Farm Visits and Undercooked Hamburgers as Major Risk Factors for Sporadic *Escherichia coli* O157:H7 Infection: Data from a Case-Control Study in 5 FoodNet Sites

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In 1996, active surveillance in 5 Foodborne Diseases Active Surveillance Network (FoodNet) sites revealed up to a 9-fold difference in *Escherichia coli* O157:H7 (O157) infection incidence between sites. A matched case-control study of sporadic O157 cases was conducted in these sites from March 1996 through April 1997. Case subjects were patients with non–outbreak-related diarrheal illness who had O157 isolated from their stool samples. Control subjects were healthy persons matched by age and telephone number exchange. Overall, 196 case patients and 372 controls were enrolled. O157 infections were associated with farm exposure, cattle exposure, eating a pink hamburger (both at home and away from home), eating at a table-service restaurant, using immunosuppressive medication, and obtaining beef through a private slaughter arrangement. Variations in cattle exposures may explain a part of the regional variability of O157 infection incidence. O157 control measures should focus on reducing risks associated with eating undercooked hamburger, dining at table-service restaurants, and farm exposures.

Escherichia coli O157:H7 (*E. coli* O157) was recognized as a significant foodborne pathogen in the early 1980s and continues to be a major cause of diarrheal illness in North America. *E. coli* O157 infections are the primary cause of hemolytic uremic syndrome (HUS) in children [1]. In the United States, >70,000 *E. coli* O157 infections are estimated to occur each year [2], and >200 outbreaks were reported to the Centers for Disease Control and Prevention (CDC) from 1994 to 2000 (J. Rangel, CDC; unpublished data).

Many foods have been associated with *E. coli* O157 outbreaks. These include those of bovine origin (e.g., ground beef [3], roast beef [4], and raw milk [5]) and foods likely contaminated by bovine feces (e.g., lettuce [6], alfalfa sprouts [7], and apple cider [8]). Nonfoodborne outbreaks have been associated with attending child day care [9], drinking contaminated water [10], and swimming in unchlorinated water [11, 12].

Risk factors for sporadic *E. coli* O157 infection have been examined in previous case-control studies in limited populations, several of which have identified eating

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undercooked or raw meat, ground beef, or hamburgers as a risk factor [13–17]. Other risk factors identified in these studies include drinking unchlorinated well water [17], swimming in a pond [17], having a household member with diarrhea [17], and eating at a picnic or special event [15].

To better determine the burden of *E. coli* O157 infections and other foodborne illnesses in the United States, the Foodborne Diseases Active Surveillance Network (FoodNet) was initiated in 1995 as a collaborative effort between the CDC, the US Department of Agriculture (USDA), the US Food and Drug Administration (FDA), and selected state health departments [18]. In 1996, active surveillance for all laboratory-diagnosed cases of *E. coli* O157 infection was initiated at all FoodNet surveillance areas (also known as "FoodNet sites"; Minnesota, Oregon, and selected counties in California, Connecticut, and Georgia) then in existence.

Results of active surveillance for 1996 revealed a high degree of variability among these sites in the incidence of detected *E. coli* O157 infections: from 0.6 cases (Georgia) to 5.0 cases (Minnesota) per 100,000 population [18]. Differences in laboratory practices and physicians' knowledge of laboratory practices appeared to account for only some of the difference in detected incidence between sites [19, 20]. Even after accounting for these factors, we still observed real regional differences in the incidence of *E. coli* O157 infections. To further define risk factors for sporadic *E. coli* O157 infection, we conducted a matched case-control study from 1 March 1996 through 30 April 1997 at the FoodNet sites.

METHODS

In 1996, the FoodNet catchment area consisted of Minnesota, Oregon, and selected counties in California (Alameda and San Francisco), Connecticut (Hartford and New Haven), and Georgia (Cobb, Clayton, Douglas, DeKalb, Fulton, Gwinnett, Rockdale, and Newton). The FoodNet surveillance area covered an estimated population of 14,281,096 persons (5.4% of the US population). Cases were identified via active laboratory surveillance: surveillance personnel within each site contacted each of the 263 laboratories serving the catchment areas to ascertain all *E. coli* O157 cases confirmed by culture. The laboratories were contacted either weekly or monthly, depending on their size.

A case was defined as diarrheal illness in a person living in a FoodNet site whose stool culture yielded *E. coli* O157:H7 or Shiga toxin–producing *E. coli* O157:NM and whose illness was not part of a recognized outbreak. Diarrhea was defined as $\geqslant$3 loose stools in a 24-h period. One to 2 control subjects were identified for each case patient and were matched with the case patient by age (0 to <6 months, 6 to <24 months, 2 to <6 years, 6 to <12 years, 12 to <18 years, 18 to <40 years, 40 to <60 years, and $\geqslant$60 years) and telephone number exchange. Most controls were obtained by a sequential digit dialing method. For children <2 years of age, controls could be obtained by sequential digit dialing (California and Georgia) or from 1 of 2 additional sources: the FoodNet site's birth registry (Connecticut, Minnesota, and Oregon) or a list of children, obtained from the case patient's physician, who had been seen recently during healthy child visits.

Case patients were interviewed within 21 days of their stool sample collection date, and controls were interviewed within 7 days after the patient's interview. Patients were excluded if their diarrhea started >10 days before their stool sample was collected, if they were unreachable by telephone within 21 days after their stool collection date, if a household member had bloody diarrhea in the 28 days before the patient's illness onset date, or if the patient could not recall their illness onset date. Potential controls were excluded if they had diarrhea in the 28 days before the patient's onset date. In addition, all subjects were excluded if they could not speak English, if they did not have a home telephone, if they or a household member had a confirmed infection with *E. coli* O157 in the 28 days before the patient's stool sample collection date, or if they were unable to complete the interview. We obtained appropriate informed consent and conducted this study in accordance with guidelines for human research as specified by the US Department of Health and Human Services.

Questionnaire description. Case patients were asked about their symptoms, hospitalization, number of days lost from work or school, and treatment. Case patients and controls were both asked about their antibiotic and antacid use and any immunocompromising conditions or chronic illnesses that existed in the 4 weeks before the case patient's onset of illness, as well as travel, child day care, exposure to farms and cows, meat-handling practices, sources of drinking water and ground beef, and consumption of fruits, vegetables, and meats during the

Table 1. *Escherichia coli* O157:H7 cases found in active surveillance and in participants enrolled in case-control study of sporadic *E. coli* O157:H7 illness in 5 Foodborne Diseases Active Surveillance Network (FoodNet) sites (Minnesota, Oregon, and selected counties in California, Connecticut and Georgia), 1996–1997.

	No. (%) of cases, by study type			
	Active surveillance		Case-control study	
Site	Total	Outbreak-associated	Case patients	Controls
California	22 (6)	3 (3)	7 (4)	12 (3)
Connecticut	39 (10)	18 (17)	13 (7)	22 (6)
Georgia	16 (4)	0 (0)	10 (5)	19 (5)
Minnesota	246 (62)	78 (72)	112 (57)	212 (57)
Oregon	73 (18)	11 (8)	54 (28)	107 (29)
Total	396 (100)	108 (100)	196 (100)	372 (100)

5-day period before the case patient's date of disease onset. In all, the questionnaire solicited information on 157 variables. Participants who ate ⩾4 different food items in each of the 3 food categories (meats, vegetables, and fruits) were considered to have a varied diet. FoodNet interviewers gathered information from a parent or guardian of children <12 years of age and obtained permission from a parent or guardian before interviewing persons <18 years of age.

Statistical analysis. EpiInfo, version 6.04b (CDC) [21], PC-SAS, versions 6.12 [22] and 8.1 (SAS Institute) [23], and LogXact-4 for Windows, version 4.1 (Cytel Software) [24], were used in univariate and multivariate analyses. We performed multivariable analysis of the relationship between sporadic *E. coli* O157 infection and the set of exposure and potential confounder variables and produced a multivariable conditional logistic regression model for sporadic illness with *E. coli* O157. Candidate variables included those associated with disease status ($P \leqslant .06$) in a single-variable conditional logistic model, variables previously shown to be associated with *E. coli* O157 infection, and variables that made epidemiologic sense in the context of the study. We also derived additional candidate variables from items measured on the questionnaire. For example, we constructed a variable that coded for whether study participants obtained their ground beef via a private slaughter arrangement from an open-ended question that asked about ground beef sources. We pursued a variety of model selection strategies, including automatic forward, backward, and best subset selection strategies based on F-test and χ^2 score criteria, as well as manual strategies based on examining changes in the regression parameter vector and model fit criteria, such as Akaike's information criterion. To evaluate the effect of missing values on model stability, we used simple imputation and subsequent model fit comparison [25]. From the final model, we calculated population-attributable fractions for the model components to describe the relative importance of each "exposure" to the overall disease process [26].

RESULTS

During the study period, 396 *E. coli* O157 cases were identified in the catchment areas (table 1). The greatest number of cases were reported in Minnesota (246 cases [62%]), followed by Oregon (73 [18%]), Connecticut (39 [10%]), California (22 [6%]), and Georgia (16 [4%]). There were 108 outbreak-associated cases, of which 74 (69%) were associated with attending child day care, 10 (9%) with drinking apple cider, 8 (7%) with eating lettuce, 5 (5%) with attending a wedding, 4 (4%) with swimming in a lake, 2 (2%) with eating at a fast-food (i.e., non–table service) restaurant, and 2 (2%) with eating a hamburger at a table-service restaurant. We enrolled 196 (68%) of the 288 patients identified as having a sporadic case, as well as 372 controls. Infected persons enrolled and those not enrolled in the study were similar in age and other demographic factors. Children <6 years of age accounted for 24% of enrolled case patients but only 9% of the catchment population (figure 1). Nearly one-half of the case patients enrolled (91 patients [46%]) were <12 years of age. Bloody stools were reported by 180 (92%) of the enrolled case patients, and 97 (49%) of those enrolled recalled having had a large amount of blood in their stool. Other common symptoms among case patients included abdominal cramps (181 patients [92%]), fever (97 [50%]), and vomiting (96 [49%]).

In univariate analyses, sporadic *E. coli* O157 infection was

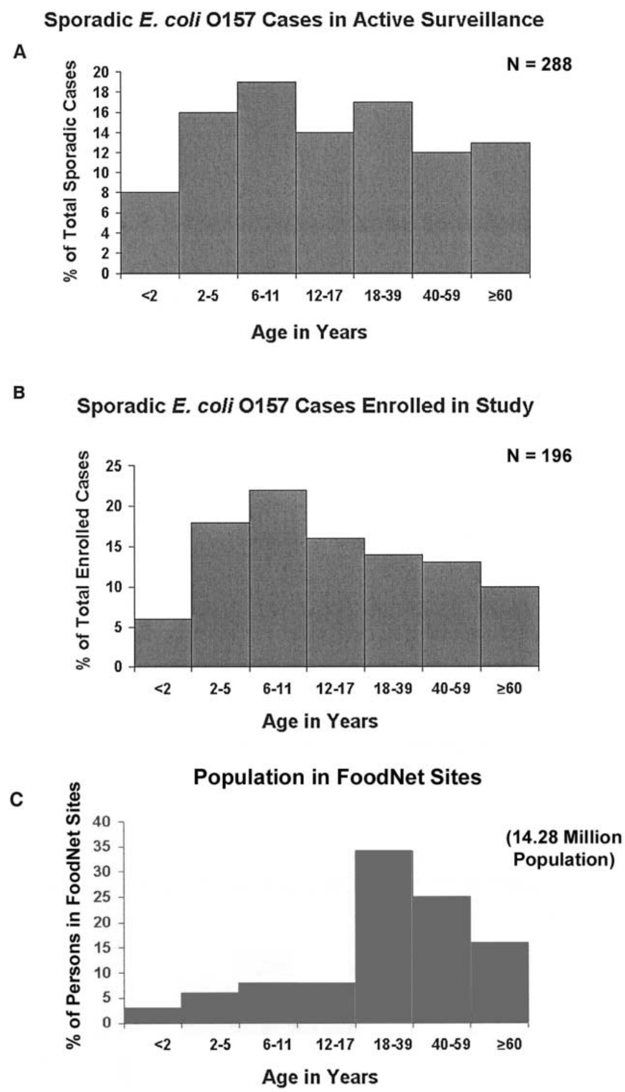

Figure 1. Comparison of age distribution among sporadic *Escherichia coli* O157:H7 cases in active surveillance *(A), E. coli* O157:H7 infections in patients enrolled in a case-control study *(B),* and population in Foodborne Diseases Active Surveillance Network (FoodNet) sites (Minnesota, Oregon, and selected counties in California, Connecticut and Georgia), 1996–1997 *(C).*

associated with eating a pink hamburger at home, eating a pink hamburger away from home, and eating in a table-service restaurant (table 2). Additionally, among persons aged ⩾6 years, it was associated with visiting a farm that had cattle and taking immunosuppressive medications (such as prednisone); and among children <6 years of age, it was associated with living on a farm or visiting a farm and having a child <2 years of age in the household (table 2). Persons with a varied diet had a decreased risk for *E. coli* O157 infection. When we placed these variables into a multivariate model, we found them all to be independently associated with *E. coli* O157 infection (table 2).

We next explored identified risk factors in more detail. We found that eating a nonpink hamburger was not associated with sporadic *E. coli* O157 infection (i.e., persons who did not recall specifically eating a pink hamburger were not at increased risk for *E. coli* O157 infection from eating a hamburger) (matched OR [MOR], 1.1; 95% CI, 0.6–1.8; $P = .8$). Among persons who ate hamburgers in restaurants, case patients were less likely than controls to have eaten a hamburger only at a major fast-food restaurant (32 [63%] of 51 case patients vs. 100 [91%] of 110 controls; MOR, 0.09; 95% CI, 0–0.6; $P = .01$). In fact, eating pink hamburger from a major fast-food restaurant was rarely reported: only 3 (3%) of 102 study participants who ate hamburgers only at major fast-food restaurants reported eating a pink hamburger, compared with 6 (21%) of 22 who ate hamburgers only at other types of restaurants ($P < .01$).

Among persons who consumed ground beef or hamburgers at home, obtaining beef through a private slaughter arrangement was a risk factor for *E. coli* O157 infection (12 [16%] of 77 case patients vs. 18 [9%] of 202 controls; MOR, 5.6; 95% CI, 1.1–54; $P = .02$). Private slaughter arrangements are made between livestock owners and individuals who purchase an animal and arrange for it to be slaughtered and processed locally by a custom processor for private consumption only. Approximately 2% of Minnesota cattle are processed in this way [27]. This exposure varied by site: 7% of case patients in Minnesota and 7% of those in Oregon but none of the study participants in California, Connecticut, and Georgia reported obtaining privately slaughtered ground beef.

Risk factors associated with farm and cattle exposure varied by age group. Because of small sample size, a meaningful analysis of risks associated with exposure to farm cattle was not possible for the group of subjects aged <6 years. We also found considerable variation among sites in frequency of exposure to farms with cattle: 21 (18%) of 112 case patients in Minnesota and 11 (20%) of 54 case patients in Oregon reported visiting a farm that had cattle. None of the case patients in California, Connecticut, or Georgia and only 1 control each in California and Connecticut and none in Georgia reported exposure to farms that had cattle.

Because a varied diet was associated with a decreased risk for infection with *E. coli* O157, we further examined the correlation between risk for infection and eating foods from particular groups. We found that consuming ⩾4 vegetable or fruit items from those listed on the questionnaire was associated with a decreased risk for *E. coli* O157 infection: 140 [38%] of 372 controls ate ⩾4 servings of fruits or vegetables, whereas only 48 [25%] of 195 case patients did so (MOR, 0.5; 95% CI, 0.3–0.7; $P = .0006$).

Table 2. Risk factors for sporadic *Escherichia coli* O157:H7 infection in 5 Foodborne Diseases Active Surveillance Network (FoodNet) sites (Minnesota, Oregon, and selected counties in California, Connecticut and Georgia), 1996–1997

	Enrolled case patients, *n/N* (%)	Enrolled controls, *n/N* (%)	Univariate analysis		Multivariate analysis		
Exposure[a]	(n = 196)	(n = 372)	MOR (95% CI)	*P*	MOR (95% CI)	*P*	PAR[b]
Ate at table-service restaurant	91/193 (47)	127/357 (36)	1.7 (1.2–2.5)	.005	1.7 (1.0–2.9)	.04	20
Ate pink hamburger at home	16/170 (9)	15/338 (4)	2.1 (0.97–4.6)	.06	5.0 (1.7–15)	.004	8
Ate pink hamburger away from home	13/153 (9)	5/316 (2)	6.4 (1.8–23)	.005	5.0 (1.3–20)	.02	7
Diet variability	116/192 (60)	300/366 (82)	0.3 (0.2–0.5)	.0001	0.4 (0.2–0.7)	.007	—
For persons ⩾6 years of age							
Visited farm with cows	14/193 (7)	5/368 (1)	6.2 (2.0–19)	.001	10 (1.8–53)	.007	8
Used immunosuppressive medication	8/193 (4)	4/372 (1)	4.3 (1.1–17)	.03	11 (1.6–72)	.02	5
For persons <6 years of age							
Lived on farm or visited farm	17/195 (9)	8/369 (2)	6.2 (2.1–19)	.001	5.2 (1.3–22)	.02	6
Child <2 years of age in household	14/196 (7)	11/372 (3)	3.1 (1.2–80)	.02	5.4 (1.2–25)	.03	6

NOTE. MOR, matched OR; PAR, population attributable risk.

[a] Exposure to variables listed were during the 5 days before case patient's diarrhea onset, except for immune suppressive medication, which referred to the previous 4 weeks

[b] Calculated from the 139 matched pairs for whom all information was available

DISCUSSION

This is the first broad population-based case-control study of sporadic *E. coli* O157 infections conducted as part of FoodNet, a multiple-state active surveillance program [18]. The study yielded 3 major findings. First, cattle remain the primary reservoir of public health importance for *E. coli* O157. This was shown by the association of sporadic *E. coli* O157 infection with eating undercooked ground beef, exposure to cattle on farms, and consuming locally slaughtered beef (i.e., obtaining beef through a private slaughter arrangement). Second, *E. coli* O157 infection was associated with eating in a table-service restaurant but not in a fast-food restaurant; this was likely associated with more handling and serving of undercooked ground beef at table-service restaurants. Third, the more frequent exposure of Minnesota and Oregon residents to cattle on farms or locally slaughtered beef probably contributes to the higher observed incidence of *E. coli* O157 infections in these sites.

A multiple-center study conducted from 1990 to October 1992 implicated eating at fast-food restaurants as a risk factor for *E. coli* O157 infection [17]. Subsequently, a well-publicized outbreak of *E. coli* O157 infections from December 1992 through February 1993 in the Pacific Northwest was associated with eating at a fast-food chain. As a result, the FDA changed the recommended cooking practices for ground beef within its Model Food Code [28]. In 1994, the USDA declared *E. coli* O157:H7 an adulterant in ground beef, and the sale of raw ground beef known to contain this pathogen was prohibited. Also in 1994, the National Livestock and Meat Board's Blue Ribbon Task Force recommended developing objective measures of doneness, such as those used in automated cooking systems [29]. The results of our study, which did not show an association between *E. coli* O157 infection and eating in fast-food restaurants, suggest that these changes have lowered the risk of acquiring *E. coli* O157 infections at fast-food restaurants. In contrast, we found that eating at a table-service restaurant had a relatively large attributable risk for *E. coli* O157 infection (table 2). Whereas pink hamburgers were readily available at table-service restaurants, few participants in our study reported eating a pink hamburger at a fast-food restaurant. In addition, cross-contamination of other food items with raw beef products may be an important source of sporadic *E. coli* O157 infections associated with table-service restaurants that cannot be well assessed by a study of sporadic cases. Cross-contamination from beef was likely the cause of 9 restaurant- or delicatessen-associated *E. coli* O157 outbreaks in the United States from 1982 through 2000 (J. Rangel, CDC; unpublished data).

Concerns have been raised that because ground beef sometimes turns brown prematurely, hamburger that is not pink on the inside may still not be adequately cooked [30]. In this study, subjective evaluation of hamburger color was used as a measure of adequate cooking. Only eating hamburgers that were pink was associated with *E. coli* O157 infection. To be certain that pathogens have been killed, the USDA recommends cooking hamburgers thoroughly, until they obtain an internal temperature of 71°C (160°F). Our results suggest, however, that when consumers do not use a thermometer, they can still decrease their risk of illness by ensuring that the inside of the hamburger is not pink.

The differences in disease risk associated with exposures to farms and cattle by age group may be due to the higher frequency of acquired immunity among adults who had *E. coli* O157 or other Shiga toxin–producing *E. coli* (STEC) infections in childhood. Farm exposure has been implicated in outbreaks of *E. coli* O157 infection [31], and, in a descriptive study of sporadic *E. coli* O157 infections in Scotland, researchers found a high proportion of case patients living on or visiting farms [32]. These findings are logical, because cattle are an important reservoir of *E. coli* O157 and other STEC [33, 34], and they transiently shed these organisms in their feces [35, 36]. *E. coli* O157 can survive for many months in the environment, depending on conditions [37, 38]. Reymond et al. [39] found that levels of antibodies to *E. coli* O157 and other STEC were higher in Ontario dairy farm families than in urban Toronto residents, and, in another study, antibodies to Shiga toxin 1 appeared to be protective in an STEC outbreak due to *E. coli* O111:H− in which seronegative urban farm visitors became ill but seropositive farm residents did not [40]. The differences in frequency of exposure to farm- and cattle-associated risk factors among participant from different sites probably explains a portion of the large variation in *E. coli* O157 infection incidence among these FoodNet sites. Exposure to farms with cattle and consumption of privately slaughtered beef was more common among both case patients and controls in the more rural sites (Minnesota and Oregon) than among those in the more urban ones (California, Connecticut, and Georgia). Future studies of sporadic *E. coli* O157 infection should include further exploration of farm-specific risk factors.

Immunosuppression is a well-documented risk factor for bacterial illness but has not been previously documented for *E. coli* O157 infection. Our finding that it is a risk factor for *E. coli* O157 infection validates recommendations that persons with suppressed immune systems avoid eating undercooked hamburger and use good hand-washing procedures [41], particularly after exposure to raw ground beef, farms, and cattle.

Several risk factors identified in outbreaks of *E. coli* O157 infection during the period of the study, such as day care exposure, consuming apple cider and lettuce, swimming in a lake, and eating at a fast-food restaurant, were not associated with sporadic *E. coli* O157 infection in our study. This lack of association may be due to cases caused by these exposures being successfully linked to outbreaks (and thus excluded from our study) or to study design factors, such as questionnaire limitations or study size. The fact that 74 (19%) of the 396 *E. coli* O157 illnesses identified in the catchment area were linked to child day care exposure indicates the importance of this venue in disease transmission. *E. coli* O157 infection is readily transmitted in child day care settings, and the introduction of this pathogen into these settings may frequently result in an outbreak [9]. The lack of association between apple cider consumption and sporadic *E. coli* O157 infection may be in part due to the questionnaire not distinguishing between drinking fresh apple cider and processed apple cider.

With regard to interpreting attributable fractions, 2 points should be noted. First, because we excluded outbreak-related cases from our study, our attributable fractions give only a partial picture of the overall disease risk attributable to a particular risk factor. Second, the attributable fractions describe the reduced probability of disease in this population were the risk factor to be completely removed: we did no counterfactual modeling to estimate the changes that would result from modifying rather than eliminating the exposure.

Current public health recommendations for cooking ground beef may reduce the impact of 3 of the 4 major risk factors identified by this study: eating undercooked hamburgers at home, eating undercooked hamburgers away from home, and eating in a table-service restaurant. These 3 risk factors are likely the result of directly eating contaminated ground beef or eating foods contaminated from raw beef. Our findings indicate that consumers can reduce their risk for illness due to *E. coli* O157 in the home by properly handling raw ground beef and cooking hamburgers thoroughly, either until they are no longer pink on the inside or until a digital instant-read thermometer reads 71°C (160°F). Similarly, restaurants should standardize hamburger cooking procedures to eliminate undercooked hamburgers and incorporate strategies to reduce cross-contamination from beef.

Although public health recommendations on handling and cooking ground beef appear to be effective in preventing sporadic *E. coli* O157 infection, they rely heavily on education and compliance by vast numbers of individual consumers and commercial food-service operators. Thus, they are not likely to be completely effective. A logical addition to these recommended precautions is to irradiate ground beef at the source of production. One study has shown that, if consumers are educated about irradiation, they accept the idea and are willing to purchase irradiated food products [42]. Adoption of this safe, approved technology by even a few large meat processors would have far-reaching public health benefits.

Our finding that a varied diet was protective is intriguing. One possible reason for this is that a varied diet simply decreases the opportunities for exposure to risky food items. However, a varied diet could increase a person's resistance to disease by providing bowel flora that help protect against colonization with pathogens [43], by providing certain micronutrients [44] or other substances [45], or by other methods [46]. This finding, however, must be interpreted with caution, because our study was not designed to assess diet variability or the possible protective effects of a varied diet, and further work is needed.

Outbreaks of *E. coli* O157 infections associated with direct transmission from animals to humans have been reported in the United States and elsewhere [47–49]. These reports have led to recommendations to prevent the transmission of enteric pathogens at venues where the public is allowed access to farm animals (e.g., petting zoos and animal exhibits) [47, 49]. Our findings support these recommendations, which include limiting contact between high-risk persons (e.g., young children, persons with suppressed immune systems, and elderly individuals) and animals in these venues and encouraging people to wash their hands thoroughly after farm environment and cattle exposures.

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