# **Risk Factors for Non-O157 Shiga Toxin-Producing Escherichia coli Infections, United States**

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Shiga toxin-producing *Escherichia coli* (STEC) causes acute diarrheal illness. To determine risk factors for non-O157 STEC infection, we enrolled 939 patients and 2,464 healthy controls in a case-control study conducted in 10 US sites. The highest population-attributable fractions for domestically acquired infections were for eating lettuce (39%), tomatoes (21%), or at a fast-food restaurant (23%). Exposures with 10%–19% population attributable fractions included eating at a table service restaurant, eating watermelon, eating chicken, pork,

**N** on-O157 Shiga toxin-producing *Escherichia* coli (STEC), which encompasses all STEC serogroups other than O157, causes an estimated 219,000 US infections annually (1). Typical symptoms are diarrhea, abdominal cramps, and vomiting, and hemolytic uremic syndrome occurs in 1% (2); deaths from STEC are rare. Incidence is highest among children (2). Most strains isolated from US residents belong to 1 of 6 serogroups, defined by O antigens (3–5) (S.

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Browning, Centers for Disease Control and Prevention, December 18, 2020 email).

Non-O157 STEC infections were underdiagnosed for decades because laboratories lacked practical detection methods (4,6–9). Culture-independent diagnostic tests for Shiga toxin became available in 1995. The number of laboratories using enzyme immunoassays and PCR tests to identify non-O157 STEC has been increasing since then. Reported infections increased further after non-O157 STEC infection was designated a nationally notifiable infection in 2000 (2,10).

Investigations of non-O157 STEC outbreaks have identified transmission routes, including foodborne, waterborne, from contact with animals and their environments, and person-to-person contact (11,12). Because little is known about risk factors for sporadic infections, the Foodborne Diseases Active Surveillance Network (FoodNet) conducted a large, multisite, case-control study to identify risks for sporadic non-O157 STEC infections in the United States. Centers for Disease Control and Prevention (CDC) and Food-Net site institutional review boards approved the study protocol. We obtained verbal consent from all

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persons ≥18 years of age and parents or legal guardians of children <18 years of age and verbal assent (in addition to parent or guardian consent) from children 12–17 years of age.

# Methods

During 2012-2015, FoodNet conducted active, population-based surveillance for laboratory-diagnosed STEC infections in 10 sites, covering an estimated 49 million persons (15% of the US population in 2014). The catchment area included Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, and Tennessee and selected counties in California, Colorado, and New York. We recruited patients from each site for a consecutive 36-month period during July 1, 2012-September 1, 2015. We defined a case as isolation of non-O157 STEC from a clinical specimen of an ill person residing in a FoodNet site. We excluded cases in which a pathogen other than non-O157 STEC was detected in a non-O157 STEC-positive specimen, or the patient was lost to follow-up, did not speak English or Spanish, was part of an outbreak (except for the index patient in each site), or was not the first case in their household. We attempted to enroll 3 controls per case, matched on county and stratified by age groups: 0-1, 2-5, 6-17, 18-39, 40-59, or ≥60 years. We selected controls in all except the youngest age group from commercially available lists of residential telephone numbers, by county, that included age ranges. We selected controls <2 years of age from birth registries. We enrolled controls within 60 days after the matched case-patient's specimen collection date. We excluded controls who did not speak English or Spanish.

We interviewed patients and controls or their guardians by telephone using a standard questionnaire that covered 385 variables and had sections on health, travel, water, animals, foods, and demographics. Most exposures, including international travel, were for the 7 days before illness began; controls were asked about exposures during the same period as case-patients. The questionnaire defined fast-food restaurants as places where food is ordered and paid for at a counter or drive-through and table-service restaurants as all sit-down or table-service restaurants.

Clinical laboratories submitted specimens that had Shiga toxin (determined by immunoassay) or Shiga toxin genes (determined by PCR) to state public health laboratories. State public health laboratory staff identified non-O157 specimens and submitted them to CDC for serologic testing to determine O and H antigens. CDC used whole-genome sequencing to confirm the absence of O157 genes on rough isolates.

We included all enrolled participants in descriptive analyses. International travel was examined in univariable analysis. Those reporting international travel were excluded from other risk factor analyses, which were conducted separately for infants <1 and persons ≥1 years of age. To control for confounding in the main risk factor analysis, we rematched controls with cases using the nearest-neighbors approach (13). For a given exposure, we calculated Gower distance on the basis of age, sex, state, and all exposures except the one under consideration (14). Using logistic regression, we established an overall threshold for Gower distance at which it was more likely that a matched control was a patient's nearest neighbor than a randomly selected control. We matched up to 20 controls within the Gower distance with the nearest case-patient and ensured that each control was matched to only 1 case-patient. Of note, distance between 85% of patient-control pairs matched during recruitment exceeded that threshold. We excluded case-patients without matches within the threshold from the analysis for the exposure under consideration. After rematching patients with controls, information was available for patients for all but 5 exposures in at least 92% of cases: municipal water away from home (89%), private well water away from home (85%), spring water away from home (85%), prepackaged iceberg lettuce (84%), and prepackaged romaine lettuce (87%). Information was available for all except 4 exposures for at least 92% of controls: municipal water away from home (91%), contact with someone with diarrheal illness (90%), private well water away from home (82%), and spring water away from home (81%). We did not conduct imputation because results were unlikely to be affected by the low rates of missing data.

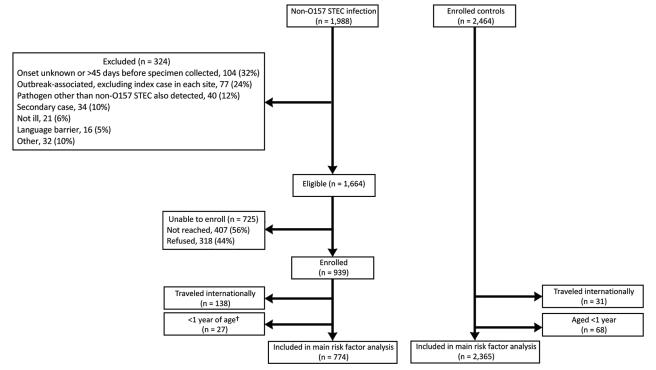
For our analyses, we calculated odds ratios (ORs) and population attributable fractions (PAFs) to identify both individual risk and percentages at which illnesses in the population could be decreased. Because prevalence of some exposures was low among case-patients, controls, or both, we applied Firth bias-reduced penalized-likelihood logistic regression to estimate ORs and 95% CIs for each exposure, after adjusting for the matched strata generated by the nearest-neighbors approach. We calculated and adjusted p values for multiple testing using the Benjamini-Yekutieli method (15). We considered associations statistically significant if adjusted p was <0.05 and 95% CIs did not include 1.0. We calculated PAF using a method described elsewhere (16) and calculated 95% CIs for PAFs using the 95% confidence limits of ORs. We did not assess the overall statistical significance of our logistic regression models because each included only the exposure under consideration and the strata of matched case-control pairs (Appendix Table 2, https://wwwnc. cdc.gov/EID/article/29/6/22-1521-App1.pdf).

### Results

We identified 1,988 non-O157 STEC case-patients and We identified 1,988 non-O157 STEC case-patients and 2,464 controls meeting inclusion criteria; we excluded 324 of the case-patients according to exclusion criteria (Figure). Of the 1,644 eligible patients remaining, 407 could not be reached and 318 refused to participate, leaving 939 (56.4%) total cases in the study. Nine serogroups accounted for 83% of isolates from enrolled case-patients: O26 (263, 28%), O103 (216, 23%), O111 (135, 14%), O121 (46, 5%), O118 (37, 4%), O186 (23, 2%), O5 (22, 2%), O145 (21, 2%), and O45 (21, 2%) (Table 1, https://wwwnc.cdc.gov/EID/ article/29/6/22-1521-T1.htm). The remainder of the results is limited to enrolled case-patients.

Nearly all patients (99%) reported diarrhea (median duration 7 days, interquartile range 5-10 days) (Table 1). Other common signs and symptoms were abdominal pain (89%), fatigue (71%), bloody feces (58%), and nausea (53%). Seventeen percent of patients were hospitalized, and 8 (1%) had hemolytic uremic syndrome develop. International travel was significantly associated with infection in univariable analysis; 138/939 (15%) patients reported international travel, compared with 31/2,464 (1%) controls (matched OR 14.2, 95% CI 9.0-23.3) (Table 1). The most common destination among patients traveling internationally was Mexico (68, 49%). The rank order of non-O157 STEC serotypes among international travelers was similar to that for domestic cases except for the absence of O121. O186 (11/23, 48%) and O118 (11/37, 30%) were the sero-groups with the highest percentages of patients who had recently traveled internationally.

Most patients (801/939) and controls (2,433/2,464), including 27 infant case-patients and 68 infant controls, had not recently traveled internationally. Patient median age was 18 years (interquartile range 4–35 years); 57% were female, 90% White, and 17% of Hispanic ethnicity (Table 2). Median age was significantly lower for patients (18 years) than for controls (22 years). Patients were also more likely than controls to be White (90% vs. 87%) and of Hispanic ethnicity (17% vs. 10%) and less likely to be Black (5% vs. 7%). Among Food-Net sites, the most cases were in Minnesota (226, 28%), followed by Tennessee (107, 13%), Oregon (91, 11%), Georgia (88, 11%), California (61, 8%), New York (58, 7%), Colorado (54, 7%), Connecticut (46, 6%), New



**Figure.** Flowchart for inclusion/exclusion in study of risk factors for non-O157 STEC infections, United States. \**Campylobacter*, n = 11; *Salmonella*, n = 8; *Cryptosporidium*, n = 7; STEC O157, n = 7; *C. difficile*, n = 2; *Giardia*, n = 2; *Cryptosporidium* and *Giardia*, n = 1; norovirus, n = 1; *Shigella*, n = 1. †An additional 3 infants who traveled internationally were included in the Traveled internationally box above. STEC, Shiga toxin–producing *Escherichia coli*.

Mexico (40, 5%), and Maryland (30, 4%). International travel was the only factor significantly associated with infection among 3/30 (10%) infants, compared with none among 68 controls (OR 32.8, 95% CI 1.5–4,607.2). No food, environmental, water, or other exposure we examined among infants who had not traveled internationally was significantly associated with illness (Appendix Table 1).

Among persons  $\geq 1$  year of age who had not traveled internationally, significant PAFs (>20%) were largest for eating lettuce (PAF 39.3%; OR 2.6), tomatoes (PAF 21.3%; OR 1.7), or at a fast-food restaurant (PAF 22.5%; OR 1.7) (Table 3, https://wwwnc.cdc. gov/EID/article/29/6/22-1521-T3.htm). Other produce exposures with high PAFs (10%-19%) were eating watermelon (PAF 19.0%; OR 2.4), including prepared inside the home (PAF 10.9%; OR 1.7); eating tomatoes prepared in a restaurant (PAF 13.7%; OR 2.5); eating exotic fruit, such as kiwi, avocado, or mango (PAF 13.2%; OR 1.7); and eating iceberg lettuce prepared in a restaurant (PAF 12.9%; OR 2.7). The highest ORs among fruit and vegetable exposures were for raspberries (PAF 2.2%; OR 7.7), cantaloupe (PAF 3.2%; OR 4.3), exotic fruit (PAF 5.8%; OR 3.9), and pineapple (PAF 3.8%; OR 3.6) prepared in a restaurant. However, <8% of patients had exposure to any 1 of those.

Eating at a table service restaurant also had a high PAF (19.4%; OR 1.7). Of the 24 food-related risk factors identified, 17 were related to preparation in a restaurant and 1 to preparation inside the home; the other 6 did not specify a place of preparation. Meats with significant high PAFs (10%–19%) were chicken prepared in a restaurant (PAF 16.3%; OR 1.6), pork prepared in a restaurant (PAF 10.2%; OR 2.9), and beef prepared at a table-service restaurant (PAF 10.1%; OR 2.1). The highest OR among meat and seafood products was for eating pink hamburger from

 Table 2. Demographic characteristics of case-patients with non-O157 Shiga toxin–producing *Escherichia coli* infection and controls without international travel, FoodNet case–control study, United States, 2012–2015\*

· · · · · · · · · · · · · · · · · · ·	Case-patients,	Controls,				
Characteristic	n = 801	n = 2,433				
Age, y median (IQR)	18 (4–35)	22 (6–39)				
Sex						
F	457/801 (57)	1,425/2,410 (59)				
M	344/801 (43)	982/2,410 (41)				
Race						
White	667/739 (90)	2,016/2,310 (87)				
Black	35/739 (5)	167/2,310 (7)				
Asian	15/739 (2)	46/2,310 (2)				
Ethnicity						
Hispanic	133/789 (17)	236/2,399 (10)†				
*Values are no. positive/no. for whom data were available (%) except as						
indicated.						

tp<0.05 compared with case-patients.

a table-service restaurant (PAF 3.4%; OR 9.0). Eating ground beef hamburger (PAF 5.8%; OR 2.4) at a table-service restaurant was also a significant risk factor. However, 9 of 21 factors significantly associated with lower risk of illness were related to beef (Appendix Table 2).

Although living or working on or visiting a farm, petting zoo, or fair (PAF 14.7%; OR 8.0) was the only significant environmental exposure with a PAF  $\geq$ 10%, many significant animal environment-associated exposures had ORs >10. Those included exposures to calves, chickens, cows, goats, horses, pigs, and sheep. Taking stomach acid-reducing medications in the 4 weeks before illness (PAF 11.3%; OR 2.1) was the only other significant risk factor with PAF  $\geq$ 10% or OR >10.

Among the 5 risk factors for STEC O26 infection, only 1, contact with someone with diarrheal illness (PAF 10.8%, OR 5.7), had a PAF  $\geq$ 10%; the other 4, all with ORs  $\geq$ 10, were animal environment exposures. Among the 7 risk factors associated with STEC O103 infection, 3 had PAFs  $\geq$ 10% and the other 4 had ORs >14. The highest PAFs were for living or working on, or visiting a farm, petting zoo, or fair (PAF 22.0%, OR 7.2) and for eating iceberg lettuce in a restaurant (PAF 20.1; OR 4.5). One risk factor was identified for STEC O111: living or working on, or visiting a farm, petting zoo, or fair (PAF 20.3%; OR 15.4) (Table 4).

## Discussion

We found non-O157 STEC infections were associated with international travel and domestic exposure to a wide variety of foods and animal environments. Among 18 food consumption risks with site of consumption indicated, 94% were in restaurants. The wide variety of foods implicated suggests that sources of infection, and thus control measures, for non-157 STEC are more similar to those for *Salmonella* than to those for STEC O157 (*17*). Control measures focused on improving the food safety system, in particular for produce and restaurants, are likely to decrease illness the most.

Our finding of large population-level risks attributable to eating at restaurants is notable because most food is consumed at home (18). FoodNet studies also identified restaurants as risks for STEC O157 (19) and *Campylobacter* (20) infections. A study from Australia linked non-O157 STEC illnesses to catered meals (21). In a review of US restaurant outbreaks, food handling and preparation practices were implicated in about half and food contaminated before entering the restaurant in about one quarter of *Salmonella* outbreaks (data for STEC not provided) (22,23). Policies that help promote a culture of food safety for restaurants include

Table 4. Risk factors associated with domestically acquired non-O157 Shiga toxin-producing Escherichia coli infections by serogroup,
FoodNet case–control study, United States, 2012–2015*

	Case-		Multiv	Multivariable analysis		
Serogroup and exposure†	patients	Controls	OR (95% CI)	PAF (95% CI)	p value§	
O26, n = 231						
Contact with someone with diarrheal illness	16/122 (13)	11/370 (3)	5.7 (2.4–14.4)	10.8 (7.6–12.2)	0.04	
Environmental						
Live or work on, or visit a farm, petting zoo, or fair						
With chickens present	11/143 (8)	1/410 (0)	35.5 (6.9–319.6)	7.5 (6.6–7.7)	0.003	
With cows present	11/140 (8)	4/399 (1)	13.6 (3.6–62.0)	7.3 (5.7–7.7)	0.04	
With cows or calves present	11/141 (8)	5/394 (1)	13.7 (3.5–65.5)	7.2 (5.6–7.7)	0.04	
Visit a farm with chickens present	7/139 (5)	1/421 (0)	24.3 (4.7–172.0)	4.8 (4.0-5.0)	0.04	
O103, n = 179						
Environmental						
Live or work on, or visit a farm, petting zoo, or fair	24/94 (26)	22/315 (7)	7.2(2.9–19.4)	22.0 (16.6–24.2)	0.008	
With cows or calves present	12/95 (13)	6/334 (2)	24.9 (5.3–169.3)	12.1 (10.2–12.6)	0.008	
With calves present	7/97 (7)	2/330 (1)	60.8 (6.7–2,615.0)	7.1 (6.1–7.2)	0.02	
Live on a farm	11/101 (11)	5/328 (2)	15.8 (3.8–77.8)	10.2 (8.1–10.8)	0.02	
Contact with wild deer or elk or their droppings	9/98 (9)	2/327 (1)	14.6 (3.7–69.1)	8.6 (6.7–9.1)	0.02	
Visit a farm with horses present	5/93 (5)	1/316 (0)	60.1 (6.4–5,983.0)	5.3 (4.5–5.4)	0.02	
Fruits and vegetables						
Iceberg lettuce prepared outside the home	24/93 (26)	37/290 (13)	4.5 (2.1–9.9)	20.1 (13.7–23.2)	0.02	
O111, n = 104						
Environmental						
Live on, visit, or work on a farm, petting zoo, or fair	13/60 (22)	11/190 (6)	15.4 (4.1–73.9)	20.3 (16.3–21.4)	0.03	

\*Values are no. exposures/no. for whom data were available (%) except as indicated. OR, odds ratio; PAF, population attributable fractions. †In the 7 d before illness unless otherwise specified. Interviewers told respondents to consider foods prepared at any home to be prepared at home and foods prepared at a restaurant or commercial food service establishment to be prepared outside the home.

‡All cases included were in nontravelers >1 y old; each serogroup-specific analysis had 2,365 noninfant, nontraveler controls. The overall number of cases for each serogroup-specific analysis is listed in the respective section header. During nearest-neighbors matching, cases and controls without a match were excluded for the exposure under consideration. Thus, the numbers of cases and controls that were matched and included in the analysis of each exposure is smaller than the total.

§p adjusted for multiple testing using Benjamini-Hochberg-Yekutieli method.

staff training in and oversight of food preparation and purchase agreement requirements that foods meet or exceed standards promoted by the Food Safety Modernization Act and the US Department of Agriculture's Food Safety and Inspection Service. Health officials can also drive improved adherence to the Food and Drug Administration Food Code or stricter local regulations.

Our analysis indicated that eating lettuce, tomatoes, and other produce commonly consumed raw accounts for a large proportion of illnesses. One review of STEC found that row crop vegetables were associated with more outbreaks than any other food and significantly more non-O157 outbreaks than beef (12). Produce also transmits a high proportion of foodborne illnesses caused by other pathogens (17,23–25). Identifying particular growing areas and farms as sources of produce associated with outbreaks would provide a more efficient targeted process for preventing contamination before produce arrives at restaurants or stores (26). Produce growers, suppliers, sellers, and commercial establishments should adhere to guidelines to assure that produce is safe when purchased. The Food and Drug Administration is charged with implementing the Produce Safety Rule, part of the Food Safety Modernization Act, which includes requiring routine inspections of large produce farms. Best practice standards for biosecurity and

water management should recognize the risk from environmental contamination caused by wildlife and from the use of untreated water contaminated with fecal matter from food-producing animals on crops (26,27). Preventing cross-contamination of produce from meat in restaurants and homes is also essential.

Further regulatory measures could decrease transmission of non-O157 STEC. In 2012, similar to the practice for STEC O157 since 1994, the Food Safety and Inspection Service named the 6 non-O157 STEC serogroups (O26, O103, O111, O121, O145, and O45) most frequently linked to human illness as adulterants in raw, nonintact beef products (28). Although we observed inverse associations for some beef exposures, the consumption of any beef at a table service restaurant had a PAF of 10.1% and pink ground beef hamburger had an OR of 9, indicating those are high-risk exposures. We found eating ground beef hamburgers from fast-food restaurants was not associated with illness, similar to the finding of a FoodNet study of STEC O157 infections conducted during 1996-1997 (19). Those findings suggest that standard hamburger cooking procedures in fast-food restaurants are effective. PAFs of 16% for chicken and 10% for pork prepared in a restaurant suggest that those meats might transmit non-O157 STEC. US outbreaks caused by O157 but not non-O157 STEC have been linked to those foods (29).

We identified a wide variety of risky exposures related to infection from animals; visiting, living on, or working on a farm, petting zoo, or fair had the highest PAF (14.7%). Visiting (PAF 8.2%) and living on (PAF 5.2%) a farm each conferred risk. The study implicated specific animal types, including calves, chickens, cows, goats, horses, pigs, or sheep, as well as contact with horse feed and with wild deer or elk or their droppings. Contact with farm animals, particularly but not exclusively ruminants, or their environments is a known risk factor for both non-O157 (20,21,27,30) and O157 STEC infections (19,32,33). Handwashing is essential for preventing infections in these settings. Guidelines have been published for behaviors in public settings with animals (34); development of guidelines for nonpublic settings could help avert infections.

Although risk factors that have high PAFs provide the largest opportunities for reducing illnesses, many exposures had significantly high ORs, particularly animal contact and environmental exposures, which also signal potential targets for reducing infections. Very high ORs (6.8–66.9) indicating high individual-level risk were identified for exposure to environments with calves, cows, chickens, goats, horses, pigs, and sheep. Other exposures with high ORs (4.3– 7.7) were, in descending order, eating raspberries in a restaurant, drinking untreated water, and eating cantaloupe in a restaurant. Drinking untreated water was also identified as a risk factor for O157 STEC infection in another FoodNet case–control study (22).

The similarity of serotypes in our study to those more recently causing illness indicates that the most notable risk factors we found likely remain current. The top 4 serogroups in our study, which accounted for 70% of isolates, were the same as the top 4 named adulterants in 2012. They were also the top 4 non-O157 STEC isolates reported to national surveillance during the study period (74% of isolates) and in the years with the most recently validated data, 2016-2018 (78% of isolates) (S. Browning, Centers for Disease Control and Prevention, December 18, 2020 email). The next 5 most common serogroups in our study were all among the top 11 serogroups nationally during the study period and 2016-2018. Regional variations in sources may influence serotype frequency but variations in laboratory practices may also affect frequency data (35,36). For example, some public health laboratories attempt to identify only the 3 most common serogroups, others test for the top 6, and others routinely send all isolates to CDC for serogrouping. It is possible that our study protocol requiring that all non-O157 STEC isolates be sent to CDC for serotyping resulted in recognition of illnesses caused by less common serogroups.

Nearest-neighbor matching approaches have a solid theoretical basis in epidemiologic research (37-39), but applying this method to matching in case-control studies of enteric diseases is recent (13). Although it is impossible to account for every possible confounder when selecting controls, this approach allows the most closely matched controls to be selected for each case. The nearest-neighbor approach permitted better control of confounding and would be expected to produce less-biased estimates than our original scheme that matched only on age, sex, and geography. One apparent benefit of our study approach was that we did not observe the large number of spurious inverse effects for vegetable and fruit items that have been seen in other studies (20,31,41).

Our study was limited to cases reported to public health departments and thus dependent on infected persons seeking health care and providers obtaining fecal specimens, so data may not be representative of all non-O157 STEC illnesses (40). We only enrolled patients residing in the FoodNet catchment area, which is not completely representative of the US population (41). In addition, patients were significantly more likely than controls to be Hispanic, possibly because controls were selected from purchased commercial lists of telephone numbers that included only landlines; persons of Hispanic ethnicity were more likely than others to live in households with only cellular telephones during the study (42). As in any case-control study, there were probably nondifferential information biases (e.g., differences in the way patients remember and report exposures compared with controls). Finally, unlike in outbreak investigations, in which a particular exposure can be confirmed as the source, associations in studies of sporadic infections do not confirm a particular source because of the possibility of residual confounding. Although we used an advanced method to control for confounding, residual confounding for some associations and for common coexposures was still likely. For example, many salads include both lettuce (PAF = 39.3%) and tomato (PAF = 21.3%); eating a tomato might be associated with illness only because it is consumed with contaminated lettuce. However, a major strength of studies of sporadic cases is that, unlike outbreak investigations, they can identify the exposures associated with the most illnesses in a population; conclusions about associations can be bolstered by information from outbreaks and microbiologic studies of sources. Studies such as ours can be used to target interventions that reduce the most illnesses in a population and evaluate the effectiveness of the intervention.

In conclusion, sporadic non-O157 STEC infections were associated with a wide variety of food and farm animal environment-associated exposures, reflecting widespread carriage by animals. As for Salmonella, non-O157 STEC are a diverse group of organisms, widely distributed in food-producing and wild animals; many foods contaminated with animal feces transmit these pathogens. Therefore, non-O157 STEC infections might best be prevented by widespread improvements in food safety systems. To have the greatest effect in reducing the incidence of these infections, control measures should focus on decreasing contamination of produce consumed raw, especially lettuce, as well as improving the safety of food consumed in restaurants and decreasing transmission from animal environments. Such measures would also decrease illnesses caused by other enteric pathogens (30,32). Control measures that could be effective include decreasing carriage of pathogens by food animals, decreasing contamination of farm environments with food animal fecal matter, and decreasing contamination of foods of animal origin at slaughter. Transmission directly from farm animal environments could be decreased by improving hand hygiene; for example, by designing systems in which handwashing is the default behavior after exposure to those environments.

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#### References

 Collier SA, Deng L, Adam EA, Benedict KA, Beshearse EM, Blackstock AJ, et al. Estimate of burden and direct healthcare cost of infectious waterborne disease in the United States. Emerg Infect Dis. 2021;27:140–9. https://doi.org/10.3201/ eid2701.190676

- Gould LH, Mody RK, Ong KL, Clogher P, Cronquist A, Garman KN, et al. Increased recognition of non-O157 Shiga toxin-producing *Escherichia coli* infections in the United States during 2000–2010: epidemiologic features and comparison with *E. coli* O157 infections. Foodborne Pathog Dis. 2013;10:453–60. https://doi.org/10.1089/fpd.2012.1401
- Brooks HT, Sowers EG, Wells JG, Greene KD, Griffin PM, Hoekstra RM, et al. Non-O157 Shiga toxin-producing *Escherichia coli* infections in the United States, 1983–2002. J Infect Dis. 2005;192:1422–9. https://doi.org/10.1086/466536
- Strockbine NA, Bopp CA, Barrett TJ. Overview of detection and subtyping methods. In: Kaper JB, O'Brien AD, editors. *Escherichia coli* O157:H7 and other Shiga toxin-producing *E. coli* strains. Washington: American Society for Microbiology; 1998. p. 331-56.
- Hoefer D, Hurd S, Medus C, Cronquist A, Hanna S, Hatch J, et al. Laboratory practices for the identification of Shiga toxin-producing *Escherichia coli* infections in the United States, 2007. Foodborne Pathog Dis. 2011;8:555–60. https://doi.org/10.1089/fpd.2010.0764
- Stigi KA, MacDonald JK, Tellez-Marfin AA, Lofy KH. Laboratory practices and incidence of non-O157 Shiga toxin-producing *Escherichia coli* infections. Emerg Infect Dis. 2012;18:477–9. https://doi.org/10.3201/eid1803.111358
- Hughes JM, Wilson, Johnson KE, Thorpe CM, Sears CL. The emerging clinical importance of non-O157 Shiga toxinproducing *Escherichia coli*. Clin Infect Dis. 2006;43:1587–95. https://doi.org/10.1086/509573
- Bettelheim KA. The non-O157 Shiga-toxigenic (verocytotoxigenic) *Escherichia coli;* under-rated pathogens. Crit Rev Microbiol. 2007;33:67–87. https://doi.org/10.1080/ 10408410601172172
- Centers for Disease Control and Prevention. Recommendations for diagnosis of Shiga toxin-producing *Escherichia coli* infections by clinical laboratories. Morb Mortal Wkly Rep. 2009;58(RR-12):1–14.
- Centers for Disease Control and Prevention. National Enteric Disease Surveillance: Shiga toxin-producing *Escherichia coli* (STEC) annual report, 2015. 2017 [cited 2023 Apr 10]. https://www.cdc.gov/nationalsurveillance/pdfs/ STEC\_Annual\_Summary\_2015-508c.pdf
- Luna-Gierke RE, Griffin PM, Gould LH, Herman K, Bopp CA, Strockbine N, et al. Outbreaks of non-O157 Shiga toxin-producing *Escherichia coli* infection: USA. Epidemiol Infect. 2014;142:2270–80. https://doi.org/ 10.1017/S0950268813003233
- Tack DM, Kisselburgh HM, Richardson LC, Geissler A, Griffin PM, Payne DC, et al. Shiga toxin-producing *Escherichia coli* outbreaks in the United States, 2010-2017. Microorganisms. 2021;9:1521. https://doi.org/10.3390/ microorganisms9071529
- Cui Z, Marder EP, Click ES, Hoekstra RM, Bruce BB. Nearestneighbors matching for case-control study analyses: better risk factor identification from a study of sporadic campylobacteriosis in the United States. Epidemiol. 2022;33:633– 41; https://doi.org/10.1097/EDE.000000000001504
- Gower JC. A general coefficient of similarity and some of its properties. Biometrics. 1971;27:857–71. https://doi.org/ 10.2307/2528823
- Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. Ann Stat. 2001;29:1165–88. https://doi.org/10.1214/aos/1013699998
- Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol. 1985;122:904– 14. https://doi.org/10.1093/oxfordjournals.aje.a114174

- Centers for Disease Control and Prevention. The Interagency Food Safety Analytics Collaboration. Foodborne illness source attribution estimates for 2020 for *Salmonella*, *Escherichia coli* O157, and *Listeria monocytogenes* using multi-year outbreak surveillance data, United States. 2022 [cited 2023 Apr 10]. https://www.cdc.gov/foodsafety/ ifsac/pdf/p19-2020-report-triagency-508.pdf
- Economic Research Service, United States Department of Agriculture. COVID-19 working paper: shares of commodity consumption at home, restaurants, fast food places, schools, and other away-from-home places: 2013–16 [cited 2023 Apr 10]. https://www.ers.usda.gov/webdocs/publications/ 100138/ap-085.pdf
- Kassenborg HD, Hedberg CW, Hoekstra M, Evans MC, Chin AE, Marcus R, et al. Farm visits and undercooked hamburgers as major risk factors for sporadic *Escherichia coli* 0157:H7 infection: data from a case-control study in 5 FoodNet sites. Clin Infect Dis 2004;38(Suppl 3):S271–8.
- McPherson M, Lalor K, Combs B, Raupach J, Stafford R, Kirk MD. Serogroup-specific risk factors for Shiga toxin– producing *Escherichia coli* infection in Australia. Clin Infect Dis. 2009;49:249–56. https://doi.org/10.1086/599370
- Hsuan C, Ryan-Ibarra S, DeBurgh K, Jacobson DM. Association of paid sick leave laws on foodborne illness rates. Am J Prev Med. 2017;53:609–15. https://doi.org/10.1016/ j.amepre.2017.06.029
- Voetsch AC, Kennedy MH, Keene WE, Smith KE, Rabatsky-ehr T, Zansky S, et al. Risk factors for sporadic Shiga toxin-producing *Escherichia coli* O157 infections in FoodNet sites, 1999–2000. Epidemiol Infect. 2007;135:993– 1000. https://doi.org/10.1017/S0950268806007564
- Angelo KM, Nisler AL, Hall AJ, Brown LG, Gould LH. Epidemiology of restaurant-associated foodborne disease outbreaks, United Sates, 1998–2013. Epidemiol Infect. 2017;145:523–34. https://doi.org/10.1017/ S0950268816002314
- Bennett SD, Sodha SV, Ayers TL, Lynch MF, Gould LH, Tauxe RV. Produce-associated foodborne disease outbreaks, USA, 1998–2013. Epidemiol Infect. 2018;146:1397–406. https://doi.org/10.1017/S0950268818001620
- Painter JA, Hoekstra RM, Ayers T, Tauxe RV, Braden CR, Angulo FJ, et al. Attribution of foodborne illnesses, hospitalizations, and deaths to food commodities by using outbreak data, United States, 1998–2008. Emerg Infect Dis. 2013;19:407–15. https://doi.org/10.3201/eid1903.111866
- Marshall KE, Hezemer A, Seelman SL, Fatica MK, Blessington T, Hajmeer M, et al. Lessons learned from a decade of investigations of Shiga toxin-producing *Escherichia coli* outbreaks linked to leafy greens, United States and Canada. Emerg Infect Dis. 2020;26:2319–28. https://doi.org/10.3201/eid2610.191418
- Bottichio L, Keaton A, Thomas D, Fulton T, Tiffany A, Frick A, et al. Shiga toxin-producing *Escherichia coli* infections associated with romaine lettuce – United States, 2018. Clin Infect Dis. 2020;71:e323–30. https://doi.org/10.1093/cid/ciz1182
- US Department of Agriculture. USDA targeting six additional strains of E. coli in raw beef trim starting Monday, May 31, 2012 [cited 2023 Apr 10]. https://www.usda.gov/ media/press-releases/2012/05/31/usda-targeting-sixadditional-strains-ecoli-raw-beef-trim-starting
- Centers for Disease Control and Prevention. National Outbreak Reporting System Dashboard. [cited 2023 Apr 7]. https://wwwn.cdc.gov/norsdashboard

- Friedman CR, Hoekstra RM, Samuel M, Marcus R, Bender J, Shiferaw B, et al; Emerging Infections Program FoodNet Working Group. Risk factors for sporadic *Campylobacter* infection in the United States: a case-control study in FoodNet sites. Clin Infect Dis. 2004;38(Suppl 3):S285–96. https://doi.org/10.1086/381598
- Friesema I, Schotsborg M, Heck M, Van Pelt W. Risk factors for sporadic Shiga toxin-producing *Escherichia coli* O157 and non-O157 illness in the Netherlands, 2008–2012, using periodically surveyed controls. Epidemiol Infect. 2015;143:1360–7. https://doi.org/10.1017/S0950268814002349
- Hale CR, Scallan E, Cronquist AB, Dunn J, Smith K, Robinson T, et al. Estimates of enteric illness attributable to contact with animals and their environments in the United States. Clin Infect Dis. 2012;54(Suppl\_5):S472-9. https://doi.org/10.1093/cid/cis051
- Heiman KE, Mody RK, Johnson SD, Griffin PM, Gould LH. *Escherichia coli* O157 outbreaks in the United States, 2003–2012. Emerg Infect Dis. 2015;21:1293–301. https://doi.org/10.3201/eid2108.141364
- Daly RF, House J, Stanek D, Stobierski MG; National Association of State Public Health Veterinarians Animal Contact Compendium Committee. Compendium of measures to prevent disease associated with animals in public settings, 2017. J Am Vet Med Assoc. 2017;215:1268–92.
- Centers for Disease Control and Prevention. Laboratoryconfirmed non-O157 Shiga toxin-producing *Escherichia coli* – Connecticut, 2000–2005. Morb Mortal Wkly Rep. 2007;56:29–31.
- Hedican EB, Medus C, Besser JM, Juni BA, Koziol B, Taylor C, et al. Characteristics of O157 versus non-O157 Shiga toxin-producing *Escherichia coli* infections in Minnesota, 2000–2006. Clin Infect Dis. 2009;49:358–64. https://doi.org/10.1086/600302
- Rosenbaum P, Rubin DB. The bias due to incomplete matching. Biometrics. 1985;41:103–16. https://doi.org/ 10.2307/2530647
- Stuart EA. Matching methods for causal inference: a review and a look forward. Statist Sci. 2010;25:1–21. https://doi.org/10.1214/09-STS313
- Shirts BH, Bennett ST, Jackson BR. Using patients like my patient for clinical decision support: institution-specific probability of celiac disease diagnosis using simplified near-neighbor classification. J Gen Intern Med. 2013;28:1565– 72. https://doi.org/10.1007/s11606-013-2443-z
- 40. Scallan E, Jones TF, Cronquist A, Thomas S, Frenzen P, Hoefer D, et al. Factors associated with seeking medical care and submitting a stool sample in estimating the burden of foodborne illness. Foodborne Pathog Dis. 2007;3:432–8. https://doi.org/10.1089/fpd.2006.3.432
- Hardnett FP, Hoekstra RM, Kennedy M, Charles L, Angulo FJ. Epidemiologic issues in study design and data analysis related to FoodNet activities. Clin Infect Dis. 2004;38(S3):S121-6. https://doi.org/10.1086/381602
- 42. Blumberg SJ, Luke JV; National Center for Health Statistics. Wireless substitution: early release of estimates from the National Health Interview Survey, January–June 2017 [cited 2023 Apr 10]. https://www.cdc.gov/nchs/data/nhis/ earlyrelease/wireless201712.pdf

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