

Investigating vomiting and/or bloody diarrhoea in *Campylobacter jejuni* infection

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Campylobacter jejuni infection frequently presents as acute enteritis with diarrhoea, malaise, fever and abdominal pain. Vomiting and bloody diarrhoea are reported less frequently. To investigate potential host, micro-organism or environmental factors that might explain the different clinical presentations, the features of laboratory-confirmed *Campylobacter jejuni* cases presenting with vomiting and/or bloody diarrhoea were compared with cases who did not report either clinical manifestation. Single variable analysis and logistic regression were employed. Explanatory variables included food, water and environmental risks. Cases who reported vomiting and/or bloody diarrhoea tended to suffer a longer illness and were more likely to require hospital admission. Independent risks identified were being a child, female gender, consumption of poultry other than chicken, pre-packed sandwiches and sausages, and reported engineering work or problems with drinking-water supply. A dose-response relationship with vomiting and/or bloody diarrhoea and increasing daily consumption of unboiled tap water was observed also. Vomiting and/or bloody diarrhoea characterized the more severe end of the disease spectrum and might relate to host susceptibility and/or infective dose. The role of unboiled tap water as a potential source of *C. jejuni* infection in England and Wales requires further investigation.

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Abbreviations: CI, confidence interval; HPA, Health Protection Agency; OR, odds ratio.

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INTRODUCTION

Campylobacter infection represents a significant and persistent public health problem in the UK. Approximately 40 000 laboratory-confirmed cases are reported annually in England and Wales (Health Protection Agency, 2005), a figure which is estimated to underascertain disease in the community by a factor of eight (Wheeler *et al.*, 1999). The disease is unpleasant and debilitating, with approximately 10 % of cases requiring hospital treatment as a result of their infection (Gillespie *et al.*, 2002). Sequelae that can accompany illness, such as reactive arthritis, toxic megacolon and Guillain-Barré syndrome, add to the disease burden (Hahn, 1998).

Infection with *Campylobacter jejuni* most frequently presents as acute enteritis. Classic medical textbook descriptions of *Campylobacter* enteritis list the commonly reported symptoms as diarrhoea, malaise, fever and abdominal pain (Blaser, 2000; Skirrow, 1996). The spectrum of diarrhoea ranges from loose stools through profuse watery diarrhoea to frankly bloody stools (Blaser, 2000). Tissue injury can occur along the bowel from jejunum to colon, and gross pathological examination of the gut in severe cases reveals a diffuse, bloody, oedematous and exudative enteritis (Blaser, 2000; King, 1962). Severe disease may be clinically, sigmoidoscopically and histologically difficult to differentiate from ulcerative colitis, and *Campylobacter* infection forms part of the differential diagnosis for inflammatory bowel disease (Lambert *et al.*, 1979). Abdominal pain may be so severe that *Campylobacter* enteritis can be confused with acute appendicitis (Blaser *et al.*, 1979; Lambert *et al.*, 1979).

In the first year of a population-based sentinel surveillance study of *Campylobacter* infection in England and Wales, diarrhoea (95 %), abdominal pain (85 %) and fever (78 %) were the most commonly reported symptoms, whilst vomiting (35 %) and bloody diarrhoea (27 %) were reported less frequently (Communicable Disease Surveillance Centre, 2001). To investigate potential host, micro-organism or environmental factors that might explain the different clinical presentations, we compared the features of *C. jejuni* cases presenting with vomiting and/or bloody diarrhoea with cases who did not report either clinical manifestation.

METHODS

The *Campylobacter* Sentinel Surveillance Scheme has been described in detail elsewhere (Gillespie *et al.*, 2002). In brief, standardized clinical and epidemiological data, generated through postal questionnaires, were integrated with microbiological typing data for laboratory-confirmed cases of *Campylobacter* infection in participating health authorities in England and Wales. The scheme began on 1 May 2000 (Communicable Disease Surveillance Centre, 2000b) and ran until 30 April 2003. The response rate was consistently over 75 % (The *Campylobacter* Sentinel Surveillance Scheme Collaborators, 2003).

Statistical analysis, performed using Stata statistical software release 8.0 (StataCorp, College Station, TX), was restricted to cases of *C. jejuni* infection who had not travelled abroad in the 2 weeks before illness to control for the confounding effect of foreign travel. Cases who were infected with more than one *Campylobacter* subtype [as defined by serotyping (Frost *et al.*, 1998), phage-typing (Frost *et al.*, 1999) and/or antimicrobial resistance pattern (Thwaites & Frost, 1999)] were excluded, as were cases whose specimen dates were either prior to, or greater than 31 days from, their onset date.

The date of illness onset was used to define the season in which illness commenced. Season was coded to compare cases with an onset in spring (March to May) with those who were ill in summer (June to August), autumn (September to November) and winter (December to February). Patients' description of their ethnic origin was classified according to the UK census 2001 (Office for National Statistics, 2001). Age values were recoded to compare infants (<1 year of age) with toddlers (1–4 years), young children (5–9 years), older children and teenagers (10–17 years), adults (18–64 years) and the elderly (≥65 years). Food exposures were coded to compare cases who had

eaten a food once or more than once in the exposure period (2 weeks prior to the onset of symptoms) with those who had not. Contact with raw meat was coded to compare no contact with once, two to five times, six to ten times and more than eleven times. Daily consumption of unboiled tap water was recoded to compare zero consumption with one to four, five to nine and ≥10 glasses drunk. Binary variables were created to compare the 10 most commonly identified serotypes of *C. jejuni* with other known serotypes. Individuals with missing information for any of the variables of interest were omitted from the analyses using those variables.

For the case–case comparison, cases of *C. jejuni* infection reporting vomiting and/or bloody diarrhoea were considered 'cases', whilst those who did not report either symptom were considered 'controls'. It is important to note that symptoms were self-reported. The demographic and clinical profiles of cases and controls were compared using Pearson's chi square test and Student's *t* test. Differences in exposure were compared initially using simple logistic regression models. Point estimates and 95 % confidence intervals (CIs) for the Mantel–Haenszel odds ratio (OR) were calculated for each explanatory variable whilst controlling for the effect of age.

Proximal (Victoria *et al.*, 1997) exposures with a *P* value of less than 0.1 were then included in a larger model to obtain maximum-likelihood estimates of the effect of exposures on the outcome of interest, whilst controlling for confounding. The distal (Victoria *et al.*, 1997) exposures age, gender, season and ethnicity were included and retained in the model throughout. The significance of exposures was tested using the likelihood ratio (LR) test, and the model was simplified accordingly.

RESULTS AND DISCUSSION

Linked epidemiological and microbiological data were available for 11 831 cases of *C. jejuni* infection referred during the study (1 May 2000 to 30 April 2003). Cases ranged from less than 1 month to 97 years of age (median 39 years), and the gender distribution was even. Nine hundred and seven of 11 693 cases (8 %) were admitted to hospital as a result of their illness.

Amongst those cases who reported their foreign travel status (11 648; 98 %), 2261 cases (19 %) had travelled abroad in the 2 weeks before illness. Cases who reported foreign travel or who did not report their foreign travel status were excluded, as were cases (51; 0.44 %) infected with more than one subtype, and 397 cases (3 %) for whom the recorded specimen date preceded the reported onset date (*n*=69) or exceeded it by >31 days (*n*=328). This left 9350 UK-acquired cases of *C. jejuni* infection for analysis.

Diarrhoea, abdominal pain and fever were reported by 9056 (96.9 %), 8114 (86.8 %) and 7440 (79.6 %) cases, respectively. Vomiting was reported by 3346 cases (35.8 %) and bloody diarrhoea by 2661 cases (28.5 %), and cases who reported one of these symptoms were more likely to report the other (χ^2 138.19; *P*<0.001). In total, 4043 cases (43.2 %) reported one or both clinical presentations. These cases were compared with the 3335 cases (35.7 %) who reported no vomiting or bloody diarrhoea. A further 1972 cases (21.1 %) who did not respond to the questions of vomiting and/or bloody diarrhoea were excluded from further analysis. Cases who reported vomiting and/or bloody diarrhoea experienced

a longer illness than cases who did not report either symptom (mean 11·8 versus 10·9 days; *t* test *P*=0·007) and were more likely to be admitted to hospital (11·8 % versus 5·1 %; χ^2 99·5; *P*<0·001).

Single variable analysis

Self-reported vomiting and/or bloody diarrhoea amongst cases of *C. jejuni* infection decreased with age (Table 1). Cases who reported vomiting and/or bloody diarrhoea were more likely to be female and were more likely to report the consumption of barbecued foods, pre-packed sandwiches,

sausages, and foods eaten in restaurants. They were more likely to have reported a number of water exposures and to have been exposed to pet cats. They were less likely to report the consumption of fish and shellfish, cheese and salad. Reported vomiting and/or bloody diarrhoea appeared to differ depending on infecting serotype.

Logistic regression analysis

Independent risks for being a case of *C. jejuni* infection who reported vomiting and/or bloody diarrhoea were being an infant and being of female gender, and the consumption of

Table 1. Risk exposures for reported vomiting and/or bloody diarrhoea in *C. jejuni* infection

Single variable logistic regression analysis (variables with a *P* value of <0·1 shown).

Exposure	Percentage exposed		OR	95 % CI		<i>P</i> value
	Cases* (<i>n</i> =4043)	Controls† (<i>n</i> =3335)		Lower	Upper	
Female gender	51·6	47·7	1·24	1·13	1·36	<0·001
Infants	3·9	1·2	1·0	—	—	—
1–4 years	9·3	5·2	0·56	0·38	0·82	0·003
5–9 years	3·5	2·2	0·49	0·31	0·77	0·002
10–17 years	5·0	3·4	0·45	0·30	0·69	<0·001
18–64 years	69·1	67·8	0·32	0·22	0·45	<0·001
≥65 years	9·3	20·2	0·14	0·10	0·21	<0·001
Foods eaten in restaurants	51·7	47·9	1·18	1·07	1·31	<0·001
Barbecued foods	17·4	14·8	1·16	1·02	1·34	0·03
Pre-packed sandwiches	44·7	41·9	1·16	1·04	1·28	0·01
Poultry other than chicken	19·6	18·1	1·14	1·00	1·29	0·05
Sausages	60·9	59·2	1·12	1·01	1·23	0·03
Salad	71·1	76·4	0·87	0·77	0·98	0·02
Cheese	77·7	82·3	0·86	0·76	0·98	0·02
Fish and shellfish	55·8	63·6	0·82	0·74	0·91	<0·001
Unpasteurized milk	8·0	6·7	1·21	1·00	1·45	0·05
Engineering work/supply problems‡	7·3	5·0	1·52	1·24	1·86	<0·001
Water from private supplies	7·2	5·1	1·43	1·14	1·78	<0·001
Bottled water	51·8	45·9	1·28	1·15	1·42	<0·001
Glasses of water§ drunk daily: none	10·5	12·6	1	—	—	—
One to four	64·0	68·0	1·18	1·00	1·39	0·05
Five to nine	22·5	17·7	1·51	1·25	1·83	<0·001
≥10	3·0	1·7	2·07	1·42	3·01	<0·001
Windsurfing	0·37	0·13	2·80	0·91	8·57	0·07
Fishing	1·64	1·01	1·60	1·04	2·47	0·03
Contact with a pet hamster	4·7	3·1	1·41	0·97	2·04	0·07
Contact with a pet cat	48·2	43·4	1·20	1·05	1·38	0·01
HS50 versus other serotypes	21·6	17·8	1·25	1·08	1·44	<0·001
HS2 versus other serotypes	5·2	4·3	1·16	0·89	1·51	0·27
HS13 versus other serotypes	24·5	22·0	1·16	1·02	1·33	0·03
HS31 versus other serotypes	7·6	8·5	0·97	0·79	1·19	0·75
HS37 versus other serotypes	4·3	5·6	0·71	0·55	0·92	0·01
HS18 versus other serotypes	3·5	5·1	0·69	0·52	0·91	0·01

*Cases of *C. jejuni* infection who reported vomiting and/or bloody diarrhoea.

†Cases of *C. jejuni* infection who did not report vomiting and/or bloody diarrhoea.

‡In relation to mains water.

§Unboiled tap water.

poultry other than chicken, pre-packed sandwiches and sausages (Table 2). The likelihood of reported vomiting and/or bloody diarrhoea increased with reported engineering work or problems with drinking water supply and with increasing daily consumption of unboiled tap water. Cases infected with serotype HS37 were less likely to report bloody diarrhoea than those cases infected with other serotypes.

We have analysed data from a large sentinel surveillance scheme for *Campylobacter* infection in England and Wales in order to identify clinical, epidemiological or microbiological features leading to reported vomiting and/or bloody diarrhoea amongst UK-acquired cases of *C. jejuni* infection. A number of points need to be considered when interpreting these findings.

Firstly, cases included in this study were those whose infections were confirmed using microbiological methods. These cases are likely to represent the more severe end of the clinical spectrum (Tam *et al.*, 2003). Secondly, exposure data were self-reported over a 2-week period prior to onset, increasing the likelihood of reporting bias. There is no reason to believe, however, that these biases operate differently in those who were included as 'cases' in the analysis compared

with 'controls'. Thirdly, it has been suggested that co-infections might provide an explanation for the observed vomiting and/or bloody diarrhoea. Data on co-infections were unavailable and a degree of uncontrolled confounding might therefore have occurred. However, in general, low levels of co-infection for campylobacters are reported in the literature (Blaser *et al.*, 1983; The Food Standards Agency, 2000), so this is unlikely to have had a major effect on the findings. Finally, it is possible that additional confounding factors not included in our analysis affected our results. However, we have captured standardized information on a wide range of exposures for a large number of cases of *C. jejuni* infection, so the likelihood of this taking place has been minimized.

We elected to consider symptoms of vomiting and bloody diarrhoea together. Our *a priori* hypothesis was that vomiting and bloody diarrhoea did not share a common aetiology. However, the fact that cases who reported one of the symptoms were more likely to report the other suggested that this was not the case. Furthermore, initial analyses (not shown) examining each symptom separately produced very similar findings, reinforcing the need for a combined analysis.

Reported vomiting and/or bloody diarrhoea was strongly related to the age of the case. This might relate to host susceptibility or might represent ascertainment bias. It is possible that the relatively immature colonic flora (Stark & Lee, 1982) and intestinal immune system (Davies, 1988) of the infant might lead to a more severe infection and hence clinical presentation (Blaser, 2000). Alternatively, these are alarming symptoms that parents might be more likely to report on behalf of their children. The observed inverse 'dose-response' relationship with increasing age group, however, suggests perhaps that the effect is a genuine one.

The direction of the association amongst the food variables independently associated with vomiting and/or bloody diarrhoea warrants comment. Whether or not these findings represent different levels of contamination with *C. jejuni* is uncertain, but since it is possible that some foods are more highly contaminated than others, this might help to explain these observations (i.e. it is not the food items *per se*, but rather the contamination levels that are important).

The direction of association with the water-exposure variables and in particular the dose-response relationship between drinking unboiled tap water and presenting with vomiting and/or bloody diarrhoea were intriguing. Case-case comparisons, as used in this study, should not be used to make statements about the magnitude or direction of population risk (McCarthy & Giesecke, 1999; Gillespie *et al.*, 2002). Nevertheless, finding a dose-response relationship adds weight to an association between an exposure and disease (Hill, 1965), suggesting that there might be a real effect on clinical presentation. We cannot be absolutely certain, however, whether increased consumption of unboiled tap water was a cause of infection (and hence symptoms) or a consequence of it.

Table 2. Independent risk exposures for reported vomiting and/or bloody diarrhoea in *C. jejuni* infection

Final logistic regression model including age, gender, season and ethnicity (non-significant distal measurements not shown).

Exposure	OR	95 % CI		P value
		Lower	Upper	
Female gender	1.25	1.07	1.46	0.01
Infants	1.0	—	—	—
1–4 years	0.37	0.12	1.13	0.08
5–9 years	0.23	0.07	0.74	0.01
10–17 years	0.20	0.06	0.63	0.01
18–64 years	0.17	0.06	0.50	<0.001
≥65 years	0.10	0.03	0.29	<0.001
Poultry other than chicken	1.26	1.03	1.54	0.02
Pre-packed sandwiches	1.20	1.02	1.41	0.03
Sausages	1.18	1.00	1.39	0.05
Salad	0.79	0.65	0.96	0.02
Cheese	0.81	0.66	0.99	0.04
Fish and shellfish	0.79	0.67	0.93	<0.001
Engineering work/supply problems*	1.52	1.10	2.11	0.01
Glasses of water† drunk daily:				
none	1	—	—	—
One to four	1.29	1.00	1.67	0.05
Five to nine	1.79	1.33	2.40	<0.001
≥10	2.02	1.10	3.70	0.02
HS37 versus other serotypes	0.66	0.46	0.94	0.02

*In relation to mains water.

†Unboiled tap water.

Outbreaks of *Campylobacter* infection linked with municipal water supplies have been reported in the past (Communicable Disease Surveillance Centre, 2000a; Melby *et al.*, 1991; Mentzing, 1981; Palmer *et al.*, 1983; Vogt *et al.*, 1982). In all of these studies, either the water supply was unchlorinated (Melby *et al.*, 1991; Mentzing, 1981) or a serious challenge to a chlorinated supply occurred prior to the outbreak (Communicable Disease Surveillance Centre, 2000a; Palmer *et al.*, 1983; Vogt *et al.*, 1982). Case-control studies of sporadic infection have failed to identify municipal mains water as a source of infection (Adak *et al.*, 1995; Eberhart-Phillips *et al.*, 1997; Kapperud *et al.*, 1992; Neal & Slack, 1997; Rodrigues *et al.*, 2001). This might represent a negligible/zero risk, or might relate to the high prevalence of exposure to drinking mains water amongst the general population in many countries, making an effect difficult to detect.

Under current UK regulations, drinking water supplied for domestic purposes or to food production premises should be regarded as wholesome if it does not contain any micro-organisms or parasites at a concentration or value that would constitute a potential danger to human health (Department of the Environment, Transport and the Regions, 2000). Indicator organisms (historically coliforms and *Escherichia coli*, but current legislation includes enterococci) are used to ensure this quality and to assess the effectiveness of water treatment (especially disinfection). However, indicator organisms such as *E. coli* might not be an adequate indicator for the presence of campylobacters in water (Environment Agency, 2002), and statutory testing for campylobacters is not undertaken.

There was only one (inverse) association between infecting serotype and presentation with vomiting and/or bloody diarrhoea in this study. This suggests, perhaps, that there is no fundamental relationship between pathogenicity and expression of surface antigens detected by phenotyping (Frost *et al.*, 1998). Further work on the genetic basis of pathogenesis could be undertaken by the molecular subtyping of the isolates referred in this study.

Conclusions

Vomiting and/or bloody diarrhoea characterized the more severe end of the disease spectrum, as evidenced by a longer illness and increased hospital admissions. Host susceptibility might be important, as witnessed by strongly age-related symptom presentation. Infective dose might also be a factor. The role of unboiled tap water as a potential source of *C. jejuni* infection in England and Wales requires further investigation.

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