Epidemiol. Infect. (1999), **122**, 359–365. Printed in the United Kingdom

A case-control study of sporadic infection with O157 and non-O157 verocytotoxin-producing *Escherichia coli*

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(*Accepted 15 December 1998*)

SUMMARY

Potential risk factors for sporadic verocytotoxin-producing *Escherichia coli* (VTEC) infection in Belgium were investigated in a matched case-control study. Thirty-seven cases, 8 infected with O157 VTEC strains (all *eaeA*-positive), 29 with non-O157 VTEC strains (13 *eaeA*-positive and 16 *eaeA*-negative) and 69 matched controls were interviewed. In a conditional logistic regression analysis, consumption of fish appeared to be a risk factor for infection (adjusted odds ratio (OR) 3·25, $P = 0{\cdot}04$). Contact with dogs (OR 0·27, $P = 0{\cdot}04$) and consumption of shellfish (OR 0·19, $P = 0{\cdot}05$) showed a negative association, corresponding to a decrease in risk. These findings might be explained if low level environmental exposure to VTEC induces protective immunity. Eating raw meat, a frequent habit in Belgium, or hamburgers, or eating in a fast-food restaurant was not more frequently reported by cases than controls. The exposures causing sporadic infections with VTEC, in particular non-O157 strains, may be very different from those which led to outbreaks, and may account for more cases overall.

INTRODUCTION

Verocytotoxin-producing *Escherichia coli* (VTEC), also called Shiga toxin-producing *E. coli* (STEC) or enterohemorrhagic *E. coli* (EHEC), are a cause of sporadic or epidemic cases of often bloody diarrhoea, that can progress to haemorrhagic colitis and haemolytic uraemic syndrome (HUS) [1]. Most information about modes of transmission of these organisms has been derived from investigation of outbreaks of O157:H7 VTEC infections [2]. The vehicle of *E. coli* O157:H7 infections was generally found to be foods of bovine origin, especially undercooked ground beef but also roast beef [3], dry-cured salami [4], untreated milk [5] or even pasteurized milk that was contaminated during bottling [6]. Some outbreaks were related to cross contamination by beef products or cow manure of foods and beverages, such as vegetables and unpasteurized apple cider [7, 8]. Contamination of drinking [9] or swimming water [10], contact with infected livestock [11] and person-to-person transmission [2] have also been reported. The epidemiology of non-O157 VTEC infections remains less well understood. Non-O157 VTEC have been isolated from various animals and foods of animal origin [12–16] but these strains lack frequently accessory virulence factors like the *eaeA* gene [13, 17]. In an outbreak of HUS caused by VTEC of serotype O111:H$^-$, a dry fermented sausage made of raw pork, beef and lamb was identified as vehicle, but the

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responsible livestock species could not be identified [18]. Person-to-person transmission was thought to be involved in a cluster of HUS cases associated with VT2-producing O111 VTEC [19].

The exact public health importance of VTEC infections in Belgium has not been fully determined yet. However, screening for O157 and non-O157 in the Academisch Ziekenhuis Vrije Universiteit Brussel (AZ-VUB) has shown that non-O157 VTEC (42% *eaeA* positive) can be isolated from 0·66% of stool samples submitted for culture, while O157 VTEC (all *eaeA* positive) can be isolated from only 0·17% of samples [20]. All these cases were sporadic. It has also been shown that the incidence of HUS in Belgian residents, 4·3 cases/100000 children < 5 years old, is comparable to rates observed in other countries [21]. The high mortality and morbidity linked to this syndrome – in a recent report with a follow-up of 10 years, in addition to 6% of children who died in the acute phase and 4% who went into end-stage renal failure, as many as 9% of survivors presented severe sequelae and 26% mild defects [22] – warrant efforts to determine the infection sources. A search for VTEC strains which we performed in raw meat samples obtained from a Belgian mass retail company showed that beef, sheep and wild meats were frequently positive for VTEC but most of these strains lack virulence factors like the *eaeA* gene, and none belonged to serogroup O157 [13].

We performed a case-control study of sporadic cases of VTEC infection in Belgium with the aim of testing hypotheses relating to risk factors for infections in our country. Cases included in the study had positive stool cultures for O157 or non-O157 VTEC, both *eaeA*-positive and *eaeA*-negative. They represented the spectrum of disease from mild illness to full-blown HUS.

METHODS

Cases were patients of the AZ-VUB with a positive stool culture or polymerase chain reaction (PCR) for VTEC, detected as described previously [20]. Both in-patients and out-patients were included. Age-matched controls were selected from the same hospitalization ward or out-patient clinic as the case. Matching occurred up to the age of 2 years by age ± 2 months, up to 8 years by age ± 1 year, up to 18 years by age ± 2 years and for adults by age ± 5 years. Controls were excluded if they had an history of diarrhoea within 2 weeks before interview, if their condition imposed dietary restrictions or if they suffered from severe underlying conditions like malignancies, except if they were matched to a case with a similar underlying condition. Hospitalized controls were only selected if they were admitted for less than 2 days.

Forty-cases and two matched controls per case were interviewed within 1 month after isolation of VTEC, using a standardized questionnaire. The following data were recorded: demographic details (age, sex, occupation, place of residence); clinical details (only for cases), contact with persons with diarrhoea; recreational activities including visits to fun fairs and swimming pools; contact with animals; eating out (restaurants, fast-food restaurants); childcare (day care centre, mother caring for several children at home or nursery school); recent foreign travel; drinking untreated water; diet including meat, milk, fruit juices, cheese, soft cheese, eggs; cooking habits and methods of meat storage. Seventy-two exposures were selected either because they were previously reported or suspected to cause VTEC infection [2–8, 10, 11, 19] or because they were food items from which VTEC were ever detected [12–18]. Three subgroups were analysed separately; children < 16 years old, patients with *eaeA*-positive VTEC isolates and patients with *eaeA*-negative VTEC isolates. Within *eaeA*-positive VTEC, the numbers were too small to analyse O157 and non-O157 strains separately.

Epi-info version 6.04 was used for the matched univariate analysis to calculate odds ratios (OR) and 95% confidence intervals (CI) by the Mantel–Haenszel method. A backward stepwise multivariate analysis was carried out using Epidemiological Graphics, Estimation, and Testing package (EGRET) in a conditional multiple logistic regression model, including all variables found to be significant factors in the univariate analysis and any potential confounders. The most important results of the univariate analysis were selected for presentation on the basis of a P-value $\leqslant 0{\cdot}10$, because the exposure was a potential confounder, or because a lack of association was of particular interest. The maximum likelihood method was used to determine the final model, using the χ^2 test to compare the fit of models with and without variables of interest [23]. A significance level of 0·05 was used. A number of potential associations were examined but most were dietary factors and therefore not independent of each other, so the significance level was not adjusted for multiple testing [24].

Table 1. *Age, clinical conditions and risk factors in patients with* eaeA*-positive and -negative VTEC isolates*

	eaeA-positive isolates	*eaeA*-negative isolates	*P*-value	
Total number	21	16		
Age				
Median	2 years	10 years	n.s.	
Range	1 month to 76 years	5 months to 66 years		
Clinical conditions				
Post-diarrhoeic HUS	5	0	$P = 0{\cdot}00002$	$P = 0{\cdot}0007$
Bloody diarrhoea	3	2	n.s.	
Non-bloody diarrhoea	12	5	n.s.	
Other abdominal symptoms	0	6	$P = 0{\cdot}003$	
No. VTEC-associated condition	1	3	n.s.	
Potential risk factors with unequal distribution				
Contact with persons with diarrhoea	7	0	$P = 0{\cdot}01$	
Ate in a fast food restaurant	2	8	$P = 0{\cdot}009$	
Consumption of raw carrots	2	9	$P = 0{\cdot}003$	

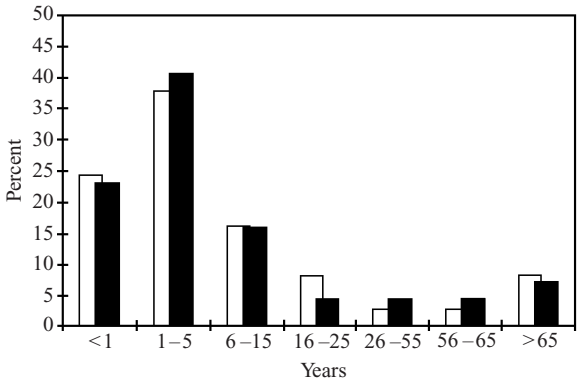

Fig. 1. Age distribution of cases ($n = 37$) (M/F ratio = 0·85) and controls ($n = 69$) (M/F ratio = 1·16).

RESULTS

The demographic characteristics of the cases and the controls were comparable (Fig. 1). Twenty-one VTEC isolates were *eaeA* positive, including isolates of serogroups O157 ($n = 8$), O26 ($n = 3$) O103 ($n = 3$), O111 ($n = 3$), O128 ($n = 1$), O145 ($n = 1$), O rough ($n = 1$) and O untypable ($n = 1$), and 16 were *eaeA* negative, including serogroups O2 ($n = 1$), O111 ($n = 1$), O128 ($n = 1$), O162 ($n = 1$), OX3 ($n = 1$), O untypable ($n = 4$) and O rough ($n = 1$), while the remaining three isolates were not fully serogrouped but did not agglutinate with O157, O26, O103 and O111 antisera. Three patients presented with a positive PCR reaction for verocytotoxin genes but no VTEC could be isolated, probably because of low levels of VTEC in the samples, as can be observed with this screening method [20]. These patients were subsequently excluded from the analysis. The median delay between submission of a stool sample to the laboratory and interview was 6 days (range: 1–35) for cases and 14 days (range: 2–55) for controls. Table 1 presents the age distribution, clinical conditions and risk factors in patients with *eaeA*-positive and -negative VTEC isolates. Some differences between these two groups of patients were observed but not between patients with *eaeA*-positive non-O157 and O157 VTEC isolates, that are thus not separately shown on the table. Patients with *eaeA*-positive isolates were younger than patients with *eaeA*-negative isolates but the difference was not significant; they presented more frequently with HUS or with diarrhoea with or without complications than patients with *eaeA*-negative isolates while the latter presented more frequently with other abdominal symptoms. As expected from the different age distribution, some potential risk factors were unequally distributed between these two groups: patients with *eaeA*-positive isolates were more frequently in contact with persons with diarrhoea but less frequently consumed raw carrots or ate in a fast-food restaurant. Twenty-two (55%) of the cases were hospitalized. A wide range of medical conditions were observed in the controls: routine follow-up visits of healthy children, follow-up visits after diseases like urologic or upper respiratory tract infections, anaemia, asthma, etc., and in hospitalized controls: admissions for minor or orthopaedic surgery or for traumatology, unspecified febrile illness, SIDS monitoring and chemotherapy for malignancy (only for the two controls of a woman

Table 2. *Univariate analysis: all cases and controls*

Variable	Exposed cases	Exposed controls	Matched odds ratios	95% confidence interval	*P*-value
Contact with cattle	3	1	6·00	0·48–314·98	0·11
Contact with farm animals	8	7	3·83	0·81–47·02	0·05
Eating meat stored in freezer	28	42	2·31	0·80–9·61	0·06
Consumption of fish	26	40	1·82	0·69–6·37	0·13
Contact with persons with diarrhoea	7	27	1·80	0·38–10·06	0·27
Consumption of cream cheese (‘fromage blanc’)	19	28	1·65	0·67–4·67	0·16
Consumption of any raw meat	14	23	1·53	0·44–4·26	0·36
Ate hamburgers	13	25	0·93	0·32–2·71	0·53
Ate in a fast food restaurant	10	20	0·92	0·29–2·84	0·53
Consumption of raw carrots	11	21	0·88	0·32–2·30	0·47
Consumption of other raw vegetables (not salad or carrots)	13	31	0·66	0·22–1·72	0·22
Any form of childcare	10	26	0·43	0·06–1·46	0·09
Contact with dogs	10	35	0·22	0·08–0·80	0·007
Consumption of shellfish	4	20	0·15	0·02–0·85	0·01

Table 3. *Univariate analysis: children < 16 years* (*29 cases and 55 controls*)

Variable	Exposed cases	Exposed controls	Matched odds ratios	95% confidence interval	*P*-value
Contact with cattle	3	1	6·00	0·62–57·68	0·10
Eating meat stored in freezer	24	33	4·13	1·02–16·63	0·01
Consumption of fish	20	30	2·29	0·75–6·96	0·09
Consumption of cream cheese (‘fromage blanc’)	15	21	2·06	0·74–5·73	0·11
Contact with farm animals	7	6	1·80	0·49–6·65	0·07
Contact with persons with diarrhoea	7	8	1·80	0·49–6·65	0·27
Consumption of any raw meat	9	20	1·06	0·24–4·48	0·58
Consumption of raw carrots	8	19	0·67	0·24–1·89	0·30
Any form of childcare	10	19	0·43	0·13–1·41	0·09
Consumption of other raw vegetables (not salad or carrots)	7	24	0·42	0·15–1·18	0·06
Contact with dogs	9	31	0·21	0·06–0·72	0·01
Consumption of shellfish	3	16	0·08	0·01–0·93	0·02

who developed diarrhoea due to O157 VTEC the day after admission for chemotherapy).

In the analysis involving all cases and controls, several exposures were unevenly distributed between cases and controls. Cases were more likely to have had contact with farm animals and less likely to have eaten shellfish or been in contact with dogs (Table 2). Cases were not more likely to have eaten in a fast-food restaurant or to have eaten raw meat, hamburgers or fish (the later appears to be significant in the multivariate analysis, see below).

Restricting the analysis to children less than 16 years old (Table 3) showed the same associations, except that eating meat stored in the freezer became statistically significant (matched OR 4·13, 95% CI 1·02–16·63, $P = 0·01$) and that contact with farm animals was no longer significant. Because these groups were very small and the power thus lower, restricting the analysis to cases with *eaeA*-positive (Table 4) or *eaeA*-negative isolates (Table 5) showed no significant associations except the consumption of cream cheese (‘fromage blanc’) that became significant in the group of cases with *eaeA*-positive isolates (matched OR 3·75, 95% CI 0·99–14·16, $P = 0·03$).

There was a positive association between eating fish and eating shellfish (OR 3·8, $P = 0·02$). For this reason, fish consumption was included in the multivariate analysis as a potential confounder. There was no inverse relationship observed between either the consumption of shellfish and raw meat or keeping

Table 4. *Univariate analysis: Patients with* eaeA-*positive VTEC* (*21 cases and 40 controls*)

Variable	Exposed cases	Exposed controls	Matched odds ratios	95% confidence interval	*P*-value
Consumption of soft cheese ('fromage blanc')	13	14	3·75	0·99–14·16	0·03
Contact with person with diarrhoea	7	6	3·00	0·62–14·43	0·11
Eating meat stored in freezer	16	24	2·50	0·58–10·77	0·14
Contact with farm animals	5	6	2·17	0·41–11·36	0·28
Contact with cattle	1	1	2·00	0·13–31·98	0·56
Consumption of fish	14	23	1·67	0·47–5·94	0·30
Consumption of any raw meat	6	15	0·80	0·11–5·30	0·56
Consumption of other raw vegetables (not salad or carrots)	6	17	0·50	0·15–1·64	0·17
Contact with dogs	8	21	0·43	0·13–1·49	0·16
Any form of childcare	6	16	0·42	0·10–1·80	0·16
Consumption of raw carrots	2	11	0·21	0·04–1·21	0·08
Consumption of shellfish	1	12	*	*	*

* Unable to calculate because Mantel–Haenszel numerator or denominator is 0.

Table 5. *Univariate analysis: Patients with* eaeA-*negative VTEC* (*16 cases and 29 controls*)

Variable	Exposed cases	Exposed controls	Matched odds ratios	95% confidence interval	*P*-value
Eating meat stored in freezer	12	18	2·13	0·50–8·99	0·24
Consumption of fish	12	17	2·00	0·52–7·67	0·23
Consumption of raw carrots	9	10	1·79	0·60–5·34	0·22
Consumption of any raw meat	8	8	1·75	0·43–9·89	0·25
Consumption of other raw vegetables (not salad or carrots)	7	14	0·93	0·25–3·43	0·59
Consumption of cream cheese ('fromage blanc')	6	14	0·72	0·21–2·47	0·41
Any form of childcare	4	10	0·44	0·06–3·52	0·37
Consumption of shellfish	3	8	0·42	0·07–2·62	0·30
Contact with persons with diarrhoea	0	2	*	*	*
Contact with dogs	2	14	*	*	*
Contact with cattle	2	0	*	*	*
Contact with farm animals	3	1	*	*	*

* Unable to calculate because Mantel–Haenszel numerator or denominator is 0.

Table 6. *Conditional logistic regression analysis: all cases and controls*

Exposure	Odds ratio	95% confidence interval	*P*-value
Contact with farm animals	4·77	0·64–35·16	0·12
Consumption of fish	3·25	1·05–10·07	0·04
Eating meat stored in freezer	2·77	0·66–11·59	0·16
Contact with dogs	0·27	0·08–0·95	0·02
Consumption of shellfish	0·19	0·04–1·00	0·05

meat in the freezer ($P = 0{\cdot}33$ and $P = 0{\cdot}50$, respectively) or fish and raw meat or keeping meat in the freezer ($P = 0{\cdot}20$ and $P = 0{\cdot}42$, respectively).

In the conditional logistic regression analysis, three exposures were significant. Consumption of fish was a risk factor, and contact with dogs and consumption of shellfish reduced the risk (Table 3). No interaction was seen between children and a history of contact with someone with diarrhoea ($P = 0{\cdot}31$), consumption of fish and raw meat or meat being kept in the freezer

($P = 0{\cdot}68$ and $P = 0{\cdot}38$, respectively). It was not possible to calculate an interaction term for shellfish and fish.

Numbers were insufficient to carry out a multivariate analysis of children, *eaeA*-positive or *eaeA*-negative cases separately.

DISCUSSION

Although consumption of raw meat is a very common habit in Belgium, as shown in this study, as well as in studies of sources of *Yersinia enterocolitica* infection conducted in our country [25] and although meat is frequently reported as the vehicle of infection in outbreak reports, it was not associated with VTEC infection in this study. About one third of both cases and controls reported consumption of raw meat, within 2 weeks before onset of diarrhoea or before interview. Other exposures which might be expected to be associated with VTEC infection (eating in a fast-food restaurant and eating beef burgers) were also not found to be more frequently reported by cases than controls. The risk of infection may be related to the frequency of consumption, of turnover in retailers or to methods of preparation that are country-specific.

The exposures that emerged from the multivariate analysis were unexpected. The finding that consumption of fish was a risk factor was surprising since fish is generally not known to be contaminated with VTEC, although one study reported 6 of 62 (10%) fish samples to be positive with VT DNA probes; no VTEC could be isolated however [14]. First results of a screening in 50 fresh retail fish samples initiated after obtaining these results were negative (D. Piérard, unpublished observation). We cannot exclude chance as the explanation for the association of consumption of fish with VTEC infection since the statistical significance was low and a number of hypotheses were examined in the whole study, making a type 2 error more likely. Prospective studies, in particular isolation studies of fresh retail fish, should address this point.

Contact with dogs ($P = 0{\cdot}02$) and consumption of shellfish ($P = 0{\cdot}05$) seem to confer some protection against infection. Perhaps early low-dose and long-term exposure to less pathogenic VTEC (such as *eaeA*-negative strains) carried by these vehicles could lead to immunity. Indeed, studies have shown that dogs can harbour VTEC, which are generally *eaeA*-negative, in their stools [12, 17] and isolation of VTEC has been reported from shellfish and vegetables [14]. Similarly, it has been suggested that acquired immunity could be the reason why a decreased risk of becoming ill with campylobacter was found in persons handling raw chicken, frequently eating chicken dishes or having occupational contact with livestock or their faeces [26].

Risk factors for sporadic infections with VTEC, in particular for non-O157 strains, may be very different from the factors that cause outbreaks, and may also be responsible for more cases of infection overall. However, two recent case-control studies conducted in the UK [27] and the US [28] pointed to consumption of undercooked beefburger as a risk factor for sporadic infection with O157 VTEC too, in addition to consumption of cold cooked sliced meat from caterers, person-to-person spread and transmission from animals in the first but not in the latter study. The absence of association with consumption of beef meat in our study fits the observation of Caprioli and Tozzi that the pattern of transmission in continental Europe is atypical, as suggested by the low number of outbreaks and the lack of identification of beef products as infection sources during the few outbreaks that occurred in this geographical area [29]. Research into the sources of VTEC should not be limited to the well-recognized vehicles such as beef, but should be extended to more unusual foods as well as environmental exposures that may increase risk or confer protection from infection. Future research will be most fruitful if it combines epidemiological, environmental and microbiological approaches in the detailed examination of all stages of the food chain.

ACKNOWLEDGEMENTS

This study was supported in part by a grant from Quick International, 2600 Berchem, Belgium. Natasha Crowcroft was funded by the EC under agreement SOC 96 202584 05GF01 in the European Programme for Intervention Epidemiology Training (EPIET).

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