JOURNAL OF CLINICAL MICROBIOLOGY, July 2004, p. 2944–2951 Vol. 42, No. 7
0095-1137/04/$08.00+0 DOI: 10.1128/JCM.42.7.2944–2951.2004

Risk Factors for Sporadic Cryptosporidiosis among Immunocompetent Persons in the United States from 1999 to 2001

Sharon L. Roy,[1]* Stephanie M. DeLong,[2] Sara A. Stenzel,[3] Beletshachew Shiferaw,[4] Jacquelin M. Roberts,[1] Asheena Khalakdina,[5] Ruthanne Marcus,[6] Suzanne D. Segler,[7] Dipti D. Shah,[8] Stephanie Thomas,[9] Duc J. Vugia,[10] Shelley M. Zansky,[11] Vance Dietz,‡ Michael J. Beach,[1] and the Emerging Infections Program FoodNet Working Group†

Division of Parasitic Diseases[1] and FoodNet, Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases,[2] National Center for Infectious Diseases, Centers for Disease Control and Prevention, and Georgia Division of Public Health,[9] Atlanta, and Georgia Emerging Infections Program, Atlanta VA Medical Center, Decatur,[7] Georgia; Foodborne, Vectorborne, and Zoonotic Diseases Unit, Acute Disease Investigation and Control Section, Minnesota Department of Health, Minneapolis, Minnesota[3]; Oregon Department of Human Services, Portland, Oregon[4]; School of Public Health, University of California at Berkeley,[5] and Infectious Diseases Branch, Division of Communicable Disease Control, California Department of Health Services,[10] Berkeley, California; Connecticut Emerging Infections Program, Yale University School of Public Health, New Haven, Connecticut[6]; Maryland Department of Health and Mental Hygiene, Baltimore, Maryland[8]; and Emerging Infections Program, New York State Department of Health, Albany, New York[11]

Received 19 December 2003/Returned for modification 1 February 2004/Accepted 28 March 2004

Many studies have evaluated the role of *Cryptosporidium* spp. in outbreaks of enteric illness, but few studies have evaluated sporadic cryptosporidiosis in the United States. To assess the risk factors for sporadic cryptosporidiosis among immunocompetent persons, a matched case-control study was conducted in seven sites of the Foodborne Diseases Active Surveillance Network (FoodNet) involving 282 persons with laboratory-identified cryptosporidiosis and 490 age-matched and geographically matched controls. Risk factors included international travel (odds ratio [OR] = 7.7; 95% confidence interval [95% CI] = 2.7 to 22.0), contact with cattle (OR = 3.5; 95% CI = 1.8 to 6.8), contact with persons >2 to 11 years of age with diarrhea (OR = 3.0; 95% CI = 1.5 to 6.2), and freshwater swimming (OR = 1.9; 95% CI = 1.049 to 3.5). Eating raw vegetables was protective (OR = 0.5; 95% CI = 0.3 to 0.7). This study underscores the need for ongoing public health education to prevent cryptosporidiosis, particularly among travelers, animal handlers, child caregivers, and swimmers, and the need for further assessment of the role of raw vegetables in cryptosporidiosis.

Cryptosporidium sp. is protozoan parasite that causes diarrheal illness via fecal-oral transmission and has an incubation period up to 2 weeks. The first human case was reported in 1976 (1). By the year 2000, more than 3,000 cases had been reported to the Centers for Disease Control and Prevention (CDC), placing cryptosporidiosis among the top 20 most common nationally notifiable diseases, right behind infection with *Escherichia coli* O157:H7 (7).

Cryptosporidium has become a well-known cause of opportunistic infections among AIDS patients (6) and of outbreaks of gastrointestinal disease (1). However, with data from 1997 and 1998, researchers have estimated that 56% of cryptosporidiosis case-patients detected by active surveillance were not infected with human immunodeficiency virus (HIV), and 90% were not involved in outbreaks (16). Therefore, sporadic cryptosporidiosis among immunocompetent persons may represent a significant proportion of the disease burden. To better understand the epidemiology of this disease, we conducted a matched case-control study to evaluate the risk factors for sporadic laboratory-confirmed cryptosporidiosis among immunocompetent persons and to characterize the proportion of sporadic cases in this population that may be attributable to some of these risk factors.

MATERIALS AND METHODS

During 1999 through 2001, seven FoodNet sites in seven states participated in the present study: California, Connecticut, Georgia, Maryland, Minnesota, Oregon, and New York. FoodNet is a collaborative project of the Centers for Disease Control and Prevention (CDC), 10 state health departments, the U.S. Department of Agriculture, and the U.S. Food and Drug Administration (14). FoodNet monitors trends in food-borne infections by using surveillance for laboratory-confirmed illness caused by several enteric pathogens commonly transmitted through food. Under a protocol approved by CDC and state institutional review boards, case-patients within the FoodNet catchment areas who had positive stool tests for *Cryptosporidium* oocysts were contacted by telephone and enrolled in the study. Testing occurred in clinical laboratories throughout the FoodNet sites by using acid-fast staining, direct fluorescent antibody staining, or commercial enzyme-linked immunosorbent assay diagnostic kits. Case-patients who were immunocompromised or part of recognized outbreaks of cryptosporidiosis were excluded. Case-patients were categorized as immunocompro-

* Corresponding author. Present address: Education, Information, and Partnership Branch, Immunization Services Division, National Immunization Program, Centers for Disease Control and Prevention, 1600 Clifton Rd., Mailstop E52, Atlanta, GA 30333. Phone: (404) 639-8638. Fax: (404) 639-8828. E-mail: str2@cdc.gov.

† Contributing members of the Emerging Infections Program FoodNet Working Group are listed in the Acknowledgments.

‡ Present address: Global Immunization Division, National Immunization Program, Centers for Disease Control and Prevention, Atlanta, GA 30333.

TABLE 1. Demographic and health characteristics of 282 case-patients and 490 controls[a]

Variable	Category	No. of cases # (%)	No. of controls # (%)	P[a]
Sex	Male	153 (54)	232 (48)	0.09
	Female	129 (46)	255 (52)	0.09
Age[b] (yr)	<1	3 (1)	6 (1)	NA[d]
	1 to <6	99 (35)	167 (34)	NA
	6 to <12	42 (15)	69 (14)	NA
	12 to <18	27 (10)	50 (10)	NA
	18 to <26	23 (8)	39 (8)	NA
	26 to <45	68 (24)	122 (25)	NA
	45 to <65	17 (6)	32 (7)	NA
	≥65	3 (1)	5 (1)	NA
Race	White	251 (92)	429 (90)	0.36
	African American	13 (5)	32 (7)	0.30
	American Indian/Alaskan Native	5 (2)	6 (1)	0.60
	Asian/Pacific Islander	5 (2)	7 (1)	0.92
	Mixed race	0	3 (1)	NA[c]
Ethnicity	Hispanic	15 (5)	27 (6)	0.89
	Non-Hispanic	264 (95)	461 (94)	0.89
Location of primary residence	City or urban	96 (34)	151 (31)	0.24
	Suburban	56 (20)	110 (23)	0.12
	Town or village	48 (17)	106 (22)	0.12
	Rural but not farm	42 (15)	75 (15)	0.94
	Farm	39 (14)	46 (9)	0.05
State[b]	California	23 (8)	42 (9)	NA
	Connecticut	16 (6)	26 (5)	NA
	Georgia	47 (17)	85 (17)	NA
	Maryland	4 (1)	7 (1)	NA
	Minnesota	145 (51)	239 (49)	NA
	New York	22 (8)	44 (9)	NA
	Oregon	25 (9)	47 (10)	NA
Health status	Chronic medical condition	59 (21)	67 (14)	0.01

[a] Demographic and health data were missing for some case-patients and controls. Percentages and *P* values were calculated using the total number of cases or controls with complete demographic data for each variable.
[b] Case-patients and controls were matched by age and state and, therefore, *P* values were not calculated in these categories.
[c] No case-patients were of mixed race. Therefore, a matched odds ratio could not be generated.
[d] NA, not applicable.

mised if they stated they met one of the following conditions: if they had cancer or were receiving immunosuppressive chemotherapy, if they had a recent or planned organ transplant, if they had HIV/AIDS, or if they had a history of intravenous drug use, long-term steroid use, or illness due to excessive use of alcohol. Outbreak-related case-patients were identified through investigations by health department staff.

Controls were geographically matched by residence within the same FoodNet catchment area and age-matched by the following age categories: <6 months, 6 to <12 months, 1 to <6 years, 6 to <12 years, 12 to <18 years, 18 to <26 years, 26 to <45 years, 45 to <65 years, and ≥65 years. Up to two controls were matched to each case, but only one control was recruited per household. Controls ≥1 year of age were recruited by using random or progressive telephone digit dialing anchored on the telephone numbers of the case-patients. Controls <1 year of age were recruited by using either (i) progressive telephone digit dialing anchored as described above or (ii) vital records for children within the same zip codes as the case-patients, with subsequent enrollment of children whose birth dates were closest to the case-patients' birth dates.

We obtained informed consent from participants and conducted research in accordance with guidelines for human experimentation as specified by the U.S. Department of Health and Human Services. Consent for the interview was obtained directly from the case-patients or controls or from their parents or guardians if the participants were <18 years of age. FoodNet staff administered a structured questionnaire by telephone to participants ≥12 years of age or to the parents or guardians of participants <12 years of age. Participants were asked about potential exposures in the 14 days prior to the estimated date of onset of diarrhea in the matched case-patient. Exposures under investigation were grouped into several categories: contact with persons with diarrhea, contact with animals, travel, recreational water, drinking water, and food and beverage consumption. Participants were also asked questions about demographics (i.e., sex, race, ethnicity, degree of urbanization) and health status (i.e., the presence of chronic medical conditions requiring regular medication or regular medical follow-up).

Data were analyzed by using SAS (SAS System for Windows, version 8; SAS Institute, Inc., Cary, N.C.) with multivariate conditional logistic regression based on the Cox proportional hazards model. Crude odds ratio (OR) and 95% confidence interval (95%CI) values were generated for each exposure variable. Adjusted ORs were then generated controlling for demographics, degree of urbanization, and health status. Variables with statistically significant ($P < 0.05$) crude ORs and/or those that had biologic plausibility or were known risk factors for immunocompromised persons or persons in outbreak situations were included in larger multivariate models. Interaction was explored and assessed in all multivariate models. Population attributable risks (PARs) were calculated by using results from the final multivariate model.

RESULTS

FoodNet staff identified 983 case-patients during the 2-year study period. Of these, 282 case-patients were enrolled. The majority of excluded case-patients were not enrolled because of the following reasons. Thirty-four percent ($n = 238$) were excluded because they identified themselves as immunocom-

TABLE 2. Univariate association between individual exposure variables and case status, adjusted for demographics and health status[a]

Category	Exposure variable	No./total no. (%)		Matched OR (95% CI)[a]	*P*
		Cases	Controls		
Contact with persons with diarrhea	Contact with persons ≤2 yr old	28/245 (11)	23/438 (5)	2.7 (1.4–5.4)	<0.01
	Contact with persons >2 to 11 yr old	39/246 (16)	31/438 (7)	2.6 (1.5–4.5)	<0.01
	Contact with persons >11 to 17 yr old	4/247 (2)	13/440 (3)	0.6 (0.2–2.0)	0.41
	Contact with persons ≥18 yr old	31/248 (13)	46/440 (10)	1.2 (0.7–2.0)	0.54
Contact with animals	Contact with calves or cows	63/265 (24)	43/461 (9)	3.4 (2.0–5.8)	<0.01
Travel	Domestic travel	72/267 (27)	127/461 (28)	1.0 (0.7–1.4)	0.91
	International travel	33/267 (12)	8/461 (2)	7.8 (3.3–18.4)	<0.01
Recreational water	Freshwater swimming	53/266 (20)	65/464 (14)	1.6 (1.0–2.5)	<0.05
	Marine swimming	18/267 (7)	16/464 (3)	2.6 (1.2–5.6)	0.02
	Pool swimming	89/267 (33)	136/462 (29)	1.3 (0.8–1.9)	0.27
	Community/municipal pool swimming	27/86 (31)	58/135 (43)	0.6 (0.2–2.1)	0.40
	Subdivision/neighborhood pool swimming	5/86 (6)	3/135 (2)	0.9 (0.1–10.1)	0.90
	Home pool swimming	17/85 (20)	44/135 (33)	0.2 (0.05–1.0)	<0.05
	Kiddie/wading pool swimming	19/86 (22)	19/135 (14)	3.6 (0.9–14.2)	0.07
	Private pool (club, apartment, motel, etc.) swimming	35/86 (41)	28/135 (21)	3.7 (1.0–13.4)	<0.05
	Waterpark swimming	12/267 (4)	16/464 (3)	1.4 (0.6–3.5)	0.48
Drinking water	Drinking municipal water	208/261 (80)	391/457 (86)	0.7 (0.4–1.1)	0.12
	Drinking well water	105/254 (41)	147/447 (33)	1.5 (1.0–2.4)	0.07
	Drinking bottled water	126/258 (49)	220/451 (49)	1.0 (0.7–1.4)	0.88
	Filtering drinking water	65/260 (25)	147/455 (32)	0.6 (0.4–0.9)	0.02
Food and beverage consumption[b]	Raw vegetables	152/257 (59)	342/463 (74)	0.5 (0.3–0.7)	<0.01
	Lettuce or garden salad	145/258 (56)	311/463 (67)	0.6 (0.4–0.9)	<0.01
	Other salad	82/261 (31)	192/464 (41)	0.6 (0.4–0.9)	<0.01
	Cold protein salad	118/261 (45)	249/465 (54)	0.7 (0.5–1.0)	<0.05
	Cider	193/262 (74)	338/464 (73)	1.1 (0.7–1.6)	0.78

[a] All ORs have been adjusted for sex, race, ethnicity, degree of urbanization, and health status (i.e., the presence of a chronic medical condition requiring regular medication or medical follow-up).

[b] Raw vegetables include such items as carrots, tomatoes, and cucumbers. Other salad includes cold salads such as coleslaw, potato salad, and pasta salad. Cold protein salads include cold cuts, chicken salad, egg salad, and tuna salad.

promised. Twelve percent ($n = 85$) were excluded because they could not be contacted within 31 days of their stool specimen dates or within 6 weeks of onset of diarrhea. A further 12% ($n = 83$) were excluded because they were involved in known cryptosporidiosis outbreaks. Other reasons included no home phone number (9%, $n = 64$), subjects were unreachable in 15 attempts (7%, $n = 52$), subjects refused to participate (6%, $n = 39$), and 9 other miscellaneous reasons (20%, $n = 140$).

Demographic information was incomplete for 37% of excluded case-patients. Among those with information available, excluded case-patients were significantly more likely to be male (OR = 1.7, $P < 0.01$), African American (OR = 5.3, $P < 0.01$), <1 year of age (OR = 48.7, $P < 0.01$) or >25 years of age (OR = 1.9, $P < 0.01$), and living in an urban area (OR = 2.0, $P < 0.01$) compared to enrolled case-patients. Many excluded case-patients were immunocompromised: 48% of excluded males, 68% of excluded African Americans, 66% of excluded persons >25 years of age, and 63% of excluded urban dwellers. In addition, 31% of excluded children <1 year of age were outbreak related.

The 282 enrolled case-patients were matched with 490 controls. Case-patients were mostly white (92%) and non-Hispanic (95%). Approximately half (54%) were males, and 61% were <18 years of age. About half lived in urban (34%) and suburban (20%) areas, and half (51%) were from Minnesota. There were no statistically significant differences in demographic characteristics between case-patients and controls (Table 1). However, there was a statistically significant difference in the presence of a chronic medical condition that required regular medication or regular medical follow-up. A total of 21% of case-patients and 14% of controls had a chronic medical condition, of which chronic obstructive pulmonary disease, allergies (e.g., hay fever), and hypertension were the top three conditions cited.

The analyses of individual exposure variables are summarized in Table 2. Cryptosporidiosis was associated with contact with persons ≤2 years of age with diarrhea (OR = 2.7; 95% CI = 1.4 to 5.4), contact with persons >2 to 11 years of age with diarrhea (OR = 2.6; 95%, CI = 1.5 to 4.5), contact with cattle (OR = 3.4; 95% CI = 2.0 to 5.8), international travel (OR = 7.8; 95%CI = 3.3 to 18.4), and swimming in untreated freshwater (OR = 1.6; 95% CI = 1.0 to 2.5) and marine venues (OR = 2.6; 95% CI = 1.2 to 5.6). In an analysis of a subset of persons who swam in pools, swimming in a home pool was protective (OR = 0.2; 95% CI = 0.05 to 1.0) and swimming in a positive pool was a risk factor (OR = 3.7; 95% CI = 1.0 to 13.4). Filtering drinking water (OR = 0.6; 95% CI = 0.4 to 0.9) and consumption of raw vegetables (OR = 0.5; 95% CI = 0.3 to 0.7), lettuce or garden salads (OR = 0.6; 95% CI = 0.4 to 0.9), other salads (OR = 0.6; 95% CI = 0.4 to 0.9), and cold protein salads (OR = 0.7; 95% CI = 0.5 to 1.0) were also protective factors.

Since half of the study participants came from Minnesota, we also examined every variable according to residence in

TABLE 3. Multivariate association between exposures and case status[a]

Category	Exposure variable	No. (%)		OR (95% CI)	P
		Cases[b]	Controls[c]		
Contact with persons with diarrhea	Contact with persons ≤2 yr old	26 (12)	23 (6)	1.6 (0.6–3.3)	0.36
	Contact with persons >2 to 11 yr old	32 (14)	24 (6)	3.0 (1.5–6.2)	<0.01
	Contact with persons >11 to 17 yr old	4 (2)	11 (3)	0.3 (0.1–1.3)	0.10
Contact with animals	Contact with calves or cows	49 (22)	34 (8)	3.5 (1.8–6.8)	<0.01
Travel	International travel	27 (12)	8 (2)	7.7 (2.7–22.0)	<0.01
Recreational water	Freshwater swimming	46 (21)	59 (14)	1.9 (1.0–3.5)	0.03
	Marine swimming	14 (6)	14 (3)	2.5 (0.7–8.2)	0.15
	Pool swimming	76 (34)	120 (29)	1.3 (0.8–2.3)	0.30
	Water park swimming	9 (4)	14 (3)	1.0 (0.3–3.3)	0.98
Drinking water	Drinking well water	90 (40)	134 (33)	1.5 (0.9–2.5)	0.16
	Filtering drinking water	60 (27)	132 (32)	0.8 (0.5–1.2)	0.23
Food and beverage consumption	Raw vegetables[d]	136 (61)	306 (74)	0.5 (0.3–0.7)	<0.01
Ethnicity	Hispanic	14 (6)	22 (5)	2.3 (0.7–7.5)	0.15
Health status	Chronic medical condition	49 (22)	61 (15)	2.2 (1.2–4.0)	<0.01

[a] Some variables fell out of the multivariate model because there were insufficient numbers of cases in the exposed group to achieve numerical stability.
[b] The denominator for cases was 223.
[c] The denominator for controls was 412.
[d] Raw vegetables included such items as carrots, tomatoes, and cucumbers.

Minnesota or residence in the other six states. Well water consumption (OR = 2.1; 95% CI = 1.2 to 3.7), contact with ill children ≤2 years of age (OR = 3.9; 95% CI = 1.4 to 11.3), and contact with ill children > 2 to 11 years of age (OR = 5.2; 95% CI = 2.1 to 12.9) were significant risk factors in Minnesota but not outside Minnesota. Swimming in general (OR = 2.9; 95% CI = 1.5 to 5.5), swimming in freshwater (OR = 2.9; 95% CI = 1.2 to 6.9), and any travel (OR = 1.8; 95% CI = 1.1 to 2.9) were significant risk factors outside Minnesota but not in Minnesota.

The results of the final multivariate model are summarized in Table 3. In this final model, contact with persons >2 to 11 years of age with diarrhea (OR = 3.0; 95% CI = 1.5 to 6.2), contact with cattle (OR = 3.5; 95%CI = 1.8 to 6.8), international travel (OR = 7.7; 95% CI = 2.7 to 22.0), and swimming in freshwater (OR = 1.9; 95% CI = 1.0 to 3.5) remained as significant risk factors. Raw vegetable consumption (OR = 0.5; 95% CI = 0.3 to 0.7) remained as a protective factor. The presence of a chronic medical condition (OR = 2.2; 95% CI = 1.2 to 4.0) was also statistically significant.

The analysis was repeated excluding the 33 case-patients and 8 controls who had traveled internationally in the 2 weeks prior to the onset of diarrhea in the matched case-patient. The exclusion of international travelers did not change the outcome of the multivariate analysis, and the same significant variables remained with only minor differences in the values of the ORs (Table 4).

We found a seasonal pattern in the month of onset of diarrhea among our enrolled case-patients. The majority of cases (65%) occurred during the summer months of June through September (Fig. 1). This pattern was similar for both children <18 years of age and adults ≥18 years of age. We examined the variables in the final multivariate model with respect to season and found that drinking well water (OR = 2.1; 95% CI = 1.1 to 4.4), swimming in freshwater (OR = 2.1; 95% CI = 1.1 to 4.0), and contact with persons >2 to 11 years of age with diarrhea (OR = 2.8; 95% CI = 1.1 to 7.3) were significant risk factors during the summer from the end of May through the middle of September (accounting for the incubation period), whereas they were not significant during the remainder of the year in nonsummer months. International travel and contact with cattle were risk factors both during summer and nonsummer months. Raw vegetable consumption also was a protective factor regardless of the season.

We used results from the final multivariate model to calculate PARs. The largest proportion of the sporadic cryptosporidiosis cases in this population may have been attributable to contact with cattle (PAR = 16%). A smaller proportion may have been associated with international travel (PAR = 11%) and with contact with persons >2 to 11 years of age with diarrhea (PAR = 10%). Fresh water swimming (PAR = 10%) had a PAR comparable to these two better-known risk factors.

DISCUSSION

Person-to-person spread of *Cryptosporidium* spp. is thought to be one of the most common modes of transmission (21). We found significant risk for persons in contact with children >2 to 11 years of age with diarrhea. In contrast, we found no significant risk of transmission from contact with older children and adults. This suggests that the risk of transmission is influenced by the age of the index case. Young age is probably a surrogate for inadequate hygiene, fecal incontinence, and the need for more assistance during illness (27).

Contact with cattle was a risk factor for cryptosporidiosis, whereas contacts with numerous other animals, including dogs, cats, sheep, goats, pigs, horses, reptiles, and birds, showed no significant associations. The transmission of cryptosporidia

TABLE 4. Multivariate association between exposures and case status for models including and excluding persons who traveled internationally[a]

Category	Exposure variable	Including international travelers		Excluding international travelers	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Contact with persons with diarrhea	Contact with persons ≤2 yr old	1.5 (0.6–3.3)	0.36	1.9 (0.8–4.5)	0.14
	Contact with persons >2 to 11 yr old	3.0 (1.5–6.2)	<0.01	2.6 (1.2–5.2)	0.01
	Contact with persons >11 to 17 yr old	0.3 (0.1–1.3)	0.10	0.3 (0.1–1.3)	0.11
Contact with animals	Contact with calves or cows	3.5 (1.8–6.8)	<0.01	3.7 (1.9–7.2)	<0.01
Travel	International travel	7.7 (2.7–22.0)	<0.01	NA[c]	NA
Recreational water	Freshwater swimming	1.9 (1.0–3.5)	0.03	2.0 (1.0–3.7)	0.04
	Marine swimming	2.5 (0.7–8.2)	0.15	2.2 (0.6–8.2)	0.24
	Pool swimming	1.3 (0.8–2.3)	0.30	1.1 (0.6–2.0)	0.69
	Water park swimming	1.0 (0.3–3.3)	0.98	1.1 (0.3–3.9)	0.85
Drinking water	Drinking well water	1.5 (0.9–2.5)	0.16	1.5 (0.9–2.5)	0.17
	Filtering drinking water	0.8 (0.5–1.2)	0.23	0.8 (0.5–1.3)	0.31
Food and beverage consumption	Raw vegetables[b]	0.5 (0.3–0.7)	<0.01	0.5 (0.3–0.8)	<0.01
Ethnicity	Hispanic	2.3 (0.7–7.5)	0.15	1.6 (0.4–5.5)	0.49
Health status	Chronic medical condition	2.2 (1.2–4.0)	<0.01	1.9 (1.0–3.4)	0.04

[a] A number of variables fell out of the multivariate model because there were insufficient numbers of cases in the exposed group to achieve numerical stability.
[b] Raw vegetables include such items as carrots, tomatoes, and cucumbers.
[c] NA, not applicable.

from calves to humans has been well established, with documented outbreaks among veterinary hospital staff and visitors to farms (22, 18). An estimated 15 to 56% of dairy calves shed cryptosporidia and perhaps >90% of dairy farms in the United States may have *Cryptosporidium* spp. on their premises (3, 33).

Travel, particularly international travel, is a recognized risk factor for cryptosporidiosis (20). Although domestic travel was not a risk factor in our study, international travel was highly associated with cryptosporidiosis. However, when international travelers were excluded from the analyses, the multivariate risk and protective factors remained the same for noninternational travelers. In particular, freshwater swimming was found to be a risk both domestically and internationally.

Swimming in freshwater was a risk for sporadic disease in

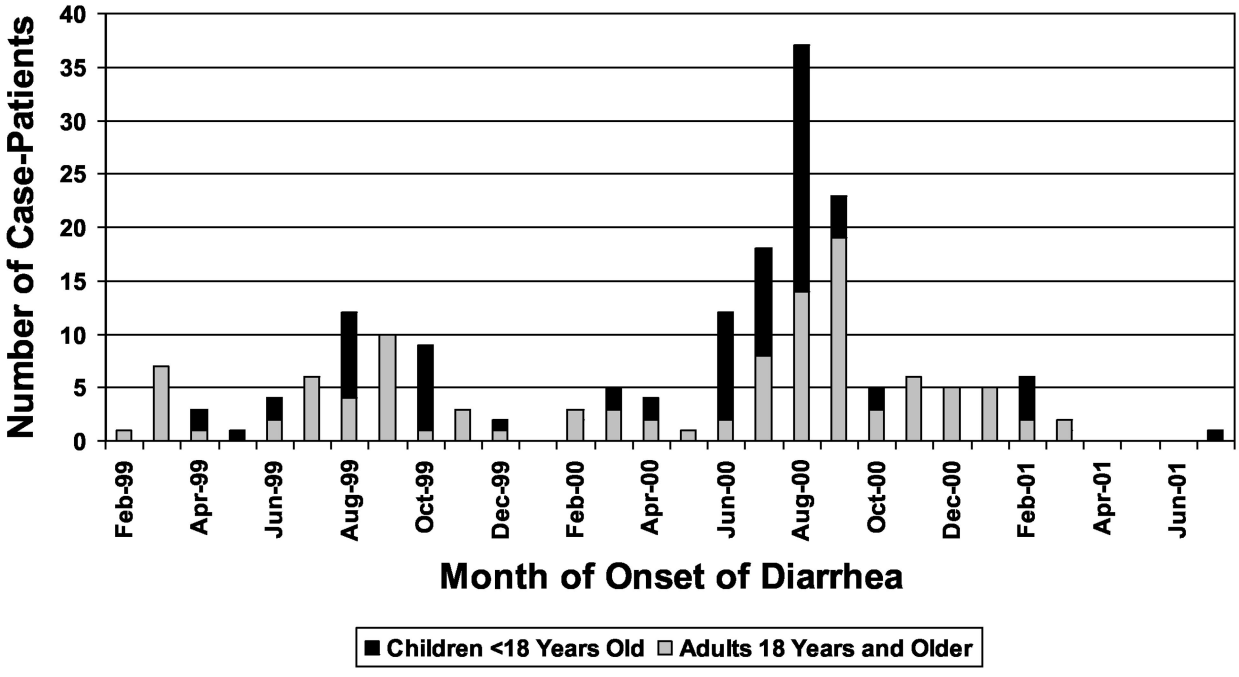

FIG. 1. Month of onset of diarrhea in cryptosporidiosis case-patients grouped by number of case-patients (n = 282) and age category.

our study, unlike swimming in pools and water parks. This finding differs from surveillance data. From 1991 through 2000, 90% of recreational water cryptosporidiosis outbreaks reported to the CDC were associated with swimming pools and water parks, whereas only 10% were associated with freshwater venues (8–12). Perhaps the transmission patterns in chlorinated recreational water venues favor outbreaks over sporadic cases. High bather densities with routine use of recreational waters by incontinent persons, including diapered children and toddlers, coupled with oocyst resistance to chlorine, a low infectious dose, and immediate release of potentially large numbers of oocysts from a single fecal accident into small volumes of water relative to lakes and oceans likely facilitate outbreaks in public pools and water parks (19). Another explanation may be that cases associated with freshwater swimming were actually not sporadic but rather were part of unknown or unreported outbreaks and therefore should have been excluded.

To further explore the risks for sporadic cryptosporidiosis associated with swimming pools, we performed a subset analysis only with persons who swam in pools. Swimming in a home pool showed a negative association that reached statistical significance in univariate analysis. Swimming in a private pool (e.g., pools in clubs, apartment complexes, and motels) was a significant risk factor. Swimming in a backyard kiddie wading pool had an OR that was greater than 3 but failed to reach statistical significance. These findings mirror the types of recreational outbreaks seen in the 1990s. Of the 29 pool-related outbreaks not involving water parks that were reported to the CDC from 1991 through 2000, 28 (97%) occurred in public-use pools (including private pools as defined above) and only one (3%) occurred in a home pool (8–12). Personal-use home pools are smaller venues holding fewer bathers so the risk of fecal contamination at any given time is less compared to public-use pools. Home pool outbreaks also may not be as readily detected as public pool outbreaks.

None of the drinking water source variables in our study were significantly associated with the development of cryptosporidiosis. Nevertheless, contaminated drinking water is a known risk factor. From 1991 through 2000, 11 drinking water outbreaks were reported to the CDC, including the 1993 Milwaukee outbreak that affected more than 400,000 persons (8–12, 26). *Cryptosporidium* oocysts are estimated to be present in 55 to 87% of surface waters tested in the United States, suggesting that low-level endemic transmission may occur through drinking water (21, 24, 32). One study using a risk assessment model to examine the potential role of tap water in transmission of endemic cryptosporidiosis in immunocompetent adults predicted a median annual risk of infection of approximately 1 in 1,000 (29).

The association between filtering drinking water and cryptosporidiosis was not statistically significant in multivariate analysis (including and excluding international travelers), although filtering was a protective factor in univariate analysis. A study during the 1993 Milwaukee outbreak also found that consistent use of point-of-use home filters with a pore size of ≤ 1 μm substantially reduced the risk of cryptosporidiosis (2). Further investigation is needed to assess the association between filtering and drinking water.

Finally, we found that raw vegetable consumption was a protective factor, seemingly contradicting much of the available data on food-borne transmission of this disease. CDC's Foodborne Disease Outbreak Surveillance System documented eight food-borne-related cryptosporidiosis outbreaks from 1990 through 2000 (13). *Cryptosporidium* oocysts have been detected in irrigation water in Central America, the United States, Israel, and Norway (4, 31, 34). Oocysts also have been found on the surface of vegetables irrigated with these waters (4, 31). Therefore, evidence suggests that fresh produce consumption is a risk factor, at least in outbreak situations. However, others have observed that consumption of fresh produce may reduce the risk for cryptosporidiosis. A recent Australian study identified the consumption of uncooked carrots as a protective factor (crude OR = 0.6; 95% CI = 0.5 to 0.9) for sporadic cryptosporidiosis (30). Several outbreaks studied in the United Kingdom also revealed a protective association with the regular consumption of raw vegetables (5). The reason for this protective association is unknown.

One explanation may be that regular consumption of oocyst-contaminated vegetables results in immunity to illness from *Cryptosporidium* infection. Serologic responses have been shown to develop after both symptomatic and asymptomatic infections. Although preexisting antibody responses may not protect against subsequent infection, they may protect against subsequent illness (28). Studies have suggested that the seroprevalence of *Cryptosporidium* antibodies in immunocompetent persons in the United States may range from 13 to 58% (23), representing past *Cryptosporidium* infection and not necessarily disease. The 50% infectious dose of *Cryptosporidium* oocysts as determined by oocyst detection in stool has been estimated to be 132 oocysts (17) but may be substantially lower by serology (28). Therefore, perhaps recurrent exposure to low doses of oocysts, such as on contaminated vegetables, results in asymptomatic infection or mild illness with resulting immunity to subsequent cryptosporidiosis.

Another explanation may be that dietary fiber plays a physiologic role. Experimental evidence revealed that gerbils fed high fiber diets were significantly less likely to become infected with *Giardia*, another protozoan parasite. The researchers concluded that mucus secretion and bulk movement of insoluble fiber reduced the attachment of *Giardia* trophozoites to the intestinal mucosa (25). Therefore, perhaps raw vegetables protect against cryptosporidiosis due to physiologic changes they induce in the gut.

Cryptosporidiosis has been previously recognized to have a seasonal pattern, with an increase in cases in North America during the summer (5). We found a similar increase in the number of enrolled case-patients with onsets on diarrhea from June through September. The seasonal risk for cryptosporidiosis associated with well water consumption and freshwater swimming during the summer may reflect indirect effects of rainfall, farming events such as calving, and environmental pollution of water supplies with farm waste (5).

The present study had a number of limitations. First, because of the long incubation period and delays in diagnosis, some participants were questioned about experiences several weeks in the past. However, case-patients and their matched controls were required to remember events equally distant in the past, so differential bias should not have been introduced. Second, more than 100 different exposure questions were in-

cluded in the present study. With an alpha level set at 0.05, at least five exposure variables were expected to be statistically significant due to chance alone. However, the statistically significant exposure variables in our final multivariate model have been previously associated with cryptosporidiosis. Third, some case-patients may have been misclassified as controls, since asymptomatic infections can occur (15). However, the inclusion of asymptomatic cases among our controls would likely have underestimated the true risk of cryptosporidiosis. Fourth, we did not have the ability to genotype the *Cryptosporidium* sp. identified in each case-patient. Therefore, we cannot comment on any differences in epidemiology between sporadic cases associated with bovine and human species. Fifth, the generalizability of our results may be limited for several reasons: the seven FoodNet sites used in our study do not comprise a nationally representative sample, the study participants were mostly white and non-Hispanic, and half of the participants came from Minnesota. To address this last concern, we analyzed the exposure variables by residence in Minnesota versus residence in one of the other six states. We found that the risk factors that differed between the two areas (i.e., well water consumption, contact with ill children, swimming, and travel) were common behaviors that would have occurred among residents of both areas. Therefore, the geographic differences were probably the result of limited study size and power rather than of exposure and activity patterns.

Our findings in this multistate case-control study suggest that the risk factors associated with sporadic cryptosporidiosis in immunocompetent persons are similar to those previously seen in immunocompromised and outbreak-related case-patients. The only exception may be the protective effect of raw vegetable consumption. Further investigation is needed to understand the mechanism and meaning of this association. Although a substantial proportion of the burden of sporadic cryptosporidiosis in our study population may have been attributable to contact with cattle, contact with children with diarrhea, and international travel, the PAR associated with swimming in freshwater appears to be similar and, therefore, requires similar efforts at public health education and intervention. Furthermore, the risks associated with swimming in nonchlorinated venues have implications for setting recreational water quality standards. Health providers and the general public need to be aware of the multiple modes of *Cryptosporidium* transmission in order to achieve a reduction in cryptosporidiosis cases in sporadic, opportunistic, and outbreak settings.

ACKNOWLEDGMENTS

Financial support for this research was provided by the CDC's National Center for Infectious Diseases, the U.S. Department of Agriculture's Food Safety and Inspection Service, and the Food and Drug Administration Center for Food Safety and Applied Nutrition.

We thank FoodNet staff in the participating sites for their efforts in participant recruitment and survey administration. We thank participating local and state health departments for their support with this project. We thank Allen Hightower and Felicia Hardnett of the CDC for their assistance and guidance with statistical analysis. Finally, we thank each of the subjects who generously participated in this research.

Contributing members of the Emerging Infections Program FoodNet Working Group included the following: Frederick Angulo, Timothy Barrett, Michael Beach, Nancy Bean, Richard Bishop, Chris Braden, Laura Conn, Stephanie DeLong, Sara Ehlers, Cindy Friedman, Patricia Griffin, Felicia Hardnett, Peggy Hayes, Mike Hoekstra, Beth Imhoff, Jeff Jones, Malinda Kennedy, Jenny Lay, Deborah Levy, Kathleen Maloney, Paul Mead, Oshine Najarian, Thomas Navin, Robert Pinner, Cathy Rebmann, Sudha Reddy, Laurence Slutsker, Karen Stamey, Bala Swaminathan, David Swerdlow, Robert Tauxe, Thomas Van Gilder, David Wallace, Stephanie Wong, and Samantha Yang (all from the CDC); Sharon Abbott, Pam Daily, Mary Ann Davis, Lisa Gelling, Alexander McNees, Janet Mohle-Boetani, Nandeeni Mukerjee, Joelle Nadle, Jan O'Connell, Kevin Reilly, Gretchen Rothrock, Michael Samuel, Sue Shallow, Ben Silk, Duc Vugia, and Ben Werner (all from California); Gary Budnick, Matthew Cartter, Terry Fiorentino, James Hadler, Robert Heimer, Robert Howard, Sharon Hurd, Gazala Kazi, Kati Kelley, Aristea Kinney, Ruthanne Marcus, Donald Mayo, Patricia Mshar, Randall Nelson, Quyen Phan, Robin Ryder, and Charles Welles (all from Connecticut); Wendy Baughman, Paul Blake, Laurel Boykin, Sabrina Burden, Shama Desai, Monica Farley, Laura Gilbert, Jane Koehler, Susan Lance-Parker, Katherine McCombs, Susan Ray, Cathy Rebmann, Matthew Sattah, Suzanne Segler, and Stepy Thomas (all from Georgia); Alicia Bustamante, Michael Carter, Yvonne Deane-Hibbert, Diane Dwyer, Lora Gay, Althea Glenn, Charmaine Gregg, Marguerite Hawkins, Kelly Henning, Kim Holmes, Jackie Hunter, Tobi Karchmer, Meghan McGavern, J. Glenn Morris, Jr., Lola Olabode, Peggy Pass, Jafar Razeq, Jeffery Roche, Dale Rohn, Christian Steiner, Alexander Sulakvelidze, Yongyu Wang, and Frances Yarber (all from Maryland); Jeff Bender, John Besser, Richard Danila, Valerie Deneen, Craig Hedberg, Heidi Kassenborg, Carlota Medus, Michael Osterholm, Kirk Smith, Dana Soderlund, Sara Stenzel, Ellen Swanson, and Julie Wicklund (all from Minnesota); Bridget Anderson, Dianna Bopp, Kathy Carlton, Hwa-Gan Chang, Barbara Damaske, Nellie Dumas, Marie Fitzgerald, Karim Hechemy, Jonathan Hibbs, Dale Morse, Candace Noonan, Brian Sauders, Perry Smith, Nancy Spina, and Shelley Zansky (all from New York); Vijay Balan, Chris Biggs, Maureen Cassidy, Paul Cieslak, Emilio DeBess, David Fleming, Bill Keene, Lore Lee, Eileen Lorber, Steve Mauvais, Teresa McGivern, Yijun Pang, Beletshachew Shiferaw, and Bob Sokolow (all from New York); Ruth Etzel, Kristin Holt, Noreen Hynes, Tamar Lasky, Denise Lewis, Phyllis Sparling, and Kaye Wachsmuth (from USDA-FSIS); and Ken Falci, Bing Garthright, and Clifford Purdy (from FDA-CFSAN).

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