MAJOR ARTICLE

Highly Resistant *Salmonella* Newport-MDRAmpC Transmitted through the Domestic US Food Supply: A FoodNet Case-Control Study of Sporadic *Salmonella* Newport Infections, 2002–2003

Jay K. Varma,[1,2] Ruthanne Marcus,[5] Sara A. Stenzel,[6] Samir S. Hanna,[7] Sharmeen Gettner,[8] Bridget J. Anderson,[9] Tameka Hayes,[3] Beletshachew Shiferaw,[10] Tessa L. Crume,[11] Kevin Joyce,[2] Kathleen E. Fullerton,[2,4] Andrew C. Voetsch,[2] and Frederick J. Angulo[2]

[1]Epidemic Intelligence Service and [2]Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, Centers for Disease Control and Prevention, and [3]Georgia Department of Health and [4]Atlanta Research and Education Foundation, Atlanta; [5]Connecticut Emerging Infections Program, New Haven; [6]Minnesota Department of Health, Minneapolis; [7]Tennessee Department of Health, Nashville; [8]California Emerging Infections Program, Oakland; [9]New York Department of Health, Albany; [10]Oregon Department of Human Services, Portland; [11]Colorado Department of Public Health and Environment, Denver

Background. A new multidrug-resistant (MDR) strain of *Salmonella* serotype Newport, Newport-MDRAmpC, has recently emerged. We sought to identify the medical, behavioral, and dietary risk factors for laboratory-confirmed *Salmonella* Newport infection, including that with Newport-MDRAmpC.

Methods. A 12-month population-based case-control study was conducted during 2002–2003 in 8 sites of the Foodborne Diseases Active Surveillance Network (FoodNet), with 215 case patients with *Salmonella* Newport infection and 1154 healthy community control subjects.

Results. Case patients with Newport-MDRAmpC infection were more likely than control subjects to have taken an antimicrobial agent to which Newport-MDRAmpC is resistant during the 28 days before the onset of diarrheal illness (odds ratio [OR], 5.0 [95% confidence interval {CI}, 1.6–16]). Case patients with Newport-MDRAmpC infection were also more likely to have eaten uncooked ground beef (OR, 7.8 [95% CI, 1.4–44]) or runny scrambled eggs or omelets prepared in the home (OR, 4.9 [95% CI, 1.3–19]) during the 5 days before the onset of illness. International travel was not a risk factor for Newport-MDRAmpC infection but was a strong risk factor for pansusceptible *Salmonella* Newport infection (OR, 7.1 [95% CI, 2.0–24]). Case patients with pansusceptible infection were also more likely to have a frog or lizard in their household (OR, 2.9 [95% CI, 1.1–7.7]).

Conclusions. Newport-MDRAmpC infection is acquired through the US food supply, most likely from bovine and, perhaps, poultry sources, particularly among persons already taking antimicrobial agents.

An estimated 1.4 million *Salmonella* infections occur annually in the United States [1]. Infections usually result in self-limited gastroenteritis that does not require antimicrobial therapy. However, invasive infections can occur, and physicians frequently prescribe antimicrobial agents for patients with severe gastroenteritis. Therapy with third-generation cephalosporins (e.g., ceftriaxone) or fluoroquinolones (e.g., ciprofloxacin) may be lifesaving for persons with extraintestinal infection or who are at high risk for complications from *Salmonella* infection [2, 3].

The prevalence of antimicrobial resistance among *Salmonella* strains has increased over the past 20 years [4–7]. For example, a multidrug-resistant (MDR) strain of *Salmonella* serotype Typhimurium, definitive type 104 (DT104), emerged during the 1990s [8]. Infection with MDR *Salmonella* Typhimurium DT104 results in greater morbidity and mortality than does infection with other *Salmonella* strains [9, 10]. National surveil-

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Reprints or correspondence: Dr. Frederick J. Angulo, Centers for Disease Control and Prevention, Mailstop D63, 1600 Clifton Rd., Atlanta, GA 30333 (fangulo@cdc.gov).

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lance has recently detected *Salmonella* strains that are resistant to extended-spectrum cephalosporins, with resistance mediated by a transferable plasmid containing an *ampC* (bla_{CMY}) β-lactamase gene [11, 12]. One such strain is *Salmonella* Newport-MDRAmpC, which exhibits decreased susceptibility to ceftriaxone, resistance to 8 other antimicrobial agents that are used in human medicine (ampicillin, amoxicillin/clavulanic acid, cephalothin, cefoxitin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline), and resistance to 1 other antimicrobial agent, a third-generation cephalosporin, that is used in veterinary medicine (ceftiofur) [13].

In recent years, *Salmonella* Newport infections have become more common due, in part, to the emergence of Newport-MDRAmpC. In 1996, *Salmonella* Newport represented 5% of *Salmonella* infections in humans in the United States; by 2003, it represented 12% of all reported *Salmonella* infections [14, 15]. From 1996 to 2001, Newport-MDRAmpC became widely disseminated, resulting in an estimated 28,000 infections in the United States during 2001 [13]. In 2002, 22% of *Salmonella* Newport isolates tested in national surveillance were found to be MDRAmpC [7]. Controlling *Salmonella* Newport, particularly Newport-MDRAmpC, has become an important food-safety issue [16], because of the increasing incidence of infection, emerging resistance to third-generation cephalosporins (which severely restricts treatment options, particularly for children), and the presence of resistance genes on a plasmid that can readily be transferred to other bacteria [17]. Epidemiological investigations, including outbreak investigations, have implicated contact with dairy cattle and consumption of ground beef, ground horse meat, and cheeses made from nonpasteurized milk as sources of Newport-MDRAmpC infection [13, 18–20]. The vast majority of Newport-MDRAmpC infections, however, are sporadic and do not occur as outbreaks. We performed a case-control study to determine the medical, behavioral, and dietary risk factors for laboratory-confirmed *Salmonella* Newport infections, including with Newport-MDRAmpC, that are not associated with outbreaks.

METHODS

Surveillance. Initiated in 1996 as part of the Emerging Infections Program of the Centers for Disease Control and Prevention (CDC), the Foodborne Diseases Active Surveillance Network (FoodNet) conducts surveillance and epidemiological studies in collaboration with selected state health departments, the US Department of Agriculture's Food Safety and Inspection Service, and the US Food and Drug Administration (FDA) [21]. At the time of the present study, FoodNet was conducting active surveillance for laboratory-confirmed *Salmonella* infection in >450 clinical laboratories located in all or part of 9 states: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New York, Oregon, and Tennessee. The population under surveillance was 37.9 million in 2002 and 41.5 million in 2003.

Enrollment of case patients. From 2002 through 2003, 8 of 9 FoodNet sites attempted to enroll patients with laboratory-confirmed *Salmonella* Newport infection in a case-control study. Although sites began this study at different times in 2002, each site enrolled patients for 12 consecutive months. In Georgia, which reports the largest number of cases of *Salmonella* infection to FoodNet of any site, we attempted to enroll every second or third case patient, depending on the county of residence; in the other 7 sites, we attempted to enroll all eligible case patients. We excluded patients from enrollment if they were <1 year of age; did not have a telephone number available or could not be reached either after 15 attempts by telephone or within 45 days of the specimen-collection date; did not speak English or Spanish; did not report diarrheal illness; had a household member with diarrhea whose illness had onset during the 28 days before that of the patient (making it a possible secondary case); or were part of a recognized outbreak. For the study, we defined an outbreak as the occurrence $\geqslant$2 ill persons with laboratory-confirmed *Salmonella* Newport infection in which a public health investigation identified a common source of infection.

Isolates of *Salmonella* Newport were sent to the CDC's National Antimicrobial Resistance Monitoring System for Enteric Bacteria laboratory for broth microdilution antimicrobial-susceptibility testing (Sensititre; TREK Diagnostic Systems). The partial-range MIC was determined for 16 antimicrobial agents: amikacin, ampicillin, amoxicillin-clavulanic acid, cefoxitin, ceftiofur, ceftriaxone, cephalothin, chloramphenicol, ciprofloxacin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfamethoxazole, tetracycline, and trimethoprim-sulfamethoxazole. When available, interpretive criteria from the Clinical and Laboratory Standards Institute were used [22]. Ceftiofur resistance was defined as $\geqslant$8 μg/mL.

For the study, we defined a case of *Salmonella* Newport infection as Newport-MDRAmpC if the patient's isolate had decreased susceptibility to ceftriaxone (MIC, $\geqslant$16 μg/mL) and resistance to ampicillin, amoxicillin/clavulanic acid, cefoxitin, ceftiofur, cephalothin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline. We defined a case of *Salmonella* Newport infection as pansusceptible if the patient's isolate was susceptible to all antimicrobial agents tested.

Enrollment of control subjects. Control subjects were persons $\geqslant$1 year of age who were living in the participating FoodNet sites and were identified by a professional survey company using a multistage, random-digit telephone-dialing methodology similar to that used in the CDC's Behavioral Risk Factor Surveillance Surveys [23, 24]. Control subjects were eligible for enrollment if they lived in a catchment area of the FoodNet study, spoke either English or Spanish, and reported not having had diarrhea during

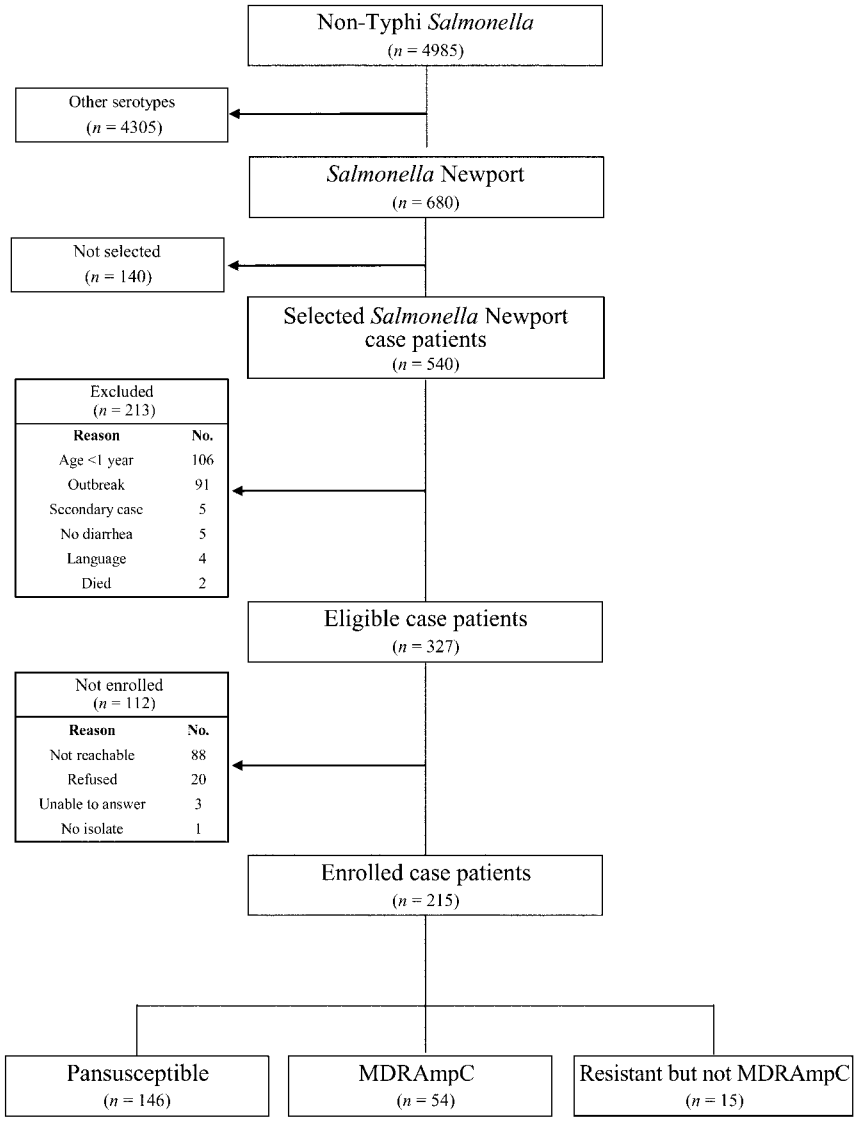

Figure 1. Ascertainment and enrollment of case patients with *Salmonella* Newport infection. MDRAmpC is a strain of *Salmonella* Newport that exhibits decreased susceptibility to ceftriaxone, resistance to 8 other antimicrobial agents that are used in human medicine (ampicillin, amoxicillin/clavulanic acid, cephalothin, cefoxitin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline), and resistance to 1 other antimicrobial agent, a third-generation cephalosporin, that is used in veterinary medicine (ceftiofur).

the 28 days before the interview. We attempted to enroll at least 10 control subjects per site per month.

Study instrument. We used a standardized questionnaire to collect data on medical history, medication use, and food, drink, and environmental exposures. For dietary and environmental variables, we asked about the 5 days before the onset of diarrhea (defined as ⩾3 loose stools in a 24-h period) for case patients or the 5 days before the interview for control subjects. After obtaining informed consent, study personnel administered the questionnaire to subjects over the telephone. If the subject was <12 years of age, the person most familiar with the subject's dietary habits, usually a parent, was interviewed. For case patients, we attempted to verify the names of antimicrobial agents taken. If the patient could not remember the name of an antimicrobial agent taken before the onset of diarrhea, we contacted the patient's physician(s) to confirm the name of and indication for the prescribed agent.

Statistical analysis. We compared case patients with Newport-MDRAmpC infection and those with pansusceptible *Salmonella* Newport infection with control subjects, excluding from the analysis cases of *Salmonella* Newport infection in which the isolate was resistant to ⩾1 antimicrobial agent but did not meet the criteria for Newport-MDRAmpC. In bivariate analysis, we compared proportions by use of the χ^2 test or, when appropriate, Fisher's exact test, and we compared continuous variables by use of the Wilcoxon rank-sum test. Sta-

Table 1. Resistance among *Salmonella* Newport-MDRAmpC isolates and among non-MDRAmpC isolates.

Antimicrobial-resistance pattern	Resistant isolates, no. (%)
Newport-MDRAmpC (n = 54)	
Ceftriaxone	4 (7)
Gentamicin	5 (9)
Kanamycin	9 (17)
Trimethoprim-sulfamethoxazole	10 (19)
Resistant but not MDRAmpC (n = 15)	
Amikacin	0 (0)
Ampicillin	8 (53)
Amoxicillin-clavulanate	2 (13)
Ceftriaxone	0 (0)
Cephalothin	2 (13)
Chloramphenicol	5 (33)
Ciprofloxacin	0 (0)
Gentamicin	1 (7)
Kanamycin	2 (13)
Nalidixic acid	0 (0)
Streptomycin	10 (67)
Sulfamethoxazole	11 (73)
Tetracycline	10 (67)
Trimethoprim-sulfamethoxazole	0 (0)
R-type ACSSuT	3 (20)

NOTE. MDR, multidrug resistant; R-type ACSSuT, resistance to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline.

tistical significance was defined as $P < .05$. In multivariate analysis, we first created separate unconditional logistic regression models to estimate the odds of illness for case patients with Newport-MDRAmpC infection and those with pansusceptible infection compared with control subjects, adjusting for study site and age group. We constructed candidate models using variables that were significant in bivariate analysis or were of strong a priori interest regardless of statistical significance. A final, polytomous model was created to include foodborne and nonfoodborne risk factors identified for case patients with Newport-MDRAmpC infection and those with pansusceptible infection [25]. To account for missing data resulting from unanswered questions about chicken consumption among case patients, we performed multiple imputation for case patients and control subjects. We used the PROC MI procedure in SAS (version 9.1; SAS Institute) to create 10 imputed data sets. In each data set, we used variables from the final Newport-MDRAmpC logistic regression model as predictors to impute a value for the chicken-consumption variable. We used the MI ANALYZE procedure to combine these 10 data sets for estimation of odds ratio (ORs) and 95% confidence intervals (CIs). Population-attributable fractions were calculated according to the method of Bruzzi et al. [26].

Ethics review. The present study was approved by the human subject research committees at the CDC and all participating sites.

RESULTS

Enrollment of case patients. We ascertained 4985 case patients with non-Typhi *Salmonella* infection over the 12 months, 680 (14%) of whom were infected with serotype Newport. Georgia selected and attempted to enroll 108 (44%) of 248 case patients; other states selected all case patients. Of the 540 selected case patients, 213 (39%) were excluded because they were not eligible for the study (figure 1). Of the excluded case patients, 106 (50%) were <1 year of age, 91 (43%) had infections that were outbreak associated, 5 (2%) had possible secondary cases, 5 (2%) did not have diarrhea, 4 (2%) did not speak English or Spanish, and 2 (1%) had died.

Four outbreaks accounted for the 91 case patients excluded because of an outbreak association: 1 outbreak of Newport-MDRAmpC infection involving 4 case patients and 3 outbreaks of pansusceptible *Salmonella* Newport infection involving 87 case patients. In the Newport-MDRAmpC outbreak, the suspected vehicle was cilantro. In 2 of the pansusceptible outbreaks, the vehicles were tomatoes (71 case patients) and honeydew melons (6 case patients); in the third pansusceptible outbreak (10 case patients), no vehicle was implicated, but the outbreak occurred in a restaurant in which public health officials identified multiple possible routes of transmission, including infected food workers and contaminated food.

Of the 327 case patients with *Salmonella* Newport infection who were eligible for the study, 215 (66%) were enrolled. Of the 112 eligible case patients who were not enrolled, 88 (79%) could not be contacted, 20 (18%) refused, 3 (3%) were unable to answer questions, and 1 (1%) had no isolate available for susceptibility testing. The median age of enrolled case patients (31 years; range, 1–87 years) was greater than the median age of nonenrolled case patients (23 years; range, 1–92 years) ($P = .01$). More enrolled case patients (61%) were female, compared with nonenrolled case patients (47%) (OR, 1.7 [95% CI, 1.1–2.7]). There were no significant differences in race/ethnicity. Enrolled and nonenrolled case patients were equally likely to be hospitalized, to have a bloodstream isolate, and to die.

Of 215 isolates from enrolled case patients, 146 (68%) were pansusceptible, 54 (25%) were Newport-MDRAmpC (some had additional resistance), and 15 (7%) had other susceptibility patterns (table 1).

Enrollment of control subjects. Study personnel attempted 11,600 telephone calls and successfully enrolled 1154 control subjects. The response rate, calculated according to the standards of the Council of American Survey Research Organizations [27], was 26%, with an upper bound of 31% and lower bound of 10%.

Demographics and medical conditions. Compared with the

Table 2. Selected demographic and medical characteristics of case patients and control subjects.

Characteristic	Case patients		Control subjects (n = 1154)
	MDRAmpC infection (n = 54)	Pansusceptible infection (n = 146)	
Female sex	33 (61)	86 (59)	683 (59)
Age, median (range), years	40 (1–86)	29 (1–87)	43 (1–98)
Race/ethnicity			
White	35 (65)	111 (76)	937 (81)
Black/African American	4 (7)	20 (14)	87 (8)
Hispanic	11 (20)	9 (6)	58 (5)
Asian	2 (4)	6 (4)	45 (4)
American Indian or Alaskan Native	1 (2)	0 (0)	5 (1)
Other or unknown	1 (2)	0 (0)	22 (2)
High school education or less	9 (17)	9 (6)	59 (5)
Residence in urban area	23 (43)	48 (33)	436 (38)
Income <$30,000/year	15 (28)	28 (19)	230 (20)
Immune suppression	10 (19)	17 (12)	123 (11)
Insulin-requiring diabetes[a]	4 (40)	1 (6)	21 (17)
End-stage renal disease[a]	0 (0)	0 (0)	1 (1)
Organ transplant[a]	1 (10)	2 (12)	2 (2)
Cancer[a]	3 (30)	5 (29)	40 (33)
Lupus[a]	0 (0)	2 (12)	4 (3)
HIV/AIDS[a]	0 (0)	0 (0)	3 (2)
Oral steroid use[a]	3 (30)	6 (35)	19 (16)
Other nonsteroid immune-suppressant use[a]	1 (10)	2 (12)	4 (3)
Cancer chemotherapy[a]	2 (20)	1 (6)	4 (3)
Radiation therapy[a]	0 (0)	1 (6)	1 (1)
Isolate source			
Feces	50 (93)	140 (96)	NA
Blood	1 (2)	3 (2)	NA
Other	3 (6)	3 (2)	NA
Hospitalized	18 (33)	48 (33)	NA

NOTE. Data are no. (%) of case patients or control subjects, unless otherwise indicated. MDR, multidrug resistant; NA, not available or not applicable.

[a] Medical conditions included in the definition of immune suppression. Numerators reflect the fact that persons could report >1 medical condition.

control subjects, the case patients with Newport-MDRAmpC infection had similar age and sex distributions but were more likely to be Hispanic (OR, 4.8 [95% CI, 2.4–9.8]) and to have only a high school education or less (OR, 3.2 [95% CI, 1.6–6.2]) (table 2). More case patients with Newport-MDRAmpC infection than control subjects had an annual income <$30,000 (OR, 1.9 [95% CI, 0.99–3.7]) and an immune-suppressing medical condition (OR, 1.9 [95% CI, 0.94–3.9]), but the differences were not statistically significant. Unlike the case patients with Newport-MDRAmpC infection, the case patients with pansusceptible infection were younger than the control subjects ($P < .01$). The demographic and medical characteristics of the case patients with pansusceptible infection were similar to those of the control subjects, except that those with pansusceptible infection were more likely to be black/African American (OR, 2.1 [95% CI, 1.3–3.6]).

Risk factor analysis. Eight variables were included in the final multivariate model: 1 lifetime exposure (had or have a stomach ulcer), 1 exposure during the 28 days before the onset of diarrheal illness (took an antimicrobial agent to which Newport-MDRAmpC is resistant), and 6 exposures during the 5 days before the onset of illness (ate Mexican-style cheese; ate runny scrambled eggs or omelets prepared in the home; ate uncooked ground beef; ate chicken; had a frog or lizard in the household; and traveled internationally).

The strongest nondietary risk factor for Newport-MDRAmpC infection was taking an antimicrobial agent to which Newport-MDRAmpC is resistant during the 28 days before the onset of illness (OR, 5.0 [95% CI, 1.6–16]) (table 3). Of the 11 case patients with Newport-MDRAmpC infection who took an antimicrobial agent during this time, 8 took agents to which

Table 3. Polytomous multivariate logistic regression analysis of risk factors for Newport-MDRAmpC ($n = 54$) and pansusceptible *Salmonella* Newport ($n = 146$) infection, adjusted for age.

Exposure	Control subjects	Newport-MDRAmpC infection			Pansusceptible infection		
		Case patients	OR (95% CI)	PAF, %	Case patients	OR (95% CI)	PAF, %
Ever had a stomach ulcer	45/1152 (4)	2/51 (4)	1.6 (0.4–7.0)	2.0	16/145 (11)	4.1 (1.9–8.5)	8.6
Took an agent to which Newport-MDRAmpC is resistant[a]	28/1154 (2)	7/54 (13)	5.0 (1.6–16)	8.4	2/146 (1)	0.7 (0.1–3.0)	…
Ate Mexican-style cheese[b]	46/1148 (4)	7/53 (13)	2.2 (0.7–7.1)	5.7	3/138 (2)	0.6 (0.2–2.0)	…
Ate runny scrambled eggs or omelets prepared in the home[b]	18/1144 (2)	4/50 (8)	4.9 (1.3–19)	6.3	3/119 (3)	2.3 (0.7–8.3)	1.7
Ate uncooked ground beef[b]	8/1153 (1)	2/52 (4)	7.8 (1.4–44)	4.6	2/137 (2)	1.4 (0.2–12)	0.3
Ate chicken[b]	802/1139 (70)	38/46 (83)	2.4 (1.0–5.6)	47.6	89/123 (72)	1.3 (0.8–2.1)	17.1
Had a frog or lizard in the household[b]	22/1153 (2)	1/54 (2)	1.2 (0.2–9.8)	0.4	7/143 (5)	2.9 (1.1–7.7)	4.1
Traveled internationally[b]	10/1153 (1)	1/54 (2)	2.9 (0.3–28)	1.7	8/146 (6)	7.1 (2.0–24)	3.5

NOTE. Data are proportion (%) of case patients or control subjects with a given exposure who developed diarrheal illness, unless otherwise indicated. CI, confidence interval; MDR, multidrug resistant; OR, odds ratio; PAF, population-attributable fraction (calculated only for variables with an adjusted OR >1).

[a] During the 28 days before the onset of illness.

[b] During the 5 days before the onset of illness.

the isolate was resistant, 7 took agents to which Newport-MDRAmpC was resistant, and 1, who took trimethoprim-sulfamethoxazole, had a Newport-MDRAmpC isolate that was additionally resistant to that agent (table 4). Six of the 11 patients with Newport-MDRAmpC infection who were taking antimicrobial agents reported the day they began antimicrobial therapy. For these 6 patients, the median time between the initiation of antimicrobial therapy and the onset of illness was 14 days (range, 0–26 days); 3 (50%) began antimicrobial therapy during the week before the onset of illness. Eight of the 11 patients reported the last day they took antimicrobial agents; 6 (75%) were taking antimicrobial agents at the onset of illness, and 2 (25%) stopped taking antimicrobial agents ⩾2 weeks before the onset of illness. The 1 case patient with Newport-MDRAmpC infection who had traveled outside the United States during the 5 days before the onset of illness reported visiting Puerto Rico, the Virgin Islands, and Martinique.

The strongest dietary risk factors for Newport-MDRAmpC infection were eating uncooked ground beef (OR, 7.8 [95% CI, 1.4–44]) and eating runny scrambled eggs or omelets prepared in the home (OR, 4.9 [95% CI, 1.3–19]) during the 5 days before the onset of illness (table 3). Eating chicken during the 5 days before the onset of illness was also associated with Newport-MDRAmpC infection (OR, 2.4; [95% CI, 1.0–5.6]). Because only 46 of the 54 case patients with Newport-MDRAmpC infection could affirm whether they had eaten chicken during this time, we performed multiple imputation for the case patients and control subjects with missing information on chicken consumption. After imputation for this one variable, the point estimate for chicken consumption in polytomous multivariate logistic regression analysis remained elevated, but the 95% CI widened (adjusted OR, 2.1 [95% CI, 0.9–5.2]). Eating Mexican-style cheese during the 5 days before the onset of illness was also more common among case patients than control subjects but was not statistically significant.

None of the factors associated with Newport-MDRAmpC infection were associated with pansusceptible *Salmonella* Newport infection in multivariate polytomous logistic regression analysis. The strongest risk factor for pansusceptible infection was traveling outside the United States during the 5 days before the onset of illness (OR, 7.1 [95% CI, 2.0–24]). The 8 case patients with pansusceptible infection who traveled internationally visited Belize, Canada, China, India, Mexico (3 patients), and the Philippines. Other independent risk factors for pansusceptible *Salmonella* Newport infection in multivariate analysis included self-reported history of a stomach ulcer (OR, 4.1 [95% CI, 1.9–8.5]) and household exposure to a frog or lizard (OR, 2.9 [95% CI, 1.1–7.7]).

DISCUSSION

In the present study, we found that Newport-MDRAmpC infections in the United States were acquired domestically, most likely through beef, egg, or chicken consumption, suggesting a bovine and, perhaps, a poultry reservoir. Illness occurred disproportionately in persons taking antimicrobial agents for reasons not related to gastroenteritis.

International travel is an important risk factor for *Salmonella* and *Campylobacter* infection among US residents [28–30]. In our study, international travel was the strongest risk factor for pansusceptible *Salmonella* Newport infection, accounting for an estimated 3.5% of sporadic pansusceptible *Salmonella* Newport infections. In contrast, infection with Newport-MDRAmpC, the highly resistant *Salmonella* strain, was not associated with inter-

Table 4. Antimicrobial agents used during the 28 days before the onset of diarrheal illness among case patients with Newport-MDRAmpC infection ($n = 11$).

Antimicrobial agent	Case patients, no. (%)[a]	Reasons (no. of case patients)
Amoxicillin[b]	2	Ear/sinus/throat/URI (2)
Amoxicillin/clavulanate[b]	4	Ear/sinus/URI (3), skin infection (1)
Cephalexin[b]	1	Skin infection (1)
Levofloxacin	1	Bronchitis/pneumonia (1)
Penicillin[b]	1	Postsplenectomy (1)
Trimethoprim-sulfamethoxazole	1	Prophylaxis in chemotherapy (1)
Unknown	2	Dental (1), fever (1)

NOTE. URI, upper respiratory tract infection; MDR, multidrug resistant.

[a] No. of case patients do not total 11 because 1 person took both cephalexin and amoxicillin/clavulanate during the 28 days before the onset of illness.

[b] Agent to which Newport-MDRAmpC is resistant.

national travel. Only 2 outbreaks of Newport-MDRAmpC infection have been reported outside the United States: 1 in France and 1 in Canada [20, 31]. Controlling the dissemination of Newport-MDRAmpC, therefore, should be a priority for public health officials in the United States and elsewhere. The global dissemination of DT104 during the 1980s and 1990s provides a vivid example of how a unique antimicrobial-resistant *Salmonella* strain can emerge and cause as a global epidemic within a few years [8]. The challenge is particularly urgent with Newport-MDRAmpC, because a mobile genetic element mediates resistance and can be readily transferred to other *Salmonella* strains and to other bacteria [32].

Cattle are likely a major domestic reservoir for Newport-MDRAmpC. Several lines of evidence support this conclusion and further suggest that this pathogen has become disseminated primarily among dairy cattle, rather than beef cattle. First, several outbreak investigations have implicated as vehicles ground beef and Mexican-style cheese—2 foods that were eaten more frequently by case patients than by control subjects in the present study—and 1 outbreak investigation implicated direct contact with cattle from dairy farms [13, 18, 19]. Second, outbreaks of Newport-MDRAmpC infection have caused severe illness in dairy cattle in several US states [33]. Third, ground beef purchased at grocery stores have yielded Newport-MDRAmpC (D. White [FDA], personal communication), and dairy cattle account for ~17% of the ground beef sold in the United States [34].

Controlling Newport-MDRAmpC will, therefore, require public health initiatives directed at dairy cattle, including enhanced pathogen surveillance from farm to table and additional research on mechanisms of transmission. Furthermore, because use of antimicrobial agents creates a selective pressure that facilitates dissemination of MDR *Salmonella* strains, reducing unnecessary use of antimicrobial agents may help to limit the spread of such strains. Such initiatives have recently included, for example, the Washington State Dairy Federation encouraging its members to replace milk replacers that contain antibiotics (which are fed to calves) with antibiotic-free products (R. Wohrle [Tacoma Pierce County Health Department, Antimicrobial Resistance Task Force], personal communication). The need for initiatives aimed at reducing the unnecessary use of antibiotics was recently highlighted by outbreaks of MDR *Salmonella* infections caused by contaminated ground beef that apparently had been produced from culled dairy cattle [20, 35] and a March 2005 public meeting at the Tufts School of Veterinary Medicine with representatives from public health organizations, the field of veterinary medicine, food-safety regulatory agencies, meat-industry groups, and food-safety consumer groups [36].

The association of Newport-MDRAmpC infection with the consumption of chicken and eggs suggests that these may also be sources of Newport-MDRAmpC. Further research is warranted to confirm these findings and to explore other potential sources of Newport-MDRAmpC. Neither chicken nor eggs have been previously described as a reservoir for Newport-MDRAmpC. However, Newport-MDRAmpC has been found in ground turkey purchased at grocery stores (D. White [FDA], personal communication). If Newport-MDRAmpC is found on poultry farms, then general efforts aimed at reducing the prevalence of salmonellae in poultry and egg products may also reduce transmission of Newport-MDRAmpC and any other emerging *Salmonella* strains to humans [37].

The association we found between use of an antimicrobial agent for another medical reason and subsequent Newport-MDRAmpC infection has previously been documented in outbreak investigations and studies of sporadic illness involving other MDR *Salmonella* strains [4, 30, 38, 39]. A proposed mechanism is that concomitant treatment with antimicrobial agents

to which the strain is resistant reduces the number of intestinal commensal bacteria and provides a selective advantage for resistant *Salmonella* strains to multiply and cause disease [40]. This mechanism seems likely for several of the Newport-MDRAmpC cases in our study, because three-fourths of the patients who took any antibiotics before their illness were still taking those antibiotics when their illness began. The strong and specific association between the use of antimicrobial agents and Newport-MDRAmpC infection, but not pansusceptible *Salmonella* Newport infection, suggests that exposure to antimicrobial-resistant *Salmonella* strains, rather than simply exposure to salmonellae, is a critical factor. At the population level, this phenomenon increases the number of people with *Salmonella* infection [39].

Our study also suggests that amphibians and reptiles are an important source of pansusceptible *Salmonella* Newport infection. A previous FoodNet study estimated that amphibians and reptiles cause ~74,000 *Salmonella* infections annually in the United States [41]. Because healthy amphibians and reptiles are long-term carriers of *Salmonella* organisms, environmental contamination is likely to play a major role in transmission. In our study, exposure to amphibians and reptiles in the household, but not outside the household, was associated with risk, suggesting that there were multiple opportunities for direct or indirect transmission. The CDC has published guidelines to help prevent the transmission of *Salmonella* organisms from amphibians and reptiles [42].

Our study design excluded cases associated with outbreaks. Three of the 4 outbreaks identified during the study were linked to produce, including tomatoes, honeydew melons, and cilantro—vehicles that have been implicated previously in *Salmonella* outbreaks [43–45]. In recent years, produce-related *Salmonella* outbreaks, including of pansusceptible *Salmonella* Newport infection, have been identified frequently in the United States, but our study did not find an association between produce and sporadic *Salmonella* Newport infection, suggesting that contamination of produce may occur only intermittently. The FDA has developed a plan to decrease foodborne illness associated with fresh produce [46].

Studies of sporadic foodborne illness are subject to important limitations. Patients ascertained through laboratory-based public health surveillance represent only a fraction of all cases in the population; such patients may differ from those not ascertained in surveillance. For example, physicians may be more likely to culture stool from a patient who complains of diarrhea after traveling outside the United States [47]. Unless sample sizes are extremely large, it is difficult for analytical epidemiological studies of sporadic illness to detect associations between illness and dietary exposures that are common among both case patients and control subjects. We do not believe that any of these issues threaten the validity of the present study. First, we enrolled a large number of control subjects from the base population. Second, the control subjects were demographically similar to the case patients. Where we identified potentially important differences across the groups, we controlled for these in the analysis (e.g., age) or incorporated other variables into the model that we considered to be the primary exposure (e.g., eating Mexican-style cheese, rather than Hispanic ethnicity). Third, by using a multivariate-analysis technique that permitted the modeling of multiple exposure variables for several different outcomes simultaneously, we were able to validate an important hypothesis: that the reservoirs and risk factors for pansusceptible *Salmonella* Newport infection are distinct from those for Newport-MDRAmpC infection.

Our study emphasizes the need to strengthen food-safety educational efforts among the general public about the necessity of cooking thoroughly ground beef and other raw meat and poultry products as well as the need to prevent the cross-contamination of other foods with these products. In addition, clinicians need to be informed about the increasing incidence of infection with *Salmonella* strains that are resistant to clinically important antimicrobial agents and the implications that this phenomenon has for the treatment of salmonellosis and for patients who require antimicrobial therapy for reasons other than gastroenteritis. Furthermore, public health officials need to advocate for efforts to reduce the unnecessary use of antimicrobial agents and for the implementation of additional interventions to mitigate the spread of Newport-MDRAmpC.

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