MAJOR ARTICLE

Outbreak of Multidrug-Resistant *Salmonella enterica* Serotype Typhimurium Definitive Type 104 Infection Linked to Commercial Ground Beef, Northeastern United States, 2003–2004

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Background. Multidrug-resistant *Salmonella enterica* serotype Typhimurium Definitive Type 104 (DT104) emerged in the 1990s and is associated with greater clinical severity than pansusceptible *S.* Typhimurium. Although infection with DT104 is common in the United States, it is rarely associated with outbreaks. From October to December 2003, a cluster of DT104 infections with indistinguishable pulsed-field gel electrophoresis patterns was identified in the northeastern United States.

Methods. A case-control study that assessed exposures compared case patients to age- and geography-matched control subjects. Information on consumer purchasing and grocery store suppliers was used to trace the implicated food to its source.

Results. We identified 58 case patients in 9 states by pulsed-field gel electrophoresis. Representative isolates were phage type DT104 and were resistant to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline (R-type ACSSuT). Of 27 patients interviewed for the case-control study, 41% were hospitalized (median duration of hospitalization, 4 days). Compared with 71 healthy control subjects, case patients had more medical comorbidities (matched odds ratio, 4.3; 95% confidence interval, 1.5–12.7). Illness was associated with consuming store-bought ground beef prepared as hamburgers at home (matched odds ratio, 5.3; 95% confidence interval, 1.9–15.3) and with eating raw ground beef ($P \leqslant .001$). Seven case patients (27%), but no control subjects, ate raw ground beef. Product traceback linked cases to a single large ground beef manufacturer previously implicated in a multistate outbreak of highly drug-resistant *Salmonella enterica* Newport infections in 2002.

Conclusions. This first multistate outbreak of highly drug-resistant *S.* Typhimurium DT104 infection associated with ground beef highlights the need for enhanced animal health surveillance and infection control, prudent use of antimicrobials for animals, improved pathogen reduction during processing, and better product tracking and consumer education.

Salmonella causes an estimated 1.4 million illnesses in the United States annually [1]. The most common serotype, Typhimurium, comprised 22% of *Salmonella* infections in 2002 [2]. *Salmonella enterica* serotype Typhimurium Definitive Type 104 (DT104) is a phage type typically characterized by resistance to ⩾5 antimicrobial agents (ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline; R-type ACSSuT) [3]. In the United States, the proportion of human *S.* Typhimurium R-type ACSSuT isolates increased from 0.6% in 1979 to 34% in 1996 and was 30% in 2001 [4, 5]. Use of antimicrobials in food animals contributes to the development of antimicrobial resistance and the dissemination of multidrug-resistant (MDR) *Salmonella* strains [6–8].

Illnesses caused by multidrug-resistant *Salmonella* species are more severe than those caused by pansusceptible *Salmonella* species, resulting in increased rates of hospitalization and death [9–11]. Although many patients with salmonellosis recover without antimicro-

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bial therapy, those with severe infections may require treatment; multidrug-resistant organisms limit effective medication choices.

In the United States, most reported DT104 infections are sporadic. Only 5 outbreaks have been reported in the literature; these have been associated with consumption of contaminated dairy products or contact with animals [12–15], suggesting a cattle reservoir. Although DT104 has been isolated from grocery store–purchased ground beef [16], no outbreaks of DT104 infection associated with ground beef have been documented.

We report the first outbreak of *S.* Typhimurium DT104 infection in the United States to have been associated with ground beef purchased from grocery stores. This outbreak was detected in December 2003, when the Maine Bureau of Health laboratory (Augusta) identified a cluster of *S.* Typhimurium cases by routine subtyping with PFGE.

METHODS

Case finding. We defined a case as an illness in a person from the northeastern United States (i.e., Maine, Massachusetts, New Hampshire, Vermont, Connecticut, Rhode Island, and New York) with laboratory-confirmed *S.* Typhimurium infection, for which *Xba*I and *Bln*I restriction-enzyme digestion patterns on PFGE were indistinguishable from those of the outbreak strain—that is, the Maine cluster isolates (*Xba*I JPXX01.0003 or JPXX01.0075 [2 closely related patterns] and *Bln*I JPXA26.0003). Possible cases were sought via PulseNet, the National Molecular Subtyping Network for Foodborne Disease Surveillance. This network of public health laboratories, which perform PFGE analyses on foodborne bacteria, permits rapid comparison of patterns through an electronic database [17]. Phage typing and antimicrobial resistance testing of 6 isolates were performed by the Centers for Disease Control and Prevention (CDC; Atlanta, GA) using standard methods [18].

Case-control study. For the case-control study, a case was defined as an illness in a person residing in the Northeast who had an onset of illness during the period of 13 October 2003 through 15 January 2004 and whose stool or blood culture yielded *S.* Typhimurium of the outbreak strain. Individuals meeting these criteria with symptom onset dates >3 days after symptom onset of another case in the same household were excluded as having possible cases of secondary transmission. Control subjects were persons recruited by random-digit dialing without a recent history of diarrhea and were matched with case patients by age group (<10, 10–24, 25–64, and ⩾65 years) and geographic location. Hypothesis-generating interviews identified commonly consumed foods (including ground beef, chicken, eggs, deli meats, and milk) and aided the development of a questionnaire. Case patients were asked about foods consumed in the 5 days preceding illness; control subjects were asked about consumption of food in the 5 days before the interview. The questionnaire also collected information on demographic characteristics, medical history, travel history, and pet exposure.

Traceback investigation. Any ground beef purchased before illness and in the possession of case patients at the time of interview was cultured at the Maine Health and Environmental Testing Laboratory (August, ME). Store beef-grinding logs identified processors' lot designations. The US Department of Agriculture (USDA) Food Safety and Inspection Service (FSIS) conducted a regulatory assessment of the processor identified from traceback and reviewed ground beef production records from August 2003 through January 2004.

Statistical analysis. Biologically plausible variables demonstrating significance on bivariate analyses were included in a logistic regression model using forward selection. All exposures with significant associations, substantial case exposure, and biologic plausibility were examined.

RESULTS

Case finding. During the period of 13 October 2003 through 15 January 2004, PulseNet identified 30 laboratory-confirmed cases of salmonellosis in Maine (11 cases), Massachusetts (10 cases), New Hampshire (4 cases), Connecticut (3 cases), and Vermont (2 cases). Geographic clustering supported the hypothesis of a single-source outbreak. In the previous 6 years, only 35 (4%) of 826 *S.* Typhimurium isolates restricted by both *Xba*I and *Bln*I were indistinguishable from the outbreak strain, indicating that this PFGE pattern was uncommon in PulseNet before October 2003. All 6 isolates submitted to CDC for phage typing and susceptibility testing were DT104 R-type ACSSuT.

Case-control study. Thirty case patients met the case-control study case definition, and 27 were enrolled. The median age was 49 years (range, 1–85 years); 19 case patients (70%) were female. Symptoms included diarrhea, abdominal cramps, fever, and vomiting (table 1). More than one-half (52%) of patients required intravenous fluids, and 67% received antimicrobial therapy. Eleven patients (41%) spent >1 night in the hospital; no deaths occurred. Three patients (11%) reported contact with a person with similar symptoms in the 2 weeks before illness; no laboratory data were available for these contacts.

Seventeen case patients were matched with 3 control subjects each, and 10 were matched with 2 control subjects each. The median age of control subjects was 41 years (range, 2–94 years); 46 (65%) of these subjects were female. Nine adult case patients (41%) had not completed high school, compared with 7 control subjects (11%; matched OR, 4.1; 95% CI, 1.3–12.5). Seventeen case patients (63%) reported that they had preexisting medical problems, compared with 23 control subjects (32%; matched OR, 4.3; 95% CI, 1.5–12.7). Medical problems reported by case patients included hypertension (7 patients), asthma (6 pa-

Table 1. Clinical characteristics of case patients infected with *Salmonella enterica* serotype Typhimurium Definitive Type 104, northeastern United States, October 2003–January 2004.

Clinical characteristic	Case patients (n = 27)
Diarrhea	26 (96)
Bloody diarrhea	8 (30)
Fever	19 (70)
Vomiting	14 (52)
Abdominal cramps	17 (63)
Received intravenous fluids	14 (52)
Received antimicrobial agents	18 (67)
Hospitalized at least 1 night	11 (41)
Duration of hospital stay, median days (range)	4 (2–7)
No. of deaths	0

NOTE. Data are no. (%) of case patients, unless otherwise indicated.

tients), and hypothyroidism (4 patients). Case patients and control subjects did not differ with regard to recent antimicrobial or antacid use, immunocompromising conditions, pet contact, or travel history.

Eating ground beef in the form of hamburgers at home was significantly associated with illness; 14 (56%) of 25 case patients and 12 (17%) of 71 control subjects reported this exposure (matched OR, 5.3; 95% CI, 1.9–15.3). This association persisted on multivariate analysis when adjusting for age, sex, preexisting medical problems, and education (matched OR, 7.3; 95% CI, 1.8–29.7). Seven case patients (26%) reported tasting or eating raw ground beef during meal preparation, compared with no control subjects (matched OR, 14.5; 95% CI 1.8–∞; $P \leqslant .001$). No other food items were associated with illness (table 2). Although case patients and control subjects purchased ground beef from several different grocery stores, and although no single store or chain was associated with illness, case patients were less likely than control subjects to have shopped at stores belonging to chain Z (4 case patients [15%] vs. 28 control subjects [39%]; matched OR, 0.2; 95% CI, 0.04–0.8).

Traceback. The 17 case patients who reported eating ground beef made purchases at 17 different grocery stores, involving 4 large chains. Purchased ground beef originated from "tube stock," a beef product coarsely ground by the manufacturer and reground in the store. Ground beef from 16 stores (94%) originated from tube stock supplied by meat processor A. The 32 control subjects who reported eating ground beef made purchases at 30 different grocery stores; of these stores, 13 (43%) received tube stock from meat processor A. Grocery stores belonging to chain Z, where control subjects were more likely to shop, did not receive ground beef from meat processor A. These findings indicate that ground beef produced by meat processor A, which was sold to stores as tube stock and purchased by consumers as ground beef at stores throughout the Northeast, is the likely source of the outbreak of *S.* Typhimurium DT104 infection.

Limited labeling information disallowed the identification of specific production lots from grinding logs or ground beef purchases. One sample of partially used, frozen ground beef from a case patient's refrigerator that was thought to be left over from a package obtained before the illness was cultured, but the culture yielded no pathogen.

Meat processor A slaughters >1000 cows daily; more than 50% of these cows are culled dairy cows originating from >30 states. USDA FSIS–targeted assessment of processor A in January 2004 revealed no operating deficiencies from August 2003 to January 2004. During the period of October through December 2003, the manufacturer cultured *Salmonella* species from 2 of 283 raw beef product samples as part of ongoing monitoring. These isolates were not serotyped and had been discarded by the time of this investigation. The ground beef in which the *Salmonella*-positive samples were found had been sold to consumers. On 29 January 2004, the USDA FSIS issued

Table 2. Food exposures among 27 case patients infected with *Salmonella enterica* serotype Typhimurium Definitive Type 104 and among 71 matched control subjects.

Food exposure	No. (%) of subjects		Matched OR (95% CI)
	Case patients	Control subjects	
Any ground beef eaten in or out of home	24 (89)	67 (94)	0.5 (0.1–2.4)
Any ground beef eaten at home	17 (63)	32 (45)	1.9 (0.8–34.4)
Ground beef eaten as hamburger at home	14 (52)	12 (17)	5.3 (1.9–15.3)
Raw ground beef tasted or eaten at home	7 (26)	0 (0)	14.5 (1.8–∞)
Chicken	23 (85)	49 (69)	2.9 (0.8–10.7)
Eggs	14 (52)	53 (75)	0.4 (0.2–1.0)
Deli meats	17 (63)	44 (62)	1.0 (0.4–2.5)
Deli cheeses	21 (78)	60 (85)	0.7 (0.2–1.9)
Milk	16 (59)	56 (79)	0.4 (0.2–1.0)
Bananas	14 (52)	23 (32)	2.6 (1.0–6.7)

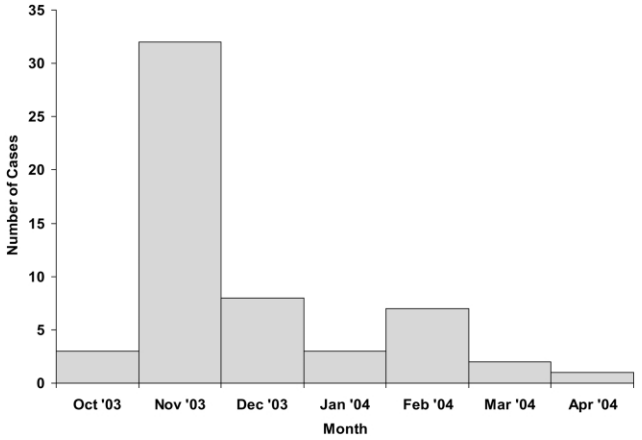

Figure 1. Cases of infection with *Salmonella enterica* serotype Typhimurium Definitive Type 104 with a PFGE-defined outbreak pattern among residents of Maine, Massachusetts, New Hampshire, Vermont, Connecticut, Rhode Island, New York, Pennsylvania, and New Jersey, October 2003 through April 2004.

a public health alert reminding consumers about the importance of handling and cooking ground beef properly because of the potential presence of *S.* Typhimurium.

Continued surveillance. Monitoring of the PulseNet database through April 2004 identified 28 additional cases of infection due to the outbreak strain in New York (19 cases), Rhode Island (3 cases), Pennsylvania (3 cases), New Jersey (1 case), Maine (1 case), and Vermont (1 case) (figure 1). Routine PFGE typing of *S.* Typhimurium was then discontinued, but when it was reinstated for the month of September 2004, 10 (3%) of 394 *S.* Typhimurium isolates were identical to the outbreak strain.

DISCUSSION

To our knowledge, this is the first multistate outbreak of *S.* Typhimurium DT104 infection in the United States associated with a commercially produced, widely distributed food. Assuming that there were an estimated 38 ill persons for every culture-confirmed case of *Salmonella* infection [1], this outbreak caused >2200 illnesses. Our investigation implicated ground beef from a large processor that supplied several grocery stores in the northeastern United States; the same processor was implicated in a large multistate outbreak of multidrug-resistant *S. enterica* Newport infection in 2002 [19].

Illness was severe. A high proportion of case patients received intravenous rehydration and required hospitalization, which is consistent with other studies and demonstrates the increased illness severity associated with multidrug-resistant *Salmonella* infection, compared with pan-susceptible *Salmonella* infection [9, 10, 20]. In contrast to earlier investigations, illness was not associated with prior antibiotic use [9, 20], illustrating that illness due to multidrug-resistant organisms can occur without this risk factor.

The duration of the outbreak (⩾7 months) implies that illnesses were not due to a single lot or production run of contaminated product (figure 1). Rather, it suggests that there was continual exposure to contaminated ground beef, most likely from a reservoir of infected cattle, amplified through centralized processing or contamination of the processing facility. Targeted regulatory assessments by the USDA FSIS of the meat processing plant did not reveal any operating deficiencies, indicating that current procedures for processing ground beef may not be adequate to prevent illness.

The meat processor that was the apparent source of this outbreak produces much of its ground beef from culled dairy cows, a practice that may promote the dissemination of multidrug-resistant *Salmonella* species. DT104 has been frequently isolated from dairy cattle, and cows that appear to be healthy can excrete DT104 and other pathogens in their feces, especially within 1 week after culling [6, 21, 22]. Although cows presented for slaughter are visually inspected by veterinarians and those with obvious signs of serious illness are removed, there is no practical technology available to screen for mild, subclinical, or asymptomatic infections. Meat from one contaminated animal is commingled with meat from hundreds of other carcasses in large production facilities and widely distributed. Geographically dispersed illnesses may not be recognized as part of an outbreak, and this may explain why more outbreaks of DT104 infection associated with ground beef have not been previously recognized.

The factors selecting for multidrug-resistant *Salmonella* species on dairy farms have not been clearly defined, but antimicrobial use patterns likely play a role. In a 2002 USDA survey of dairy cattle farms, 56% of farms administered medicated milk replacers, with the majority adding antimicrobial agents to the formula. In addition, 87% of farms fed calves waste milk—that is, milk that is banned for human consumption, because some of it contains antimicrobials from antimicrobial-treated cows; 17% of farms included antimicrobials in heifer rations. Antimicrobials used on farms for therapeutic and nontherapeutic uses have been associated with infection due to multidrug-resistant organisms in humans [23–25].

Control of multidrug-resistant organisms will be advanced by administering antimicrobials to animals only for medical purposes and by eliminating the use of growth-promoting antimicrobials. Several organizations, including the World Health Organization and the Institute of Medicine [30], have called for the discontinuance of the nontherapeutic use in food animals of antimicrobials used in humans. The European Union has moved to eliminate all antimicrobials used to treat humans from use as growth promoters in animals by 2006 [31, 32], an approach instituted by Denmark in 1998 [33]. Studies evalu-

ating the effect of these efforts showed not only decreased rates of antimicrobial-resistant bacteria in animals, food products, and humans, but also minimal to no adverse effects on productivity or profits [7, 33–37].

Rapid tests need to be developed that would allow systematic testing for the detection of infected animals at slaughter and of meat contaminated with multidrug-resistant organisms during processing. Condemnation or diversion of contaminated meat into a cooked, ready-to-eat product and prohibition of sale of raw meat contaminated with multidrug-resistant *Salmonella* species would reduce the public's exposure to the pathogen. Finally, improved record-keeping from processing facility to the point of retail could substantially facilitate identification of contaminated meat in outbreaks and allow removal of the meat from the market, a practice endorsed by the Council of State and Territorial Epidemiologists [29].

Eating undercooked ground beef appears to be a long-standing cultural practice, because outbreaks of infection in which this behavior has been documented have occurred for decades [26, 27]. Because it is unlikely that untreated raw meat will ever be microbially safe for direct consumption, consumers should be discouraged from eating or tasting raw or undercooked ground beef. Irradiation, a process approved by the USDA FSIS and the US Food and Drug Administration, would significantly reduce the risk of illness associated with a variety of pathogens transmitted through ground beef. It is a safe practice, and many agencies, including the CDC and World Health Organization, support its use [28].

There are limitations to this study. Recall bias may have been introduced, because, in many cases, >1 month passed between the illness and the interview. This may explain why not all case patients recalled eating ground beef before illness. We did not identify DT104 in a meat sample, and *Salmonella* isolates recovered from industry ground beef sampling had been discarded, making it impossible to know whether the isolates matched the outbreak strain. We were also unable to identify suspect ground beef production lots for testing. However, the scientific basis for epidemiologic implication of foods and food producers in outbreak investigations has been well established and is applicable in this investigation [38].

In summary, we describe the first outbreak of DT104 infection in the United States associated with commercially processed, widely distributed ground beef. Illness was severe, and the outbreak appears to be ongoing. Decisive actions along the farm-to-table continuum are needed, along with additional research to better understand the ecologic characteristics of multidrug-resistant *Salmonella* species in live animals. Changes in agricultural practices, microbiologic standards for ground beef manufacture, production record-keeping practices, and consumer behavior, as well as other food safety measures, are crucial for the prevention of multidrug-resistant *Salmonella* infection.

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