Clinical Features of Human Salmonellosis Caused by Bovine-Associated Subtypes in New York

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Abstract

The objective of this study was to identify patient symptoms and case outcomes that were more likely to occur as a result of *Salmonella* infections caused by bovine-associated subtypes (isolates that matched contemporary bovine isolates from New York by serovar and pulsed-field gel electrophoresis pattern), as compared to salmonellosis caused by non-bovine-associated subtypes. Data were collected in 34 counties of New York that comprise the Foodborne Diseases Active Surveillance Network (FoodNet) catchment area of the Centers for Disease Control and Prevention Emerging Infections Program. Patients with specimen collection dates between March 1, 2008 and March 1, 2010 were included. Symptoms and outcomes of 40 cases infected with bovine-associated *Salmonella* subtypes were compared to those of 379 control-cases infected with *Salmonella* isolates that were not bovine-associated. Cases were significantly more likely to have invasive salmonellosis (odds ratio, 3.8; p -value=0.02), after adjusting for age group, gender, and race. In addition, there was a marginal association between case status and the presence of blood in the stool (p -value=0.1) while ill. These findings might have implications for patient management, as a history of consuming undercooked foods of bovine origin or having direct contact with cattle in the few days prior to illness could be useful for suggesting a more proactive diagnostic approach as well as close monitoring for the need to implement more aggressive therapy.

Introduction

SALMONELLA ENTERICA POSES a formidable public health challenge, resulting in approximately 1.2 million illnesses, 20,000 hospitalizations, and 400 deaths annually in the United States alone (Scallan *et al.*, 2011). The economic cost of salmonellosis, including medical expenses and lost productivity, is estimated to be \$4.4 billion annually in this country (Scharff, 2012). Disease manifestations may include diarrhea, fever, anorexia, abdominal pain, vomiting, and malaise. Although clinical disease generally resolves within 3–7 days, *Salmonella* can also produce invasive infections that may be fatal. Children under the age of 5, elderly adults, and immunocompromised individuals are especially susceptible to severe disease (Sirinavin *et al.*, 1988; Chiu *et al.*, 1999; Arshad *et al.*, 2008; Jones *et al.*, 2008).

Dairy cattle are considered a key source of several *Salmonella* serovars that are a threat to human health, including multidrug-resistant *Salmonella enterica* serovar Newport and *Salmonella enterica* serovar Typhimurium (Gupta *et al.*, 2003; Dechet *et al.*, 2006; Varma *et al.*, 2006; Karon *et al.*, 2007). Foodborne transmission can occur through fecal contamina-

tion of beef carcasses at the time of slaughter (Wells *et al.*, 2001) or alternatively through contamination of crops, either by manure used as fertilizer or by manure-contaminated irrigation water (Hanning *et al.*, 2009). Milk and other dairy products pose less of a public health risk because of commercial pasteurization, although consumption of unpasteurized dairy products persists (Lejeune and Rajala-Schultz, 2009; Oliver *et al.*, 2009). Direct contact is another important route of transmission, particularly among dairy farm workers and their families, members of the veterinary profession, and individuals who interact with dairy cattle in public settings such as open farms, petting zoos, and county/state fairs (Gupta *et al.*, 2003; Karon *et al.*, 2007). Dairy cattle infected with *Salmonella* can shed organisms intermittently and for variable periods following clinically apparent (Cummings *et al.*, 2009a) or subclinical infections (Wells *et al.*, 2001; Huston *et al.*, 2002; Fossler *et al.*, 2004; Blau *et al.*, 2005). The USDA National Animal Health Monitoring System (NAHMS) Dairy 2007 study, based on a single sampling visit to 121 herds in 17 major dairy states, found that 14% of cows and 40% of herds were *Salmonella*-positive based on fecal culture results (Centers for Epidemiology and Animal Health, 2009).

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The objective of this study was to identify clinical features of human salmonellosis caused by bovine-associated subtypes, using the case-case study design (McCarthy and Giesecke, 1999). We specifically evaluated whether various patient symptoms and case outcomes were more likely to occur as a result of *Salmonella* infections caused by bovine-associated subtypes, as compared to infections caused by non-bovine-associated subtypes.

Methods

Study population

This case-case study was conducted using culture-confirmed human salmonellosis cases within the New York State Department of Health's (NYSDOH) Foodborne Diseases Active Surveillance Network (FoodNet), with specimen collection dates between March 1, 2008 and March 1, 2010. Patients were excluded if they had a typhoidal *Salmonella* infection (either Typhi or Paratyphi A). FoodNet is a core program within the Centers for Disease Control and Prevention (CDC) Emerging Infections Program (EIP) that conducts active, population- and laboratory-based surveillance for specific foodborne pathogens, including *Salmonella*. The NYS EIP catchment area includes 34 counties in the Albany, Buffalo, and Rochester areas, representing approximately 4.3 million residents.

Under Public Health Law, laboratories and physicians in New York are required to report all salmonellosis cases to local health departments (LHDs) and to submit isolates to the NYSDOH Wadsworth Center Public Health Laboratory for diagnostic confirmation and speciation. The LHDs submit all case information to the NYSDOH via a secure electronic data collection system. Within the NYS EIP, surveillance officers actively monitor clinical microbiology laboratories and contact LHDs in order to ascertain all laboratory-confirmed salmonellosis cases, and they review case reports for accuracy and completeness.

Laboratory methods

Serotyping and pulsed-field gel electrophoresis (PFGE) were performed on all *Salmonella* FoodNet isolates received by the NYSDOH during the study period. Typing data were forwarded to Cornell University for PFGE pattern comparison using BioNumerics software (Applied Maths Inc., Austin, TX). A total of 422 bovine *Salmonella* isolates obtained in New York between March 1, 2007 and March 1, 2010 (from both clinical and asymptomatic dairy cattle) were used for this comparison. Bovine isolates were sent to the USDA, APHIS National Veterinary Services Laboratories (NVSL) in Ames, Iowa for serotyping using standard protocols. PFGE subtyping of bovine isolates was performed in the Food Science Laboratory at Cornell University. The standard CDC PulseNet protocol for *Salmonella* subtyping (Ribot *et al.*, 2006) was used for all study isolates. *Xba*I was used as the restriction enzyme, and *Xba*I-digested *Salmonella enterica* serovar Braenderup (CDCH9812) DNA was used as a reference size standard (Hunter *et al.*, 2005).

Questionnaire

LHD staff collected standardized data for each case as part of the routine investigation of *Salmonella* infections, generally

by administering a questionnaire to each patient by telephone. Data included demographic information, specimen source and collection date, clinical features, hospitalization (yes or no, with dates of admission and discharge if applicable), vital status, and exposure history during the 5 days prior to disease onset. Clinical symptom data included presence or absence of diarrhea, blood in stool, vomiting, abdominal pain, nausea, fever, headache, and painful muscles/joints, in addition to highest body temperature and duration of diarrhea if present. Following removal of patient identifiers, data were prepared by the NYS EIP staff and forwarded to Cornell University for analysis.

Cases and control-cases

Cases were defined as patients infected with *Salmonella* isolates that matched contemporary bovine isolates by serovar and PFGE pattern. Control-cases were defined as patients infected with *Salmonella* isolates that were not associated with cattle based on those criteria. All patients infected with *Salmonella enterica* serovar Dublin were classified as cases because this serovar is host-adapted to cattle (Uzzau *et al.*, 2000). Patients infected with six other serovars (Newport, Typhimurium, Infantis, 4,5,12:i:-, Agona, and Montevideo) were classified as potential cases because of the importance of these serovars in both bovine and human hosts. The first five were among the leading serovars shed by dairy cattle with clinical *Salmonella* infections in a recent comprehensive study on the incidence of salmonellosis among herds in New York and other northeastern states (Cummings *et al.*, 2009b), and Montevideo is consistently one of the most prevalent serovars shed by asymptomatic cattle (CEAH, 2009). All six are among the top 20 serovars isolated from people with laboratory-confirmed salmonellosis in the United States (CDC, 2008). For patients infected with one of the aforementioned serovars, PFGE patterns from the human isolates were compared with those from cattle. In order to be considered bovine-associated, an isolate had to have a PFGE pattern indistinguishable from that of isolates obtained from two or more cattle in the state of New York between March 1, 2007 and March 1, 2010; patients infected with such isolates were thus classified as cases. Human isolates that differed from the most similar bovine isolate by one to three visible bands were excluded from the analysis, as were human isolates with a PFGE pattern matching that of just a single bovine animal. Patients infected with isolates that differed from the most similar bovine isolate by four or more visible bands were classified as control-cases (van Belkum *et al.*, 2007).

Patients infected with *Salmonella* serovars other than those previously listed were classified as control-cases if the serovar was not detected in New York cattle during that time frame. If the serovar was detected in cattle, the human isolate had to differ from the most similar bovine isolate by four or more visible bands in order for that patient to be considered a control-case; otherwise, the human isolate was excluded from the analysis.

Statistical analysis

Data were imported into a commercially available statistical software program (SAS, version 9.2; SAS Institute Inc., Cary, NC) for variable coding and analysis. Age was

converted into a categorical variable (<5 years of age, 5–19 years, 20–60 years, and >60 years of age). Date of specimen collection was used to create a variable for season (winter, December–February; spring, March–May; summer, June–August; and fall, September–November). Clinical symptoms were analyzed as dichotomous variables (yes/no). Fever was considered “yes” if the patient reported a history of fever or a highest body temperature of at least 100.0°F. Duration of diarrhea was also analyzed dichotomously, with ≤7 days considered typical and >7 days considered severe. Invasive disease was defined as isolation of *Salmonella* from blood rather than a stool or other sample.

Analysis was performed to compare clinical features of cases and control-cases. Univariable descriptive analysis was performed on all variables related to clinical presentation. Bivariable analysis using the chi-squared test was used to determine whether each variable was independently associated with case/control classification. A multivariable logistic regression model was used to identify symptoms occurring among patients infected with bovine-associated subtypes, with case/control status serving as the dichotomous outcome variable. Initial selection of variables was based on the bivariable analysis screening (p -value < 0.25), and a backward elimination approach was used to identify a final multivariable model. Separate logistic regression models were also used to determine whether infections with bovine-associated subtypes were more likely to result in invasive disease, hospitalization, or death, with the outcome (yes/no) serving as the dichotomous outcome variable in each model. Age group, gender, and race were included in these outcome models as potential confounders, and relevant two-way interaction terms were investigated for significance. For all models, p -values of < 0.05 were considered significant.

Results

Between March 1, 2008 and March 1, 2010, the NYSDOH received isolates from 835 of the 851 non-typhoidal *Salmonella* cases that were identified within the NYS FoodNet catchment area. Of these, 40 (4.8%) were classified as cases and 379 (45.4%) as control-cases based on our PFGE pattern criteria (Table 1). Females comprised 50.0% of the cases and 59.9% of the control-cases. Among patients who reported their race (94.7%), white individuals comprised 97.4% of the cases and 89.1% of the control-cases. The median age among cases was 31.5 years, whereas that among control-cases was 31 years. Cases were equally likely to present in the summer or fall (32.5%), as determined by the date of specimen collection, whereas control-cases most often presented in the summer (36.4%). Typhimurium was the most common serovar among both cases (67.5%) and control-cases (12.1%; Table 2).

Bivariable analysis revealed that more cases (12.5%) than control-cases (4.2%) had invasive salmonellosis (p -value = 0.03). Although not statistically significant, there was a greater tendency for cases to have blood in the stool (51.6% vs. 38.2%, p -value = 0.1) and to be febrile (81.8% vs. 69.6%, p -value = 0.1) during their illness. There was no significant difference between cases and control-cases with respect to age group, gender, race, season of illness, hospitalization, presence of other clinical symptoms (diarrhea, vomiting, abdominal pain, nausea, headache, and painful muscles/joints), or

TABLE 1. COMPARISON OF CHARACTERISTICS BETWEEN CASES ($N=40$) AND CONTROL-CASES ($N=379$) FROM THE STATE OF NEW YORK: MARCH 1, 2008 TO MARCH 1, 2010

Variable	Cases % (n)	Control-cases % (n)	p-value
Age group (years)			0.9
<5	17.5 (7)	15.6 (59)	
5–19	17.5 (7)	17.9 (68)	
20–60	45.0 (18)	50.1 (190)	
>60	20.0 (8)	16.4 (62)	
Gender			0.2
Male	50.0 (20)	40.1 (152)	
Female	50.0 (20)	59.9 (227)	
Race			0.2
White	95.0 (38)	84.2 (319)	
Black	2.5 (1)	7.9 (30)	
Other	0	2.4 (9)	
Not reported	2.5 (1)	5.5 (21)	
Season			0.8
Summer	32.5 (13)	36.4 (138)	
Fall	32.5 (13)	25.6 (97)	
Winter	15.0 (6)	14.2 (54)	
Spring	20.0 (8)	23.7 (90)	

duration of diarrhea. There was one reported *Salmonella*-related death, in a control-case who was infected with *Salmonella enterica* serovar Derby.

Multivariable logistic regression analysis showed that cases were significantly more likely to have invasive salmonellosis (odds ratio [OR], 3.8; 95% CI, 1.2–11.8; p -value = 0.02), after accounting for age group, gender, and race (Table 3). There was not a significant interaction between case/control classification and either age group, gender, or race in the model. Case status was not a significant risk factor for hospitalization (p -value = 0.3) when controlling for those demographic variables. There was a marginal association between case status and the presence of blood in the stool (p -value = 0.1) while ill.

Discussion

The case-case study design is an adaptation of the conventional case-control approach (McCarthy and Giesecke, 1999). It has been used to study clinical features and risk factors associated with particular subtypes of *Salmonella* (Gupta *et al.*, 2003; Van Beneden *et al.*, 1999; Kist and Freitag, 2000; Voetsch *et al.*, 2009; Aiken *et al.*, 2010), *Campylobacter* (Smith *et al.*, 1999; Gillespie *et al.*, 2002), and *Clostridium difficile* (Morgan *et al.*, 2008). One of its main advantages is the removal of selection bias imposed by the surveillance system, as both cases and control-cases were subjected to the same selection process in order to be detected by the NYSDOH as a laboratory-confirmed case. Another principal advantage is the negation of recall bias (a form of information bias), because both cases and control-cases had salmonellosis and thus would be expected to have similar degrees of data recall.

Other studies have examined the association between infection with specific *Salmonella* serovars and clinical features of disease, including patient symptoms and case outcomes such as hospitalization and death (Jones *et al.*, 2008; Kist and Freitag, 2000; Kennedy *et al.*, 2004; Vugia *et al.*, 2004). To our

TABLE 2. DISTRIBUTION OF *SALMONELLA* SEROVARS AMONG CASES, CONTROL-CASES, AND EXCLUDED PATIENTS IN THE STATE OF NEW YORK BETWEEN MARCH 1, 2008 AND MARCH 1, 2010

Cases		Control-cases		Excluded	
Serovar	% (n)	Serovar	% (n)	Serovar	% (n)
Typhimurium	67.5% (27)	Typhimurium	12.1% (46)	Enteritidis	46.9% (195)
Dublin	17.5% (7)	Enteritidis	9.5% (36)	Typhimurium	21.4% (89)
Newport	12.5% (5)	Heidelberg	8.4% (32)	Thompson	5.3% (22)
Infantis	2.5% (1)	Newport	5.5% (21)	Oranienburg	4.3% (18)
		Saintpaul	4.5% (17)	Newport	3.4% (14)
		Braenderup	4.2% (16)	Montevideo	1.9% (8)
		Hadar	3.7% (14)	Infantis	1.7% (7)
		Javiana	3.7% (14)	Tennessee	1.7% (7)
		B,5:i:-	2.9% (11)	Other serovars	9.4% (39)
		Muenchen	2.6% (10)	Not typed	4.1% (17)
		Panama	2.4% (9)		
		Agona	2.1% (8)		
		Berta	2.1% (8)		
		Paratyphi B var. L-tartrate+	2.1% (8)		
		B,5:b:-	1.8% (7)		
		Hartford	1.8% (7)		
		Poona	1.8% (7)		
		Stanley	1.8% (7)		
		Miami	1.6% (6)		
		Montevideo	1.6% (6)		
		Schwarzengrund	1.3% (5)		
		Bovismorbificans	1.1% (4)		
		Derby	1.1% (4)		
		Ealing	1.1% (4)		
		Manhattan	1.1% (4)		
		Mississippi	1.1% (4)		
		Other serovars	16.9% (64)		

knowledge, however, no studies have addressed this issue using a case-case approach that defined cases not by serovar but rather by host association (infection with a *Salmonella* isolate that matched contemporary bovine isolates from the same region by serovar and PFGE pattern). Another strength of this study was its inclusion of patient demographic data, as age group, gender, and race have all been found to be associated with severity of salmonellosis (Arshad *et al.*, 2008; Jones *et al.*, 2008; Vugia *et al.*, 2004) and thus could serve as confounding variables.

It is possible that the number of patients with invasive salmonellosis in this study was underestimated, considering that some patients with positive fecal cultures may also have had extraintestinal disease. The use of blood cultures to detect *Salmonella* infection is a practice that might be more likely to occur with young children, elderly adults, and immunocompromised individuals, as well as any patients with severe disease symptoms. Thus, adult patients with mild or moderate symptoms may not have had blood cultures performed even if some degree of extraintestinal disease was present. However, any underestimation would be expected to occur equally among cases and control-cases, and such non-differential misclassification would bias our results toward the null.

Patients with salmonellosis caused by a bovine-associated subtype were significantly more likely to have invasive disease, as ascertained by isolation of *Salmonella* from blood rather than a stool or other sample. These patients were marginally more likely to have blood in the stool during their

course of illness. An important factor contributing to increased disease severity among cases was the prevalence of infection with *Salmonella* Dublin, which is a host-adapted serovar in cattle (Uzzau *et al.*, 2000). In this study, 71% (5/7) of the cases infected with *Salmonella* Dublin had invasive

TABLE 3. ASSOCIATION BETWEEN INVASIVE DISEASE AND STATUS AS A CASE (INFECTED WITH A BOVINE-ASSOCIATED *SALMONELLA* SUBTYPE) AMONG PATIENTS IN THE STATE OF NEW YORK, AS ESTIMATED BY A LOGISTIC REGRESSION MODEL THAT ACCOUNTED FOR DEMOGRAPHIC VARIABLES

Variable	Odds ratio	95% Confidence interval	p-value
Case/control status			
Case	3.8	(1.2, 11.8)	0.02
Control-case	1.0	—	—
Age group (years)			
<5	2.5	(0.6, 10.4)	0.2
5–19	0.2	(0.02, 2.4)	0.2
20–60	0.7	(0.2, 2.8)	0.6
>60	1.0	—	—
Gender			
Male	2.2	(0.8, 5.9)	0.1
Female	1.0	—	—
Race			
White	1.0	—	—
Black	0.9	(0.1, 7.1)	0.9
Other	5.6	(0.9, 32.9)	0.06

salmonellosis. This serovar's virulence and predilection for invasive disease among human patients have been well documented (Arshad *et al.*, 2008; Jones *et al.*, 2008; Kennedy *et al.*, 2004; Vugia *et al.*, 2004). Investigators using CDC FoodNet data from five states between 1996 and 1999 found that 71% (Vugia *et al.*, 2004) of human *Salmonella* Dublin infections were invasive, whereas 64% of such infections were invasive in a FoodNet study during 1996–2006, which ultimately included 10 states (Jones *et al.*, 2008). In contrast, these studies found that invasive salmonellosis was rare among patients infected with common serovars that are unrestricted in their host range (*Enteritidis*, *Typhimurium*, and *Newport*), with estimates ranging from 1% to 7%.

The link between infection with a bovine-associated subtype and invasive salmonellosis might have implications for patient management. Physicians typically do not have access to serovar data until several days after isolating *Salmonella* from a patient, as serotyping is generally only performed at state public health laboratories. Initial therapeutic decisions are made in the absence of such data, and current recommendations are to treat most seemingly uncomplicated cases with fluid and electrolyte replacement but no antimicrobial agent (American Medical Association, 2004; Thielman and Guerrant, 2004). This study suggests that it would be advantageous for physicians to know that a patient's infection likely originated from a bovine source (undercooked foods of bovine origin or direct contact with cattle in the few days prior to illness), based on information provided by the patient upon presentation. Although patient histories obviously vary in their completeness and accuracy, bovine-associated exposure information recalled by a patient could be a valuable clue that warrants close monitoring for the need to implement a more aggressive therapeutic approach, due to the association with invasive salmonellosis. Localized infections that can arise with invasive disease include osteomyelitis, septic arthritis, endocarditis, meningitis, cholecystitis, pyelonephritis, and pneumonia (Heymann, 2008).

Bovine-associated exposure information provided by a patient upon presentation could also be useful for suggesting a more proactive diagnostic approach at the outset. Survey studies have shown that only 38–44% of physicians requested a stool sample for bacterial culture from their most recent patient with acute diarrheal illness (Hennessy *et al.*, 2004; James *et al.*, 2008). Yet these may be overestimates, as only 21% of patients with acute diarrhea who visited a physician reported being asked to provide a stool specimen (Herikstad *et al.*, 2002). Furthermore, the decision for physicians to request a sample for bacterial culture appears more dependent on patient symptoms than exposure history (Hennessy *et al.*, 2004; James *et al.*, 2008). However, the link between infection with a bovine-associated subtype and invasive salmonellosis implies a greater need to reach a rapid diagnosis via fecal and blood cultures, as opposed to more conservative patient management.

The extremely low case fatality found in this study (one reported *Salmonella*-related death) precluded analysis of the impact of infection with bovine-associated subtypes. Such low mortality is a reflection of current standards of care, and it coincides with the decreasing salmonellosis case fatality reported in other studies over time (MacCready *et al.*, 1957; Saphra and Winter, 1957; Jones *et al.*, 2008; Cummings *et al.*, 2010; Ruzante *et al.*, 2011).

Conclusion

Patients with salmonellosis caused by a bovine-associated subtype were significantly more likely to develop invasive disease, as compared to patients infected with a non-bovine-associated *Salmonella* subtype. Thus, a history of consuming undercooked foods of bovine origin or having direct contact with cattle in the few days prior to illness could be useful for guiding decisions on patient management. Additional research is needed to determine if these results are consistent across larger samples and in other geographic regions.

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Disclosure Statement

No competing financial interests exist.

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