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Clinical Outcomes of Patients With Nontyphoidal *Salmonella* Infections by Isolate Resistance—Foodborne Diseases Active Surveillance Network, 10 US Sites, 2004–2018

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Abstract

Background.—Nontyphoidal *Salmonella* causes an estimated 1.35 million US infections annually. Antimicrobial-resistant strains are a serious public health threat. We examined the association between resistance and the clinical outcomes of hospitalization, length-of-stay ≥3 days, and death.

Methods.—We linked epidemiologic data from the Foodborne Diseases Active Surveillance Network with antimicrobial resistance data from the National Antimicrobial Resistance Monitoring System (NARMS) for nontyphoidal *Salmonella* infections from 2004 to 2018. We defined any resistance as resistance to ≥1 antimicrobial and clinical resistance as resistance to ampicillin, azithromycin, ceftriaxone, ciprofloxacin, or trimethoprim-sulfamethoxazole (for the subset of isolates tested for all 5 agents). We compared outcomes before and after adjusting for age, state, race/ethnicity, international travel, outbreak association, and isolate serotype and source.

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Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Results.—Twenty percent of isolates (1105/5549) had any resistance, and 16% (469/2969) had clinical resistance. Persons whose isolates had any resistance were more likely to be hospitalized (31% vs 28%, $P = .01$) or have length-of-stay ≥3 days (20% vs 16%, $P = .01$). Deaths were rare but more common among those with any than no resistance (1.0% vs 0.4%, $P = .01$). Outcomes for patients whose isolates had clinical resistance did not differ significantly from those with no resistance. After adjustment, any resistance (adjusted odds ratio 1.23, 95% confidence interval 1.04–1.46) remained significantly associated with hospitalization.

Conclusions.—We observed a significant association between nontyphoidal *Salmonella* infections caused by resistant pathogens and likelihood of hospitalization. Clinical resistance was not associated with poorer outcomes, suggesting that factors other than treatment failure (eg, strain virulence, strain source, host factors) may be important.

Keywords

drug resistance; *Salmonella* ; hospitalization; length of stay; death

Nontyphoidal *Salmonella* (hereafter, *Salmonella*) causes an estimated 1.35 million infections per year in the United States [1], and antimicrobial-resistant *Salmonella* is a serious public health threat [2]. Although most infections are self-limited, antimicrobials are important for patients with severe infections and those who are at high risk for invasive disease due to extremes of age or immune compromise [3, 4].

Understanding the relationship between resistance and clinical outcomes is important, because more than 250 000 resistant *Salmonella* infections are estimated to occur among US patients, representing an almost 12% increase from 2017 to 2019 [2]. Previous US studies have assessed the relationship between antimicrobial-resistant infections and clinical outcomes including bloodstream infections [5–10], hospitalization [6, 8–13], length-of-stay [6, 8–10], and mortality [8, 9, 13], with most larger studies noting increased odds of severe outcomes among resistant infections [14]. However, these analyses focused chiefly on periods from the 1980s to the 2000s, and both population health and antimicrobial resistance have since evolved [15, 16]. Furthermore, prior analyses typically did not adjust for several patient and isolate factors, making it difficult to draw conclusions about possible reasons for outcomes.

We examined the association between antimicrobial resistance and clinical outcomes in US patients with *Salmonella* infections, considering current resistance patterns and treatment guidelines. We examined patient and isolate factors to assess whether they influenced the outcome of resistant or susceptible infections. To do this, we linked epidemiologic data from the Foodborne Diseases Active Surveillance Network (FoodNet) with resistance data from the National Antimicrobial Resistance Monitoring System (NARMS) from 2004 through 2018.

METHODS

Surveillance Systems

FoodNet is an active, population-based surveillance system that collects epidemiological information from patients with specific foodborne illnesses, including *Salmonella* infections (www.cdc.gov/foodnet). From 2004 to 2018, the FoodNet catchment area included the entire population of 7 US states (Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, and Tennessee) and selected counties in California (3 counties), Colorado (7 counties), and New York (34 counties). In 2018, FoodNet sites encompassed approximately 49 million people comprising 15% of the US population [17]. FoodNet variables included patient demographics (age, sex, race, ethnicity, state of residence), patient exposures (outbreak association, international travel), patient symptoms (collected during 2011–2018 only: fever, diarrhea, bloody diarrhea), patient outcomes (hospitalization and length-of-stay, death), and isolate variables (serotype, specimen source).

NARMS is a national surveillance system that monitors antimicrobial resistance in enteric pathogens. During 2004–2018, clinical laboratories in the United States submitted *Salmonella* isolates to their corresponding state or local US public health laboratories, where serotype was determined. US public health laboratories then submitted every twentieth clinical *Salmonella* isolate and additional isolates from local and multistate outbreaks to the Centers for Disease Control and Prevention (CDC), where the NARMS laboratory performed antimicrobial susceptibility testing. Public health laboratories also reported some patient demographics and isolate information to NARMS. For the years 2006–2008, some FoodNet sites enhanced their sampling schemes to submit every fourth, fifth, or tenth surveillance isolate as described by Krueger et al [8].

Data from the 2 systems were linked using a common state laboratory unique isolate identifier. When there were discrepancies between data collected by the 2 different systems for the same variables (eg, age, sex, outbreak association, isolate source, serotype), the FoodNet value was used. If the FoodNet value was unknown or missing, the value from NARMS was used.

Inclusion and Exclusion Criteria

We included *Salmonella* isolates of any serotype other than Typhi or Paratyphi A, B, or C [Paratyphi B var. L(+) tartrate + was included]. We included only cases with a record in the FoodNet database [18], a specimen collection date during 2004–2018, and a corresponding isolate submitted to NARMS. We excluded cases if the isolate did not meet laboratory quality metrics.

Antimicrobial Susceptibility Testing

All isolates were tested by the CDC NARMS laboratory for antimicrobial susceptibility using broth microdilution (Sensititre®, Westlake, Ohio, USA) as previously described [15]. Antimicrobial classes were defined by the Clinical and Laboratory Standards Institute (CLSI) [15]. The gram-negative Sensititre panels included 13–14 antimicrobials and changed slightly during the study period; in total, 17 antimicrobials from 10 classes

were tested: aminoglycosides included amikacin (2004–2010 only), gentamicin, kanamycin (2004–2013 only), and streptomycin; β-lactam combination agents included amoxicillin-clavulanic acid; cephems included cefoxitin, ceftiofur (2004–2015 only), and ceftriaxone; folate pathway antagonists included sulfisoxazole and trimethoprim-sulfamethoxazole; macrolides included azithromycin (2011–2018 only); penicillins included ampicillin; penems included meropenem (2016–2018 only); phenicols included chloramphenicol; quinolones included ciprofloxacin and nalidixic acid; and tetracyclines included tetracycline.

Resistance Definitions

We classified isolates as resistant, intermediate, or susceptible according to criteria established by CLSI when available [15]. For azithromycin, we considered isolates to be resistant if they had a minimum inhibitory concentration (MIC) of ≥32 μg/mL based on the current CLSI investigational azithromycin breakpoint for *Salmonella* Typhi. For streptomycin, we used NARMS-established breakpoints and considered isolates to be resistant if they had an MIC of ≥64 μg/mL (2004–2013) or ≥32 μg/mL (2014–2018); the latter breakpoint could not be applied to previous years due to limited concentrations tested. (These breakpoints for azithromycin and streptomycin are not used to predict clinical efficacy.)

We examined resistance by class and antimicrobial agent. An isolate with resistance to ≥1 antimicrobial within a class was considered resistant to that class. We included isolates with intermediate interpretation to ciprofloxacin in the resistant group because MICs in the intermediate range (≥0.12–0.5 μg/mL) have been shown to affect clinical outcome [19–21]. Isolates with intermediate resistance to other antimicrobials were considered not resistant; this affected <1% of isolates for all antimicrobials except amoxicillin-clavulanic acid (2.6%; Table 1).

We considered an isolate to have any resistance if it was resistant to ≥1 antimicrobial; to have multidrug resistance if it was resistant to ≥1 antimicrobial from ≥3 classes; and to have clinical resistance if it was resistant to ≥1 of ampicillin, azithromycin, ceftriaxone, ciprofloxacin, or trimethoprim-sulfamethoxazole (no isolates were resistant to meropenem). We restricted analyses involving clinical resistance to isolates that were tested for all 5 agents. We considered an isolate to have no resistance if it was susceptible to ciprofloxacin and was not resistant to any other antimicrobials tested.

We selected specific resistance patterns for analysis because previous studies documented a link between the pattern and more severe clinical outcomes or because the pattern is of clinical or public health interest and is tracked by the NARMS program [8, 22]. These patterns included resistance to at least ampicillin, chloramphenicol, streptomycin, sulfisoxazole, and tetracycline (ACSSuT); resistance to at least ampicillin, streptomycin, sulfisoxazole, and tetracycline without resistance to chloramphenicol (ASSuT); resistance to at least ampicillin, amoxicillin-clavulanic acid, and ceftriaxone (AAuCx); resistance to at least ampicillin, chloramphenicol, streptomycin, sulfisoxazole, tetracycline, amoxicillin-clavulanic acid, and ceftriaxone (ACSSuTAuCx); and resistance to at least ceftriaxone and ciprofloxacin (including intermediate interpretation; CxCip).

Statistical Analysis

We compared characteristics of *Salmonella* infections with any resistance with those with no resistance using χ^2 or Fisher exact test. Primary outcomes for bivariate analyses included hospitalization, length-of-stay ≥3 days, and death. Infections caused by *Salmonella* with any resistance, multidrug resistance, clinical resistance, or select resistance patterns were compared with infections caused by isolates with no resistance. Proportional differences were considered statistically significant if the *P* value was ≤.05.

For the adjusted analyses, primary outcomes were limited to hospitalization and length-of-stay ≥3 days due to the small number of deaths. We used logistic regression to calculate adjusted odds ratios (aORs) for both primary outcomes. Covariates included in the model were age (5-knot restricted cubic spline to account for nonlinearity in the age association), sex, race/ethnicity (American Indian/Alaskan Native [any ethnicity], Hispanic or Latino [any other race], White non-Hispanic, Black non-Hispanic, Asian or Pacific Islander non-Hispanic, multiple race non-Hispanic, other race non-Hispanic, and unknown), outbreak association, FoodNet site, season of first positive culture (January–March, April–June, July–September, October–December), specimen source (abscess, blood, cerebrospinal fluid, stool, urine, other noninvasive site, other sterile site, unknown), serotype (a categorical variable with values corresponding to each of the top 10 serotypes and other/unknown; Table 2), and international travel in the 7 days before illness began.

We calculated aORs for each of the same resistance categories in the bivariate analysis using cases with no resistance as the reference group. We attempted to determine aORs for individual antimicrobials or classes by including them in the model, but due to the high correlation between antimicrobials (Supplementary Table 1), models tended to fit poorly and thus are not reported. An aOR was considered statistically significant when the 95% confidence interval (CI) excluded 1.0. Analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA) or R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) using the rms package 6.2–0.

RESULTS

A total of 5602 *Salmonella* FoodNet records corresponded to isolates with antimicrobial susceptibility results in NARMS. Fifty-three linked records (0.9%) were excluded from further analysis because the submitted specimen did not meet laboratory quality criteria or because the record was a duplicate, leaving 5549 cases in the analysis. Of these, 1105 (20%) showed resistance to ≥1 antimicrobial; resistance was most common to tetracycline (12%), sulfisoxazole (11%), streptomycin (10%), and ampicillin (10%) (Table 1). Two hundred twenty-six isolates (4.1%) had the resistance pattern ACSSuT, followed by ASSuT (n = 157; 2.8%), AAuCx (n = 150; 2.7%), ACSSuTAuCx (n = 32; 0.6%), and CxCip (n = 28; 0.5%). Eighty-five percent of isolates belonged to 1 of 20 common serotypes (Table 2). Serotypes with the highest percentage of resistant isolates were Hadar (73%), I 4,[5],12:i:- (49%), Heidelberg (44%), Typhimurium (34%), and Agona (31%). Heidelberg (16%) and Hadar (11%) were also among the serotypes most associated with invasive infections.

Compared with patients whose isolates showed no resistance, patients whose isolates showed resistance were similar in age, sex, and symptoms ($P > .05$ for all comparisons) but were less likely to be associated with an outbreak (12% vs 14% $P = .03$) and more likely to have traveled internationally (16% vs 8%, $P < .01$) (Table 3). Significant differences occurred among race/ethnicity groups between those with and without resistant infections ($P < .01$); patients whose isolates showed resistance were more likely to be Black non-Hispanic (143/925 [15%] vs 462/3643 [13%], $P = .03$) or Asian non-Hispanic (71/925 [8%] vs 144/3643 [4%], $P < .01$) and less likely to be White non-Hispanic (555/925 [60%] vs 2491/3643 [68%], $P < .01$). Among travelers, those with resistant infections were more likely to have traveled to Asia (49/149 [33%] vs 32/277 [12%], $P < .01$) and less likely to have traveled to Mexico (34/149 [23%] vs 94/277 [34%], $P = .02$). Patients with resistant infections were also more likely to have an isolate source other than stool (189/1105 [17%] vs 503/4444 [11%], $P < .01$).

Compared with patients whose isolates showed no resistance, patients whose isolates had any resistance were more likely to be hospitalized (31% vs 28%, $P = .01$), to have a hospitalization length-of-stay ≥3 days (20% vs 16%, $P = .01$), or to die (1% vs 0.4%, $P = .01$) on unadjusted bivariate analysis (Table 4). Patients whose isolates had multidrug resistance were also more likely to be hospitalized (34% vs 28%, $P < .01$) or to have a hospitalization length-of-stay ≥3 days (21% vs 16%, $P < .01$); similar results were found for patients with isolates resistant to amoxicillin-clavulanic acid, ampicillin, chloramphenicol, streptomycin, sulfisoxazole, tetracycline, all cephems, and resistance patterns including ACSSuT, AAuCx, and ACSSuTAuCx. Patients with isolates resistant to trimethoprim-sulfamethoxazole or ciprofloxacin were not more likely to be hospitalized or to have a length-of-stay ≥3 days, but those whose isolates were resistant to ciprofloxacin were more likely to die (2% vs 0.4%, $P < .01$). However, patients whose isolates had clinical resistance were not significantly more likely to have any outcome associated with severe disease.

After adjustment for age, sex, race/ethnicity, state, international travel, outbreak association, season, serotype, and specimen source, patients with resistant isolates had higher odds of hospitalization; the association was significant for patients whose isolates showed any resistance (aOR 1.23, 95% CI 1.04–1.46]), multidrug resistance (1.40 aOR, 95% CI 1.12–1.75), or the common resistance patterns ACSSuT (aOR 1.79, 95% CI 1.28–2.50) and AAuCx (aOR 1.73, 95% CI 1.18–2.55) (Figure 1A). Clinical resistance and resistance patterns ASSuT, ACSSuTAuCx, and CxCip were not significantly associated with hospitalization (Figure 1A). Only patterns ACSSuT (aOR 1.70, 95% CI 1.17–2.49) and AAuCx (aOR 1.57, 95% CI 1.02–2.42) were significantly associated with an outcome of hospitalization length-of-stay ≥3 days (Figure 1B).

DISCUSSION

We found that infections caused by *Salmonella* with any antimicrobial resistance or multidrug resistance were associated with more severe clinical outcomes, including hospitalization, hospital length-of-stay ≥3 days, and death. This association remained for the outcome of hospitalization after adjustment for demographic factors, international travel, serotype, and isolate source. Moreover, infections caused by *Salmonella* strains

with any resistance or multidrug resistance were also associated with (nonsignificant) aORs above 1.0 for length-of-stay ≥3 days. However, our data analysis suggests that factors other than treatment failure may be responsible for difference in outcomes: infections caused by *Salmonella* strains with clinical resistance were not significantly associated with hospitalization and had a (nonsignificant) aOR <1.0 for length-of-stay ≥3 days. Furthermore, ciprofloxacin and trimethoprim-sulfamethoxazole were among the only individual antimicrobials that showed no significant association with hospitalization or length-of-stay on unadjusted analysis, although these antimicrobials were recommended for first-line treatment during most of the study period [23].

The lack of association between clinical resistance and poor clinical outcome, along with the known association with overall resistance, indicate that infection with a resistant organism may be a marker for, but not necessarily the direct cause of, a poor clinical outcome. This finding has clinical implications: Clinicians using an antimicrobial that is effective against a resistant *Salmonella* strain should recognize that such patients are still at increased risk of more severe clinical outcomes than patients with susceptible strains.

There are several possible explanations for an association between resistance and poor clinical outcomes beyond treatment failure. Host factors such as comorbidities or foods consumed may play a role. For example, persons at risk of poorer outcomes may have more exposures that result in infections with resistant strains. Persons with comorbidities may spend more time in hospitals or other healthcare settings, which can be reservoirs of resistant strains [24, 25]. Some serotypes tend to be more resistant than others, and particular serotypes and strains have reservoirs in particular host animals and may more often contaminate foods derived from those animals [26]. Therefore, people's diets may affect the serotype and resistance profile of their *Salmonella* strains. Strain factors may also affect outcomes. Virulence varies by serotype [27, 28]. Certain serotypes cause illness disproportionately to their representation in foods, animals, or the environment; some serotypes, such as Dublin or Choleraesuis, have strong associations with both antimicrobial resistance and severe illness [29–31]. Some analyses have suggested a correlation between virulence and resistance [27, 28, 32]. The optimal approach to identifying and defining markers for virulence in *Salmonella* is still being studied [33].

Our findings are similar to previous US studies that have shown an association between resistance and more severe clinical outcomes. A meta-analysis of 9 US studies found that multidrug resistance was significantly associated with outcomes of bloodstream infection, hospitalization, and death compared with no resistance [14]. The meta-analysis findings are compelling, but many of the individual studies were small or serotype-specific, and they took variable approaches to adjusting for patient and isolate factors. Most patients in these studies had infections that occurred during 1984 to 2013, earlier than many patients in our analysis [5–13]. Therefore, it is noteworthy that the current analysis, which used a robust dataset, more recent data reflecting modern resistance profiles, and a more complete approach to adjustment for other factors, found largely similar results.

This analysis has several limitations. National surveillance data do not include strain type, underlying health conditions, antimicrobial use, duration of illness, or treatment failure.

Salmonella isolates were not routinely sequenced until 2015 [15], so we were unable to adjust for the role of specific virulence markers on clinical outcomes. Furthermore, adjustment for serotype is complicated by the number of serotypes capable of causing human illness [34]; our data set contained more than 200 serotypes, but our model only considered the top 10. Therefore, we were unable to directly adjust for less common serotypes known to be associated with resistance, such as Dublin. Furthermore, substantial diversity within serotypes has been appreciated following the implementation of whole genome sequencing (WGS) [35]. Missing data for variables such as travel and race/ethnicity may have influenced the final models. Sensitivity analyses classifying unknown travel status as "no travel" did not affect the statistical significance for any individual antimicrobial or other resistance combination but did alter the directionality (ie, >1.0 vs <1.0) of some aORs with non-significant confidence intervals. Resistance to some antimicrobials was rare overall and typically occurred in combination with resistance to other antimicrobials, making it difficult to isolate the impact of resistance to individual agents. An association between more severe outcomes and clinical resistance is possible and could have been missed; however, our findings suggest that if such an association is present, it is likely not a major contributor to poor outcomes. Finally, we were not able to assess resistance to agents that were not tested pheno-typically. Such resistance is generally believed to be rare based on the assessment of resistance determinants in sequenced *Salmonella* isolates [36] but could affect the classification of a small number of isolates.

CONCLUSIONS

Antimicrobial resistant *Salmonella* infections in the United States remain associated with worse clinical outcomes. However, clinical resistance alone was not associated with worse outcomes, suggesting that factors other than treatment failure, for example, strain virulence, strain source, or host factors, may be important. These findings underscore the importance of ongoing efforts to reduce and prevent transmission of resistant enteric pathogens, including interventions to limit the entry of resistant strains into the United States and the spread of resistance within agricultural, environmental, and healthcare settings. Further studies are needed to assess the direct and indirect economic costs attributed to resistant *Salmonella* and to clarify the role of host and strain factors in determining clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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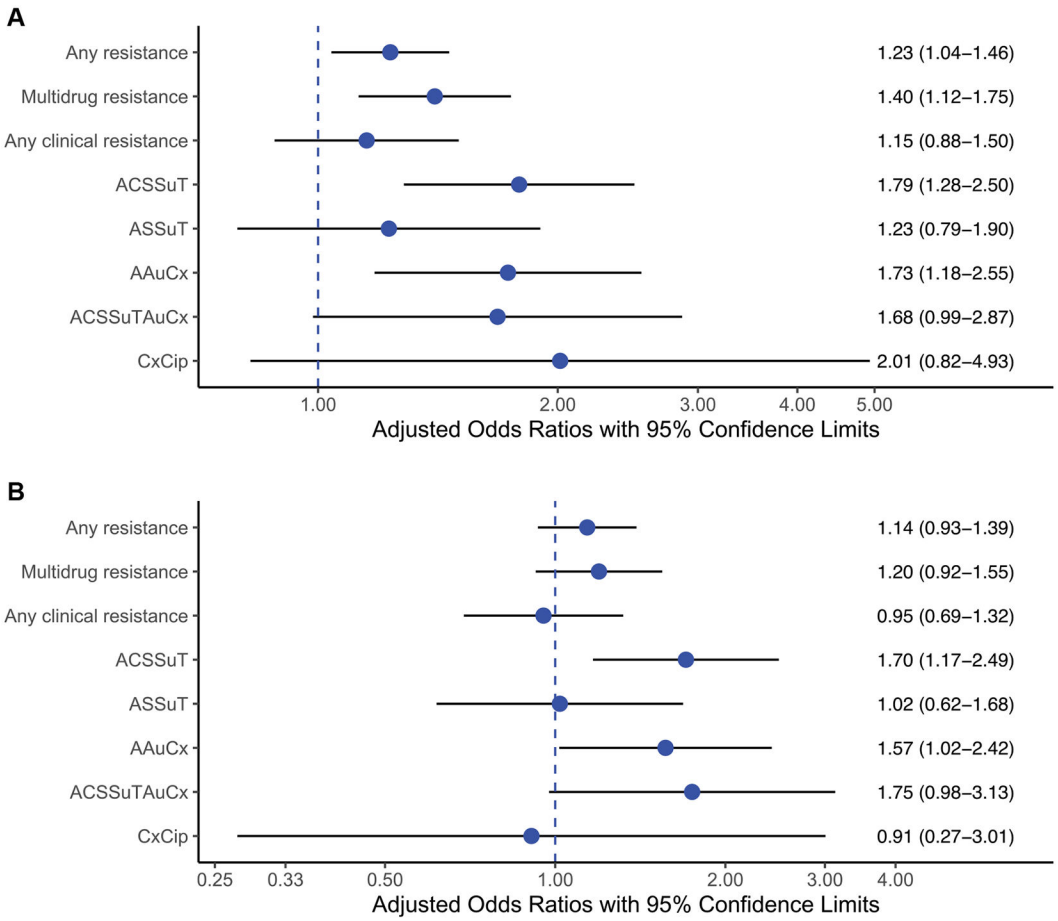

Figure 1.

Adjusted odds ratios for clinical outcomes by resistance classification compared with no resistance—Foodborne Diseases Active Surveillance Network, 10 US sites, 2004–2018. Any resistance: resistance to ≥ 1 antimicrobial; multidrug resistance: resistance to ≥ 1 antimicrobial from ≥ 3 classes (as defined by the Clinical and Laboratory Standards Institute); any clinical resistance: resistance to ≥ 1 antimicrobial among ampicillin, azithromycin, ceftriaxone, ciprofloxacin, or trimethoprim-sulfamethoxazole (with or without resistance to other agents; only isolates tested for these five agents were included in the model for clinical resistance); AAuCx: resistance to at least ampicillin, amoxicillin-clavulanic acid, and ceftriaxone; ACSSuT: resistance to at least ampicillin, chloramphenicol, streptomycin, sulfisoxazole, and tetracycline; ACSSuTAuCx: resistance to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, tetracycline, amoxicillin-clavulanic acid, and ceftriaxone; ASSuT: resistance to at least ampicillin, streptomycin, sulfamethoxazole, and tetracycline (but without resistance to chloramphenicol); CxCip: resistance to ceftriaxone and ciprofloxacin. Isolates with intermediate interpretation to ciprofloxacin were considered resistant for the above definitions. Odds ratios were adjusted for age, sex, race/ethnicity, state, international travel, outbreak status, season, serotype, and specimen source.

Table 1.

Resistance and Intermediate Susceptibility of *Salmonella* Isolates, by Antimicrobial—Foodborne Diseases Active Surveillance Network, 10 US Sites, 2004–2018 (n = 5549)

Antimicrobial Class[a] and Agents	Resistant n (%)	Intermediate n (%)
Aminoglycosides		
Amikacin[b]	1 (<0.1)	0 (0)
Gentamicin	91 (1.6)	20 (0.4)
Kanamycin[c]	81 (2.4)	2 (<0.1)
Streptomycin	629 (11.3)	N/A
B-lactam combination agents		
Amoxicillin-clavulanic acid	161 (2.9)	150 (2.7)
Cephems		
Cefoxitin	147 (2.6)	19 (0.3)
Ceftiofur[d]	115 (2.8)	4 (0.1)
Ceftriaxone	172 (3.1)	2 (<0.1)
Folate pathway antagonists		
Sulfisoxazole	619 (11.2)	N/A
Trimethoprim-sulfamethoxazole	93 (1.7)	N/A
Macrolides		
Azithromycin[e]	11 (0.3)	N/A
Penems		
Meropenem[f]	0 (0)	0 (0)
Penicillins		
Ampicillin	590 (10.6)	3 (0.1)
Phenicols		
Chloramphenicol	264 (4.8)	48 (0.9)
Quinolones		
Ciprofloxacin	18 (0.3)	216 (3.9)
Nalidixic acid	191 (3.4)	N/A
Tetracyclines		
Tetracycline	708 (12.8)	18 (0.3)

Abbreviation: N/A, not applicable (no intermediate range defined by the Clinical and Laboratory Standards Institute).

[a] Defined according to the Clinical and Laboratory Standards Institute.

[b] In total, 2406 isolates were tested for susceptibility to amikacin (2004–2010).

[c] In total, 3358 isolates were tested for susceptibility to kanamycin (2004–2013).

[d] In total, 4125 isolates were tested for susceptibility to ceftiofur (2004–2015).

[e] In total, 3179 isolates were tested for susceptibility to azithromycin (2011–2018).

[f] In total, 1424 isolates were tested for susceptibility to meropenem (2016–2018).

Table 2.

The Most Common[a] Nontyphoidal *Salmonella* Serotypes by Invasiveness and Resistance Status—Foodborne Diseases Active Surveillance Network, 10 US Sites, 2004–2018 (n = 5549)

Serotype (n)	Invasive[b] n (%)	Any Resistance[c] n (%)	Multidrug Resistance[c,d] n (%)	Clinical Resistance[c,e] n (%)
Enteritidis (1061)	79 (7.4)	166 (15.6)	28 (2.6)	98 (16.1)
Typhimurium (784)	56 (7.1)	269 (34.3)	207 (26.4)	83 (23.9)
Newport (658)	12 (1.8)	70 (10.6)	48 (7.3)	27 (7.1)
Javiana (441)	18 (4.1)	18 (4.1)	2 (0.5)	3 (1.1)
I 4, [5],12:i:- (331)	7 (2.1)	162 (48.9)	127 (38.4)	111 (56.6)
Heidelberg (161)	26 (16.1)	70 (43.5)	35 (21.7)	18 (31.0)
Infantis (142)	5 (3.5)	32 (22.5)	22 (15.5)	21 (21.7)
Saintpaul (138)	7 (5.1)	30 (21.7)	10 (7.2)	6 (9.7)
Mississippi (135)	3 (2.2)	4 (3.0)	1 (0.7)	0 (0)
Montevideo (127)	7 (5.5)	8 (6.3)	5 (3.9)	3 (5.2)
Muenchen (125)	2 (1.6)	12 (9.6)	4 (3.2)	3 (4.6)
Braenderup (103)	6 (5.8)	8 (7.8)	4 (3.9)	5 (8.1)
Paratyphi B var. L(+) tartrate+ (87)	7 (8.0)	6 (6.9)	4 (4.6)	3 (5.0)
Thompson (82)	0 (0)	4 (4.9)	3 (3.7)	2 (3.5)
Oranienburg (75)	12 (16.0)	1 (1.3)	0 (0)	0 (0)
Bareilly (65)	1 (1.5)	8 (12.3)	4 (6.2)	2 (5.0)
Agona (64)	3 (4.7)	20 (31.3)	9 (14.1)	5 (25.0)
Poona (46)	7 (15.2)	1 (2.2)	0 (0)	0 (0)
Stanley (40)	1 (2.5)	11 (27.5)	4 (10)	4 (21.1)
Hadar (37)	4 (10.8)	27 (73.0)	9 (24.3)	6 (42.9)
Other or unknown (847)	67 (7.9)	178 (21.0)	88 (10.4)	69 (16.3)
Total (5549)	330 (5.9)	1105 (19.9)	614 (11.1)	469 (15.8)

[a]Based on the rank order of serotypes from isolates included in this analysis.

[b]Includes isolate source from blood or other invasive site (eg, abscess, cerebrospinal fluid, or other normally sterile body site).

[c]Includes decreased susceptibility to ciprofloxacin.

[d]Multidrug resistance = resistance to ≥3 classes of antimicrobials (as defined by the Clinical and Laboratory Standards Institute).

[e] Clinical resistance = resistance to ≥1 of ampicillin, azithromycin, ceftriaxone, ciprofloxacin, or trimethoprim-sulfamethoxazole (n = 2969 isolates tested for these 5 agents were included in assessment of clinical resistance; percentages have been adjusted accordingly).

Table 3.

Characteristics of Patients With Nontyphoidal *Salmonella* Infections by Isolate Resistance—Foodborne Diseases Active Surveillance Network, 10 US Sites, 2004–2018 (n = 5549)

Characteristic	Total n (%)[a]	No Resistance n (%)[a]	Any Resistance[b] n (%)[a]	*P* Value[c]
Total patients	5549	4444	1105	—
Age group	…	…	…	.65
<5 y	1301 (23.4)	1058 (23.8)	243 (22.0)	…
5–17 y	874 (15.7)	696 (16.1)	178 (16.1)	…
18–64 y	2616 (47.1)	2088 (47.8)	528 (47.8)	…
≥65 y	758 (13.7)	602 (14.0)	155 (14.0)	…
Sex	…	…	…	.22
Female	2919 (52.6)	2356 (53.0)	563 (51.0)	…
Male	2627 (47.4)	2086 (47.0)	541 (49.0)	…
Race/ethnicity	…	…	…	**<.01**
White, non-Hispanic	3046 (66.7)	2491 (68.4)	555 (60.0)	**…**
Black, non-Hispanic	605 (13.2)	462 (12.7)	143 (15.5)	**…**
Hispanic or Latino[d]	569 (12.5)	444 (12.2)	125 (13.5)	…
Asian, non-Hispanic[e]	215 (4.7)	144 (4.0)	71 (7.7)	…
AI/AN (any ethnicity)	57 (1.2)	47 (1.3)	10 (1.1)	…
Multiple race, non-Hispanic	43 (0.9)	30 (0.8)	13 (1.4)	…
Other race, non-Hispanic	33 (0.7)	25 (0.7)	8 (0.9)	…
Outbreak-associated	…	…	…	**.03**
Yes	754 (13.6)	626 (14.1)	128 (11.6)	…
No	4795 (86.4)	3818 (85.9)	977 (88.4)	…
Travel-associated	…	…	…	**<.01**
Yes	426 (9.6)	277 (7.9)	149 (16.4)	**…**
Africa	28 (4.9)	21 (7.6)	7 (4.7)	.25
Asia	81 (19.0)	32 (11.6)	49 (32.9)	**<.01**
Canada	5 (1.2)	5 (1.8)	0 (0)	.17
Caribbean	82 (25.2)	52 (18.8)	30 (20.1)	.73
Central America	24 (5.6)	19 (6.9)	5 (3.4)	.14

Characteristic	Total n (%)[a]	No Resistance n (%)[a]	Any Resistance[b] n (%)[a]	*P* Value[c]
Europe	45 (10.5)	35 (12.6)	10 (6.7)	.06
Mexico	128 (30.0)	94 (33.9)	34 (22.8)	**.02**
South America	15 (3.5)	10 (3.6)	5 (3.4)	.89
Other/unknown	25 (5.9)	15 (5.4)	10 (6.7)	.10
No	4009 (90.4)	3251 (92.1)	758 (83.6)	…
Fever [f]	…	…	…	.39
Yes	1598 (67.7)	1272 (68.2)	326 (66.1)	…
No	761 (33.3)	594 (31.8)	167 (33.9)	…
Diarrhea [f]	…	…	…	.74
Yes	2370 (92.0)	1862 (91.9)	506 (92.3)	…
No	206 (8.0)	164 (8.1)	42 (7.7)	…
Bloody diarrhea [f]	…	…	…	.97
Yes	866 (36.0)	683 (36.0)	183 (35.9)	…
No	1542 (64.0)	1215 (64.0)	327 (64.1)	…
Isolate source	…	…	…	**<.01**
Blood	310 (5.6)	206 (4.6)	104 (9.4)	…
Urine	319 (5.7)	252 (5.7)	67 (6.1)	…
Stool	4857 (87.5)	3941 (88.7)	916 (82.9)	…
Other invasive	20 (0.4)	14 (0.3)	6 (0.5)	…
Other non-invasive[g]	43 (0.8)	31 (0.7)	12 (1.1)	…

Abbreviation: AI/AN, American Indian/Alaskan Native.

[a]Percentages sum to 100% within columns under each bolded subheading. Percentages were calculated excluding missing data; variables with >5% missing data include race/ethnicity (17.7% missing), travel (20.1% missing), and symptoms (18.1%–24.9% missing during 2011–2018).

[b]Includes intermediate interpretation to ciprofloxacin.

[c]The *P* values reflect comparisons of proportions in the columns labeled “No resistance” and “Any resistance.” A value of <.05 was considered statistically significant (bold font).

[d]Excludes patients who reported race as American Indian/Alaskan Native.

[e]Includes 212 patients who reported race as Asian and 3 patients who reported race as Pacific Islander.

[f]Symptoms were reported for 2011–2018 only (total n = 3143 for those years).

[g] Includes unknown source.

Table 4.

Clinical Outcomes by Isolate Resistance Category Compared With No Resistance—Foodborne Diseases Active Surveillance Network, 10 S Sites, 2004–2018 (n = 5549)

Resistance Category (n)	Hospitalization n/d (%)	*P* Value	Length of Hospital Stay ≥ 3 D n/d (%)	*P* Value	Death n/d (%)	*P* Value
No resistance (n = 4444)	1229 (28)	Ref	728 (16)	Ref	17 (0.4)	Ref
Any resistance[a] (n = 1105)	347 (31)	**.01**	216 (20)	**.01**	11 (1)	**.01**
Multidrug resistance[b] (n = 614)	209 (34)	**<.01**	130 (21)	**<.01**	4 (0.7)	.31
Clinical resistance[c] (n = 469)	141 (30)	.42	77 (16)	.70	3 (0.6)	.22
Resistance to classes and agents						
Any aminoglycoside (n = 668)	220 (33)	**<.01**	139 (21)	**<.01**	5 (0.7)	.18
Gentamicin (n = 91)	22 (24)	.46	12 (13)	.41	0 (0)	1.00
Kanamycin (n = 81)	25 (31)	.52	15 (19)	.61	1 (1)	.28
Streptomycin (n = 629)	210 (33)	**<.01**	136 (22)	**<.01**	5 (0.8)	.14
Any cephem (n = 176)	68 (39)	**<.01**	45 (26)	**<.01**	1 (0.6)	.50
Cefoxitin (n = 147)	61 (42)	**<.01**	42 (29)	**<.01**	1 (0.7)	.44
Ceftiofur (n = 115)	43 (37)	**<.01**	33 (29)	**<.01**	1 (0.9)	.37
Ceftriaxone (n = 172)	66 (38)	**<.01**	43 (25)	**<.01**	1 (0.6)	.50
Any folate pathway inhibitor (n = 620)	205 (33)	**<.01**	129 (21)	**<.01**	5 (0.8)	.13
Sulfisoxazole (n = 619)	205 (33)	**<.01**	129 (21)	**<.01**	5 (0.8)	.13
TMP-SMX (n = 93)	23 (25)	.53	12 (13)	.34	2 (2)	.06
Any quinolone (n = 242)	70 (29)	.67	41 (17)	.82	5 (2)	**<.01**
Ciprofloxacin (n = 234)	64 (27)	.92	37 (16)	.82	5 (2)	**<.01**
Nalidixic acid (n = 191)	51 (27)	.77	29 (15)	.66	4 (2)	**<.01**
Ampicillin (n = 590)	208 (35)	**<.01**	133 (23)	**<.01**	4 (0.7)	.30
Amoxicillin-clavulanic acid (n = 161)	63 (39)	**<.01**	43 (27)	**<.01**	1 (0.6)	.47
Chloramphenicol (n = 264)	99 (38)	**<.01**	65 (25)	**<.01**	3 (1)	.10
Tetracycline (n = 708)	229 (32)	**.01**	143 (20)	**.01**	5 (0.7)	.21
Resistance patterns						
ACSSuT[d] (n = 226)	92 (41)	**<.01**	62 (27)	**<.01**	3 (1)	.07
ASSuT[e] (n = 157)	48 (31)	.42	31 (20)	.26	1 (0.6)	.47

Resistance Category (n)	Hospitalization n/d (%)	*P* Value	Length of Hospital Stay ≥ 3 D n/d (%)	*P* Value	Death n/d (%)	*P* Value
AAuCx[f] (n = 150)	60 (40)	**<.01**	40 (27)	**<.01**	1 (0.7)	.45
ACSSuTAuCx[g] (n = 32)	32 (41)	**.01**	23 (29)	**<.01**	1 (3)	.12
CxCip[h] (n = 28)	10 (36)	.34	4 (14)	.51	0 (0)	1.00

Boldface indicates a significant *P* value (<.05).

Abbreviation: ACSSuT, resistance to at least ampicillin, chloramphenicol, streptomycin, sulfisoxazole, and tetracycline; ASSuT, resistance to at least ampicillin, streptomycin, sulfamethoxazole, and tetracycline (but without resistance to chloramphenicol); AAuCx, resistance to at least ampicillin, amoxicillin-clavulanic acid, and ceftriaxone; ACSSuTAuCx, resistance to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, tetracycline, amoxicillin-clavulanic acid, and ceftriaxone; Any resistance, resistance to ≥1 antimicrobial; Any clinical resistance, resistance to ≥1 antimicrobial among ampicillin, azithromycin, ceftriaxone, ciprofloxacin, or trimethoprim-sulfamethoxazole (with or without resistance to other agents); only isolates tested for these five agents were included in the model for clinical resistance; CxCip, resistance to ceftriaxone and ciprofloxacin; Multidrug resistance, resistance to ≥1 antimicrobial from ≥3 classes (as defined by the Clinical and Laboratory Standards Institute); TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Includes intermediate interpretation to ciprofloxacin.

[b] Resistance to ≥3 antimicrobial classes as defined by the Clinical and Laboratory Standards Institute (intermediate interpretation to ciprofloxacin is considered resistance).

[c] Resistance to 1 or more antimicrobials among ampicillin, azithromycin, ceftriaxone, ciprofloxacin (or intermediate interpretation), and trimethoprim-sulfamethoxazole (antimicrobials recommended for treatment of salmonellosis); n = 2969 isolates were included in this analysis.

[d] Resistance to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline (with or without resistance to other agents).

[e] Resistance to ampicillin, streptomycin, sulfamethoxazole, and tetracycline (without resistance to chloramphenicol and with or without resistance to other agents).

[f] Resistance to ampicillin, amoxicillin-clavulanic acid, and ceftriaxone (with or without resistance to other agents).

[g] Resistance to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, tetracycline, amoxicillin-clavulanic acid, and ceftriaxone (with or without resistance to other agents).

[h] Resistance to ceftriaxone and resistance or intermediate interpretation to ciprofloxacin (with or without resistance to other agents).