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Diabetes mellitus, anti-secretory drugs and other risk factors for campylobacter gastro-enteritis in adults: a case-control study

K. R. NEAL[1]* AND R. C. B. SLACK[2]

[1] *Department of Public Health Medicine, University of Nottingham, Nottingham NG7 2UH*
[2] *Nottingham Health Authority, Nottingham NG1 6GN*

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SUMMARY

The epidemiology of notified cases of campylobacter gastroenteritis in adults in Nottingham Health District was investigated using a case-control study with a postal questionnaire to ascertain data on risk factors. Over a 14-month period 531 cases (a 73% response rate of all laboratory confirmed cases) and 512 controls replied.

Conditional logistic regression analysis was used to determine independent associations with infection. These included foreign travel (odds ratio (OR) 3·4; 95% confidence intervals (CI) 2·0–5·7), diabetes mellitus (OR 4·1, CI 1·1–17), medication with omeprazole (OR 3·5, CI 1·1–12) and H_2 and H_2 antagonists (OR 3·7, CI 1·3–15), contact with puppies (OR 11·3, CI 1·2–105), eating chicken (OR 1·4, CI 1·1–1·8) and drinking milk from bottles with tops damaged by a bird (OR 3·3, CI 1·0–11). Preparing main meals (OR 0·9, CI 0·8–1·0) and drinking delivered milk (OR 0·6, CI 0·4–0·9) were associated with a reduced risk of campylobacter infection.

Foreign travel was reported in 25% of cases and another 15% had significant associations with other risk factors. The majority of cases, 60%, remained unexplained, indicating the need for further evolution of sporadic cases.

INTRODUCTION

Over the past 10 years campylobacter has become the most frequently identified pathogen from faeces specimens submitted for culture in the UK. The number of notified cases has been increasing at a time when the number of notified salmonella infections remained the same [1, 2]. Unlike salmonella, most cases of campylobacter infection are apparently sporadic and few outbreaks are recognized [2, 3]. Over the past few years the rate of campylobacter infections in Nottingham has been 35% above the national average whilst the local rate of salmonella infection is similar to the national average [4]. Campylobacter remains a major public health problem with a minimum cost of £540 per episode at 1988 prices [5]. Epidemiological studies have suggeted that some risk factors for campylobacter infection may be seasonal and there may also be regional differences [6]. The main recognized association with campylobacter infections are the consumption of undercooked

Table 1. *Age, sex and social class of campylobacter cases and controls, Nottingham, England, June 1994 to July 1995*

	Cases (n = 313)	Controls (n = 512)
Mean age (.SD.)	43·9 (17·1)	44·4 (17·4)
(range)	(17–88)	(18–89)
Sex (male/female)	118/186	191/288
Social class		
1	12	22
2	83	130
3	80	118
4	29	24
5	7	12
Unclassified	102	206

* Author for correspondence.

Table 2. *Odds ratios for social factors with campylobacter infection, Nottingham, England, June 1994 to July 1995*

Exposure (in the 2 weeks before onset of illness)	Cases ($n = 313$)	Controls ($n = 512$)	Unadjusted odds ratio	95% confidence interval
Dogs	62	102	0·9	0·6–1·4
Puppies	5	1	8·2	1·1–71
Cats	51	95	0·8	0·5–1·2
Kittens	1	0	Not estimatable	
Other pets	51	76	1·1	0·7–1·7
Ill pet	13	22	0·9	0·4–1·9
Leisure animals	93	168	0·8	0·6–1·1
Animals at work	13	22	0·9	0·4–1·8
Farm visit	14	28	0·8	0·4–1·5
Swimming in public pool	57	106	0·8	0·5–1·2
Swimming in river or lakes	7	9	1·2	0·5–3·4
Watersports	6	10	1·2	0·4–3·5
Swimming in sea	28	32	1·4	0·8–2·5
Recreational walking	54	107	0·8	0·5–1·1
Camping, caravanning or stayed in a chalet	30	52	0·9	0·7–1·2
Travel abroad	70	52	4·0	2·5–6·5
Contact with child under 5 years	99	180	0·9	0·8–1·1
Changed children's nappies	29	63	0·8	0·5–1·4
Contact with children with gastro-intestinal illness	16	34	0·7	0·3–1·5
Smoking	45	101	0·7	0·5–1·1
Alcohol	98	215	0·8	0·6–1·2

Table 3. *Odds ratios for milk and water sources with campylobacter infection, Nottingham, England, June 1994 to July 1995*

Milk or water source	Cases ($n = 313$)	Controls ($n = 512$)	Unadjusted odds ratio	95% confidence interval
Doorstep delivered milk	107	212	0·7	0·5–0·9
Unpasteurized milk	13	6	3·5	1·3–9·4
Bird damaged milk bottle tops	10	6	2·6	1·0–7·3
Unclean water	11	8	1·9	1·0–3·7
Bottled water	142	205	1·2	0·9–1·7
Used a water filter	57	91	1·1	0·7–1·6

chicken, handling of raw poultry, contact with puppies, drinking milk which is either unpasteurized or from bottles which have had the foil top damaged by birds and foreign travel [2, 3, 7–11]. Campylobacter infection has been shown to be associated with proton pump inhibitors [12] and salmonella infection has been related to diabetes mellitus [13]. This report summarizes results of a case-control study conducted over 14 months to assess risk factors for campylobacter infection in adults in a largely urban area.

METHODS

Cases and controls

The study was carried out in Nottingham Health Authority from 1 June 1994 to 31 July 1995 (14 months). Cases were identified by the Nottingham PHLS laboratory and notified to the Consultant in Communicable Disease Control. All cases were included if they were aged 18 or over and campylobacter was isolated from a faecal specimen submitted

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Table 4. *Odds ratios for food frequencies with campylobacter infection, Nottingham, England, June 1994 to July 1995*

Food (see text for details of frequency score)*	Unadjusted odds ratio	95% confidence interval
Chicken	1·3	1·1–1·7
Other poultry	0·8	0·8–9·2
Undercooked poultry	2·7	1·1–7·2
Beef	0·9	0·8–1·1
Lamb	0·9	0·8–1·1
Pork, ham	0·9	0·8–1·1
Sausages	1·0	0·7–1·3
Meat pie	0·8	0·7–1·0
Offal	2·2	0·7–6·6
Pate	1·0	0·8–1·3
Hard cheese	0·8	0·6–1·0
Soft cheese	0·9	0·7–1·1
Eggs	1·0	0·9–1·2
Shellfish	1·0	0·9–1·3
Handled raw poultry	0·9	0·8–1·1
Prepared main meals	0·9	0·7–0·9
Ate in restaurant	1·4	1·1–1·7
Bought sandwiches	1·0	0·8–1·2
Take away meals	1·3	0·8–2·0
BBQs	1·3	1·0–1·7

* Score system as described in methods.

by general practitioners and hospitals for investigation of presumptive infectious diarrhoea. Each case was asked to identify two people (such as neighbours or work colleagues) of the same sex and approximate age as themselves (controls).

Questionnaire

A questionnaire that had been used for a previous study [8] was used after minor modifications (questions on bowel operations, offal, sausages meat pies, eggs and restaurant meals were added and the questionnaire reworded for the controls). Food frequency in the 2 weeks before illness was scored as follows; not eaten = 0, once = 1, 2–5 times = 2, 6–10 times = 3 and 11 or more = 4. The topics included in the questionnaire are shown in Tables 2–5. A package of a white questionnaire for the case and two coloured questionnaires for the controls with pre-paid reply envelopes were posted to each case. A postal reminder was sent aftr 3 weeks. A pilot was undertaken of this methodology in which controls were returned for 58% of the cases.

Statistical analyses

Epi-Info V6·02 was used as the database. Odds ratios were calculated using conditional logistic regression analyses with campylobacter infection as the dependent variable using the computer package Egret. All variables that were significant by univariate analysis were included in the final multivariate model.

RESULTS

Seven hundred and thirty questionnaire packs were posted to identified cases. Five hundred and thirty-one cases returned the questionnaire (73%). Of these, 313 cases had controls who responded and these 512 were included in the analyses. Two did not answer the questions but returned the questionnaire and four questionnaire packs were returned unopened by the post office.

The age, sex and social class of the study population are shown in Table 1. There were no significant differences between the cases and the controls. The large number with unclassifiable occupations were students, housewives and retired or unempolyed people who gave no further details. The unadjusted odds ratios (OR) for campylobacter infection with the questions included in the questionnaire regarding social factors, milk and water sources, food consumption and medical factors are shown in Tables

Table 5. *Odds ratios for medical factors with campylobacter infection, Nottingham, England, June 1994 to July 1995*

Medical condition or medication	Cases ($n = 313$)	Controls ($n = 512$)	Unadjusted odds ratio	95% confidence interval
Diabetes	8	4	4·1	1·1–16
Stomach operations	3	3	1·6	0·3–8·1
Cholecystectomy	3	5	1·1	0·2–5·2
Antibiotics in past month	27	33	1·3	0·8–2·2
H_2 antagonists	12	6	3·1	1·1–9·2
Proton pump inhibitors	10	5	2·8	1·0–8·4

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Table 6. *Adjusted odds ratios for significant associations with campylobacter infection, Nottingham, England, June 1994 to July 1995*

Variable	Adjusted odds ratio	95% confidence interval
Contact with puppies	11·3	1·2–105
Diabetes mellitus	4·1	1·1–17
H_2 antagonists	3·7	1·3–15
Omeprazole	3·5	1·1–12
Foreign travel	3·4	2·0–5·7
Drunk milk from bottles with tops damaged by birds	3·3	1·0–11
Unpasteurized milk	2·4	0·8–7·6
Eating undercooked poultry	2·1	0·5–8·8
Chicken*	1·4	1·1–1·8
BBQs	1·3	0·8–1·7
Restaurant meals	1·1	0·8–1·4
Main meals prepared*	0·9	0·8–1·0

* Score system described in methods.

2–6. The adjusted odds ratios from the multivariate model with significant associations with campylobacter infection included contact with puppies (OR 1·3), diabetes mellitus (OR 4·1), H_2 antagonist use (OR 3·7), omeprazole use (OR 3·5), foreign travel (OR 3·4), milk consumption from bottles with tops damaged by birds (OR 3·3) and consumption of chicken (OR 1·4).

DISCUSSION

Our study confirms the importance of well recognized risk factors for campylobacter; consumption of poultry, foreign travel, milk from bottles with bird damaged tops and the protective effect of food preparation [2, 6–11].

A number of less well recognized associations were also demonstrated, specifically, diabetes mellitus and H_2 antagonists. Our results suggest that diabetes mellitus increases the risk of campylobacter infections, similar to that seen with salmonella [13]. The exact reasons for this are unclear but diabetes impairs antibacterial defences and the presence of an autonomic neuropathy may predispose to more severe symptoms. Greater contact with medical services may lead to better case ascertainment but no diabetic was admitted to hospital. Small numbers meant that the risk of different types of diabetic control therapies could not be determined.

Campylobacter has been shown to be associated with omeprazole therapy [12] and this study confirmed this risk and additionally showed that H_2 antagonists have a similar risk. Both drugs probably increase risk by reducing stomach acid making the stomach a much less hostile environment. Campylobacters are particularly sensitive to acid and much less resistant than salmonella [14]. No significant association was seen with a history of an operation for peptic ulcers, but numbers were small.

Exposure to puppies was significantly higher in cases. Puppies and young dogs are known to excrete campylobacters and been shown to be a risk factor [9]. Of the ten cases with this risk factor, only two reported their puppy had been ill with diarrhoea as did a single control. Sub-clinical infection is likely to be an important factor. No association was seen with older dogs, cats, kittens or animals at place of work. Farm visits were not associated with increased risk.

The number of meals prepared showed a dose related protective effect, which was not seen with handling raw poultry. Similar findings have been previously reported [2] and are difficult to explain unless protective immunity develops in people who are regularly exposed to low doses of campylobacter. Campylobacters are found in a wide range of foods and not only in raw poultry [10].

Use of case-nominated controls is an efficient way of matching for socio-economic factors. The case selected controls of the same sex and a similar age. There is a risk of over-matching in that the controls may have been similarly exposed to common risk factors but this effect only reduces the strength of any associations. Patients who submit a faecal specimen may not be typical of all campylobacter cases, but this

is the only case series available. In a large UK study no differences in stool submission rates by different groups in the population were shown [15]. This suggests that the use of this case series is valid. Even if notified cases represent a more severe spectrum of the disease the findings remain important. The use of culture proven campylobacter cases leads to some bias as shown in the social class distribution. In our case series it was likely that health centre workers and people employed in catering are over represented. Differences for risk factor exposure by social class are unclear and it is difficult to see how this effected the exposure to the significant risk factors identified in this study. One can speculate about increased foreign travel and different diets, but individual behaviour is likely to be much more varied. Case-nominated controls are the group most likely to control for this potential problem.

In conclusion the epidemiology of most sporadic cases of campylobacter infection remains unexplained. In our study, foreign travel could be incriminated in 25% of cases. Factors that increased risk-diabetes, anti-secretory agents, bird-pecked milk, contact with puppies, and eating undercooked poultry-explained another 15%. Further studies are needed to explain the remaining 60% of cases.

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