total (50)	1 (2.0)	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (2.0)	1 (2.0)	0 (0.0)	3 (6.0)	1 (2.0)	2 (4.0)	44 (88.0)	6 (12.0)	3 (6.0)	0 (0.0)
All	Total (1,050)	28 (2.7)	208 (19.8)	21 (2.0)	117 (11.1)	0 (0.0)	26 (2.5)	25 (2.4)	34 (3.2)	28 (2.7)	223 (21.2)	26 (2.5)	214 (20.4)	730 (69.5)	320 (30.5)	235 (22.4)	104 (9.9)

[a] Cefoxitin testing began in 2000.
[b] For sulfonamide resistance, sulfamethoxazole was tested from 1996 through 2003, and sulfisoxazole was tested from 2004 through 2007.
[c] Includes serogroups O:6,14 (H) (1 isolate), O16 (I) (2 isolates), O:18 (K) (2 isolates), O:28 (M) (9 isolates), O:30 (N) (3 isolates), O:35 (O) (3 isolates), and O:40 (R) (2 isolates).
[d] Antimicrobial agents: AMC, amoxicillin-clavulanate; AMP, ampicillin; CEP, cephalothin; CHL, chloramphenicol; CIP, ciprofloxacin; CRO, ceftriaxone; FOX, cefoxitin; GEN, gentamicin; NAL, naldixic acid; SSS, sulfonamides; SXT, trimethoprim-sulfamethoxazole; TET, tetracycline. Fully susceptible, susceptible to all antimicrobial agents tested in NARMS panel; ≥1 agent, resistant to one or more antimicrobial agent in NARMS panel; clinically important, resistant to ampicillin, ceftriaxone, ciprofloxacin, gentamicin, and/or trimethoprim-sulfamethoxazole; ACSSuT, resistant to at least ampicillin, chloramphenicol, streptomycin, sulfonamide, and tetracycline.

lates are more likely to be resistant to one or more antimicrobial agents than stool isolates and that this association persists even within common NTS serotypes. Since invasive NTS disease occurs more often among those ≥65 years of age, patients with invasive NTS infection in the United States may present with the dual management considerations of comorbid conditions and increased risk for bacteremia with nonsusceptible isolates compared with those with uncomplicated NTS diarrhea.

Ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole are unlikely to be used alone for the empirical management of community-acquired sepsis, for the management of bacteremia due to Gram-negative organisms, or for the specific treatment of NTS bacteremia in the United States. The first-line treatment options are most commonly fluoroquinolones and extended-spectrum cephalosporins (16). Among invasive NTS isolates included in this study, 26 (2.5%) were resistant to the extended-spectrum cephalosporin ceftriaxone. Although resistance to ciprofloxacin, according to current CLSI guidelines, was not identified among invasive NTS isolates, the occurrence of nalidixic acid resistance in 28 (2.7%) invasive isolates, predominantly *Salmonella* Enteritidis, is cause for concern. Nalidixic acid correlates well with decreased susceptibility to ciprofloxacin (DCS; ciprofloxacin MIC of 0.12 to 1.0 μg/ml). While fewer data are available for invasive NTS, DCS has been associated with longer times to defervescence and greater risk for relapse among persons with *Salmonella* Typhi bloodstream infection (6, 7, 37). Resistance to nalidixic acid, usually resulting from a single chromosomal point mutation in the DNA gyrase gene, is considered to be an initial step toward the development of ciprofloxacin resistance, which is usually associated with two or more chromosomal point mutations. Consequently, the occurrence of nalidixic acid resistance among NTS bloodstream isolates warrants vigilance for the emergence of ciprofloxacin resistance. Ceftriaxone resistance was identified among NTS bloodstream isolates belonging to *Salmonella* serotypes Newport (17), Heidelberg, Dublin, Typhimurium (38), Enteritidis, and Saintpaul, in descending order of frequency. While ceftriaxone resistance remains uncommon, it is important that clinicians be aware that resistance to extended-spectrum cephalosporins may occur among invasive NTS, particularly since outbreaks of multidrug-resistant *Salmonella* Newport resistant to extended-spectrum cephalosporins have been reported in the United States (17). Consequently, clinicians should be aware of the local epidemiology of NTS and carefully review results of antimicrobial susceptibility testing once available from the clinical laboratory.

Salmonella Typhimurium, Enteritidis, and Heidelberg are among the most common *Salmonella* serotypes isolated from stool samples in the United States and are also the most frequently isolated from the bloodstream (36). However, substantial differences exist between serotypes in the proportion of isolates recovered from the bloodstream relative to isolates recovered from stool. For example, although *Salmonella* Dublin was an uncommon serotype during the period of study, the bloodstream was the source in 39 (86.7%) of 45 cases. Therefore, relative to *Salmonella* Typhimurium, *Salmonella* Dublin was much more likely to be isolated from a normally sterile site. It is usually surmised that *Salmonella* Dublin has a greater propensity to cause invasive disease (11), although it is conceivable that a similar pattern would be observed if a *Salmonella* serotype was less likely than other serotypes to cause diarrhea. Consistent with other studies (21, 36), in addition to *Salmonella* Dublin, *Salmonella* serotypes Sandiego, Schwarzengrund, Panama, Heidelberg, Oranienburg, and Enteritidis were also associated with greater risk for invasive disease than *Salmonella* Typhimurium. In our study and in previous work (34), the presence of antimicrobial resistance to one or more antimicrobial agent was associated with risk for invasive disease independent of *Salmonella* serotype. Furthermore, older individuals were at greater risk for invasive disease than those 18 to 64 years of age. Therefore, changes in predominant *Salmonella* serotypes and patterns of antimicrobial resistance among circulating strains may alter the risk for invasive NTS disease in a community. A *Salmonella* outbreak due to a serotype with greater invasive potential and the presence of resistance to antimicrobial agents should alert clinicians and public health officials to the possibility of a greater risk for NTS bacteremia among those sickened. In this setting and based on our findings, older individuals would be at even greater risk for invasive disease than younger age groups.

Patterns of antimicrobial resistance observed among invasive NTS varied considerably by *Salmonella* serogroup. Many clinical laboratories have the capacity to serologically identify common somatic antigens of *Salmonella* prior to the availability of the results of antimicrobial susceptibility testing. Therefore, we have presented antimicrobial resistance findings by serogroup. Nalidixic acid resistance, for example, was identified in serogroup O:4 (B), O:7 (C_1), and O:9 (D_1) but not among isolates from other serogroups. While small numbers limited our ability to make clear statements about the association of both serotype and serogroup with invasiveness, patterns of antimicrobial resistance in serogroups may often have been driven predominantly by one serotype. For example, bloodstream NTS isolates with R-type ACSSuT occurred only in serogroups O:4 (B), O:8 (C_2-C_3), and O:9 (D_1) in this study but appeared to be driven almost exclusively by the occurrence of R-type ACSSuT with *Salmonella* serotypes Typhimurium (12, 32), Newport (17), and Dublin (9), respectively. Of clinical concern, resistance to extended-spectrum cephalosporins was common in *Salmonella* Newport and Dublin isolates with R-type ACSSuT.

This study has a number of limitations. Although the study covers a period of 12 years and represents a large proportion of the United States population, NARMS receives a relatively small sample of NTS isolates. Consequently, only 1,050 bloodstream NTS isolates were available for evaluation in this collection. The relatively small number of bloodstream isolates limited our ability to make assessments of uncommon patterns of antimicrobial resistance, particularly within rare *Salmonella* serogroups and serotypes. Furthermore, we were unable to examine bacterial phylogeny within serotypes with respect to invasiveness (24). We were unable to examine time trends in changes in patterns of antimicrobial resistance. This was not only due to relatively small numbers of bloodstream isolates but also because we measure change on a multiplicative rather than additive scale, producing odds ratios rather than risk differences. Consequently, it was not possible to express changes relative to baseline for situations where baseline prevalence of antimicrobial resistance was zero, a common situa-

tion for several antimicrobial agents in this study. Because NARMS collects limited sociodemographic and clinical information, we were unable to thoroughly explore host risk factors for invasive NTS in the United States. However, such factors have been more thoroughly examined by others (34).

In summary, NTS is an important cause of community-acquired bacteremia in the United States, particularly affecting older persons and the immunocompromised. While antimicrobial resistance to the traditional first-line antimicrobial agents ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole occurs in a substantial minority of isolates, most remain susceptible to fluoroquinolones and extended-spectrum cephalosporins. The occurrence of nalidixic acid resistance among NTS bloodstream isolates suggests that decreased ciprofloxacin susceptibility is present, may be associated with poorer patient outcomes, and could herald future development of fluoroquinolone resistance. Furthermore, the presence of resistance to ceftriaxone underscores the need for clinicians to be aware of the results of antimicrobial susceptibility testing results and to closely monitor the clinical course of individual patients with NTS bacteremia. While the NTS serotypes causing invasive disease in the United States largely reflect those associated with enteric infections, some serotypes are associated with greater risk for invasive infection, particularly when the infecting strain is resistant to one or more antimicrobial agents. Furthermore, some patterns of antimicrobial resistance cluster within serogroups. Since many clinical laboratories can serogroup NTS isolates, serogroup information can provide broad clues to anticipated patterns of antimicrobial resistance. Ongoing surveillance for antimicrobial resistance in NTS will provide epidemiologic information to clinicians about anticipated patterns of resistance in NTS strains. As more data are collected, results will be used to detect changes in serotypes, invasiveness, and the prevalence of resistance. Such data could contribute to the evaluation of strategies for the prevention and control of antimicrobial resistance during food production.

ACKNOWLEDGMENTS

We thank the 50 state and three local departments and their public health laboratories that participate in the National Antimicrobial Resistance Monitoring System. NARMS is a U.S. Food and Drug Administration-funded program and is a collaboration among the CDC, the U.S. Food and Drug Administration Center for Veterinary Medicine, and the Food Safety and Inspection and Agricultural Research Services of the U.S. Department of Agriculture.

None of the authors has a potential conflict of interest.

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