Population-Based Sentinel Surveillance as a Means of Elucidating the Epidemiology of *Campylobacter* Infection

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Abstract

The public health significance of campylobacters lies in their role as enteropathogens of man. Zoonotic in origin, they are the most commonly reported bacterial cause of gastrointestinal infection in the developed world. Approximately 46,000 laboratory-confirmed cases are reported annually in England and Wales, and this figure underestimates community disease by a factor of eight. Infection is unpleasant and, whilst self-limiting, a tenth of cases require hospital admission for their illness. Sequelae such Irritable Bowel Syndrome, Reactive Arthritis and Guillain-Barré Syndrome compound the problem. Despite the significant public health burden posed by campylobacters, our understanding of the epidemiology of *Campylobacter* infection is limited. This deficiency relates to a combination of the natural history of the microorganism, the high disease incidence which exists and the epidemiological tools applied thus far to its study.

In order to gain a better understanding of the epidemiology of *Campylobacter* infection the Campylobacter Sentinel Surveillance Scheme was conceived in 1998 and established in 1999. Through the integration of standardised epidemiological and microbiological data, it aimed to generate systematically new hypotheses for potential vehicles of infections, or transmission pathways, for campylobacteriosis. Twenty-two health authorities, representing all NHS regions at that time in England and in Wales and with a population of over 12 million people, participated in the study, which ran from May 2000 until April 2003.

Standardised epidemiological data were captured on over 20,000 cases over the surveillance period and these were combined with microbiological data from detailed strain characterisation of patients' strains, referred at the same time. Case-case comparisons and disease determinant analysis were the epidemiological tools most commonly applied to the data.

The research carried out by the candidate demonstrated that age, gender, ethnicity, occupation and socioeconomic status are major determinants for *Campylobacter* infection in England and Wales, and that variation in behaviour throughout the week also has a bearing on risk. It has shown that campylobacteriosis cannot be considered a single disease, as exposure differences exist in cases infected with different *Campylobacter* species or subspecies, and these differences can be confounded by foreign travel status. The fact that disease incidence amongst foreign travellers is country-specific suggests that the above exposure differences will be confounded further by travel destination. It has shown that outbreaks of campylobacteriosis occur more commonly than described previously, suggesting that an opportunity for furthering our understanding of infection is being missed. Finally, the dose-response relationship for *Campylobacter* infection has been investigated, highlighting potential implications for the design of future epidemiological studies.

Policy makers should be aware that future case-control studies of *Campylobacter* infection will need to be larger or more complex, and hence more costly. Such costs should be weighed against the opportunity for a more accurate assessment of disease risk, leading to improved evidence-based policy development. Researchers should focus on assessing rapidly and by non-invasive means, previous exposure to campylobacters amongst healthy controls, improving further the accuracy of case-control studies, which remain the epidemiological method of choice for studying this disease.

This study has demonstrated that the systematic collection of standardised epidemiological information on all cases of *Campylobacter* infection, reported from large, well defined populations over a prolonged period, coupled with detailed strain characterisation, can lead to public health gains.

Acknowledgements.

I am indebted to the invaluable contribution of the co-authors of the cited work within this submission, and to all the Campylobacter Sentinel Surveillance Scheme Collaborators, especially the staff within the Campylobacter Reference Unit and the Gastrointestinal Diseases Department CDSC (as was).

Thanks are extended to Dr Madhu Goyal for her helpful supervision throughout my PhD.

This thesis represents the culmination of my education in the classical sense, and a number of people deserve particular thanks for their efforts along the way:

My parents, family and friends, especially my wife Ruth;
Linda Gander, Kevin Lyons & Steve Heffernan;
Pete Luck & Keith Williams;
Paul Riley, Mike Green & all at EP1 Porton;
Bob Adak & Sarah O'Brien.

Dedication.

This thesis is dedicated to the memory of Joshua and Matthew Golder.

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Statement identifying the degree for which approval for a final submission is sought.

I, Iain Andrew Gillespie, declare that I have not been awarded a research degree at the University of Hertfordshire or at any other institution based on the cited publications in this submission and thereby seek approval for a final submission for the degree of Doctor of Philosophy (PhD).

Iain Andrew Gillespie
August 2007

Index of cited publications.

Paper	Reference	Page
1	**Gillespie IA**, O'Brien SJ, Frost JA, Adak GK, Horby P, Swan AV et al. A Case-Case Comparison of *Campylobacter coli* and *Campylobacter jejuni* Infection: A Tool for Generating Hypotheses. *Emerg Infect Dis* 2002;8(9):937-42	91
2	**Gillespie IA**, O'Brien SJ, Adak GK, Tam CC, Frost JA, Bolton FJ *et al*. Point source outbreaks of *Campylobacter jejuni* infection - are they more common than we think and what might cause them? *Epidemiol Infect* 2003;130:367-75	97
3	Campylobacter Sentinel Surveillance Scheme Collaborators. Foreign and domestic travel and the risk of *Campylobacter* infection: results from a population-based sentinel surveillance scheme. *J Travel Med*. 2003;10(2):136-8 [Writing committee: [Writing committee: Neal KR, **Gillespie IA**, O'Brien SJ, Frost JA, Cowden JM, Tompkins D, Harrison S]	106
4	The Campylobacter Sentinel Surveillance Scheme Collaborators. Ciprofloxacin resistance in *Campylobacter jejuni*: case-case analysis as a tool for elucidating risks at home and abroad. *Journal of Antimicrobial Chemotherapy* 2002;50(4):561-8 [Writing committee: **Gillespie IA**, O'Brien SJ, Frost JA, Neal KR, Tompkins D, Cowden JM, Nash JQ, Adak GK]	109
5	The Campylobacter Sentinel Surveillance Scheme Collaborators. Ethnicity and *Campylobacter* infection: a population-based questionnaire survey. *J Infect* 2003;47: 210-6. [Writing committee: **IA Gillespie**, Adak GK, O'Brien SJ, Frost JA, Tompkins D, Neal KR, Crowcroft N]	117

Paper	Reference	Page
6	**Gillespie IA**, O'Brien SJ, Neal KR, Frost JA, Cowden JM, Syed Q; The Campylobacter Sentinel Surveillance Scheme Collaborators. Is *Campylobacter jejuni* enteritis a weekend disease?. *J Infect* 2005;50(3):265-267	124
7	**Gillespie IA**, O'Brien SJ, Frost JA, Tam C, Tompkins D, Neal KR, Syed Q, Farthing MJ. Investigating vomiting and/or bloody diarrhoea in *Campylobacter jejuni* infection. *J Med Microbiol*. 2006;55(6):741-6.	127
8	**Gillespie IA**, O'Brien SJ, Penman C, Tompkins D, Cowden JM, Humphrey TJ. Demographic determinants for *Campylobacter* infection in England and Wales: implications for future epidemiological studies. *Epidemiology and Infection*. doi: 10.1017/S0950268808000319, Published online by Cambridge University Press 27 Feb 2008.	133

Statement on the use of citations published under group authorship.

It was agreed at the planning stage of the Campylobacter Sentinel Surveillance Scheme that all publications derived from the scheme would be submitted using the group authorship of ‘The Campylobacter Sentinel Surveillance Scheme Collaborators’ and that individuals’ contributions would be acknowledged within the manuscript as a Writing Committee. Whilst all manuscripts were submitted in this way, some were published using the writing committee as authors to reflect journal style. For this reason a mixture of anonymised and authored citations are included in this submission.

Statement of the candidate's contribution to the cited publications.

Paper	Formulation	Execution	Analysis	Publication
1	50 (%)	80	100	50
2	100	80	100	80
3	100	80	100	50
4	20	80	100	60
5	100	80	100	70
6	100	80	100	80
7	100	80	100	70
8	100	80	100	90

Sarah J O'Brien

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Statement of ethical considerations.

The publications which form this thesis were derived from analyses of data generated through the Campylobacter Sentinel Surveillance Scheme. As this study was undertaken within a primary surveillance framework, ethical approval was not required.

Declaration form.

I, Iain Andrew Gillespie, declare that I have not been awarded a research degree at the University of Hertfordshire or at any other institution based on the cited publications within this submission.

Iain A. Gillespie.
August, 2007

1. Introduction.

Campylobacters are small (0.3 to 0.6 μm in diameter) motile non-sporing Gram-negative comma-shaped rods belonging to the Proteobacteria phylum of bacteria (Skirrow, 1998). Whilst playing a role in periodontal disease, the main public health significance of campylobacters lies in their role as enteropathogens of man. Zoonotic in origin, campylobacters are the commonest bacterial cause of gastrointestinal infection in the developed world. Some strains are prone to cause systemic infections (e.g. *C. fetus*) but these represent a minority of cases. At least twelve species of *Campylobacter* have been linked with human infections, although *C. jejuni* and *C. coli* predominate in developed countries. In developing countries campylobacters frequently cause diarrhoea-associated dehydration and malnutrition in infants and young children (Coker et al., 2002). Here they are commonly isolated from healthy adults, suggesting immunity following childhood exposure, but with continued exposure in adult life. Other species are also more often prevalent, especially *C. upsaliensis* and, to a lesser extent, *C. jejuni* subsp. *doylei*.

2. History.

In contrast to other common gastrointestinal pathogens, the history of campylobacters is comparatively short (detail provided in Appendix 1). This relates largely to their exacting growth requirements (optimally 5-7% O_2 and 10% CO_2 at 42-43°C) rather than a lack of interest in them or their recent emergence. Indeed, campylobacters were probably first described in 1886 by Theodore Escherich, who noted spiral bacteria in the intestinal mucus of infants who had died of 'cholera infantum' (Kist, 1985). However, he was unable to grow the organisms and considered their role to be prognostic rather than causative. These findings, along with similar observations made by other German bacteriologists between 1887 and 1894, passed under the medical radar at the time as they were published in German, and interest waned due to a lack of culturability.

Research into the veterinary aspects of *Campylobacter* infection continued, however, perhaps due to the economic impact of the microorganism in this setting. Commissioned by the British Government to investigate epizootic abortion in cattle and sheep which was not infrequent at the time, McFadyean and Stockman were probably the first, in 1906, to isolate campylobacters from the uterine mucus of a pregnant sheep from a flock of ewes which was experiencing an abortion rate of 33% (Skirrow, 2006). Theodore Smith and colleagues were the first to describe vibrionic abortion in cattle in detail, to investigate their pathogenicity and to demonstrate their antigenic similarity (Smith, 1918; Smith & Taylor, 1919b; Smith, 1919; Smith, Little, & Taylor, 1920; Smith, 1923). They noted that the foetus suffered secondarily as a result of increasing interference of the placental circulation by the microorganism, which they named *Vibrio fetus*.

Attention then turned to the role of vibrios in diarrhoeal disease in animals. Through repeated washing, grinding, suspension and culture of intestinal mucosa, Jones, Orcutt and Little isolated, in 1931, tiny motile vibrios from cows and calves suffering from 'epidemic winter scours' (Jones & Little,

1931a; Jones & Little, 1931b). Demonstrating the absence of other potentially causative microorganisms, pathogenicity and antigenic-relatedness which was distinct from the vibrios causing vibrionic abortion, they proposed along with Orcutt the name *Vibrio jejuni* to reflect the focus of infection (Jones, Orcutt, & Little, 1931). Whilst investigating the cause of swine dysentery in 1944, Doyle noted that, of a number of organs tested, only the colonic wall from a diseased pig was capable of inducing disease when fed to susceptible pigs (Doyle, 1944). He subsequently isolated vibrios from the colon of a dysenteric hog which was later termed *Vibrio coli* (Doyle, 1948).

Human diarrhoeal disease due to a vibrio was first reported by Levy in 1946 (Levy, 1946). Investigating a large outbreak of milkborne gastroenteritis affecting 357 inmates in two prisons in Illinois, he observed vibrio-like microorganisms in mucous from faeces submitted by acutely ill patients. Their significance was at first disregarded as they could not be cultured, however their presence in samples from 31 patients stimulated further study, and 16 of 306 stool samples taken three weeks into the outbreak were visually positive for the organism. Morphologically-similar vibrios were isolated from blood samples from 13 of 39 patients, and were observed to resemble those of the *V. fetus* described by Smith, and more closely those of *V. jejuni* described by Jones and colleagues.

The next major development occurred in 1957 and arose from combining findings from human and veterinary medicine. Elizabeth King examined in detail the cultural, biochemical, and serological characteristics of 32 human and 13 veterinary vibrio isolates and compared these to the disease presentation and the available epidemiological information (King, 1957). These studies demonstrated the existence of a group of ‘related vibrios’ which were physiologically (they grew best at 42°C) and antigenically distinct from *V. fetus*, and were prone to cause diarrhoeal disease in children, rather than the systemic or abortive disease caused by *V. fetus* in predisposed humans.

The application of veterinary techniques to human medicine was to provide the technical breakthrough which allowed the isolation of the bacteria from faeces. Having isolated related vibrios from the blood of one of two linked cases of diarrhoea in Belgium in 1972, Jean-Paul Butzler approached a veterinary colleague for assistance in examining the patients' stool samples. Dekeyser diluted, homogenised and centrifuged the samples, and vibrios isolated from the filtered supernatants were antigenetically similar to each other and that from the blood sample (Dekeyser et al., 1972). Examination of 1000 'pathogen-negative' stool samples by this method resulted in the isolation of 35 strains of related vibrios, suggesting a significant role for these bacteria in the human gastrointestinal tract. The following year Butzler extended this work by demonstrating that the pathogen was more prevalent in diseased children (5%) and adults (4%) than in children without diarrhoea (1.3%) (Butzler et al., 1973). Inexplicably the findings of Dekeyser and Butzler did not receive the deserved attention, and it was not until Skirrow reported similar findings in the United Kingdom (UK) in 1977 that the importance of campylobacters was established (Skirrow ,1977).

3. The disease, its incidence and impact.

As with many bacterial infections, the dose necessary for infection or illness is a product of the degree of exposure, the survivability and/or pathogenicity of the microorganism and the susceptibility/response of the host. Information on the dose-response relationship for human *Campylobacter* infection is scant, with only one detailed study published. Black and colleagues fed doses ranging from 10^2 to 10^9 organisms ml^{-1} to 111 adult volunteers and observed a dose-response relationship with infection but not illness, underlying the importance of host response (Black et al., 1988). Another researcher developed symptoms and mounted an immune response after consuming 500 organisms in 180ml of milk (Robinson, 1981). Recent modelling work combining data from the former feeding study above and two milkborne outbreaks suggests an exponential rather than linear dose-response relationship (Teunis et al., 2005).

The incubation period for *Campylobacter* infection is variable and difficult to establish, but review articles generally quote mean incubation periods of three days, ranging from eighteen hours to eight days (Skirrow & Blaser, 2000), with an inversely proportional relationship between infective dose and incubation period (Skirrow, 1998; Blaser, 2000). Campylobacters which survive gastric transit multiply readily in the duodenum and jejunum, where they colonise the intestinal mucosa and adhere to intestinal cell surfaces (Ketley, 1997). The normal absorptive capacity of the intestine is then disturbed by a combination of cell invasion, toxin production or activation of the immune response. Laboratory-confirmed cases often experience prodromal symptoms of fever, headache, myalgia and malaise (Blaser, 2000), with diarrhoea, malaise, abdominal pain and fever most common during the enteric phase. Diarrhoea may range from loose stools to massive watery diarrhoea or grossly bloody stools, with patients experiencing more than ten episodes per day at the height of their illness.

The incidence of laboratory-confirmed cases of *Campylobacter* infection is provided in figure 1. The increase in incidence between 1977 and ~1990 is largely an artefact of increasing interest in the pathogen and improvements in isolation. Nevertheless, campylobacters emerged as the most commonly reported bacterial cause of gastrointestinal disease in England and Wales in 1984 - reports exceeding those for salmonellosis in that year. Incidence continued to increase throughout the 1990s and peaked in 2000 with almost 58,000 cases reported. Incidence then declined for a short period, but has increased again in the last two years, with over 46,000 cases reported in 2006.

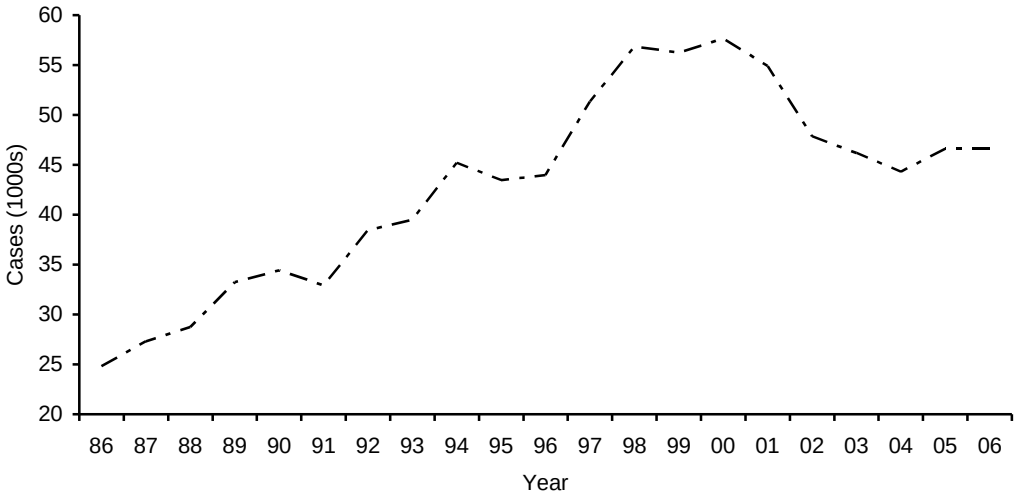

Figure 1. *Campylobacter* spp. Laboratory reports of faecal isolates reported to the Health Protection Agency Centre for Infections. England & Wales, 1986-2006.

A reporting pyramid for infectious intestinal disease (IID) exists in the UK, where decreasing proportions of community cases present to general practice, submit a stool specimen, have an aetiological agent identified successfully and have that result reported nationally. A Government-funded study (Food Standards Agency, 2000), conducted to assess this underestimation, found that for every laboratory-confirmed case of *Campylobacter* infection reported nationally there were 1.7 positive results, 4.1 healthcare consultations and 8.7 community cases (Wheeler et al., 1999). Assuming these proportions remain unaltered, an estimated 405,000

Campylobacter infections would have occurred in England and Wales in 2006, with 190,000 general practice consultations. The same study estimated that each case of *Campylobacter* infection cost the nation £315, based on 1995 prices. Bringing these figures up to date (Anon., 2007), the cost of campylobacteriosis in England & Wales in 2006 would have been approximately £220,039,652.

Campylobacter enteritis is usually self-limiting, with symptoms resolving gradually after the acute phase and lasting on average seven to ten days (Skirrow & Blaser, 2000). A spectrum of illness exists, however, and almost ten percent of cases require hospital admission as a result of their illness. Infections can manifest extra-intestinally, most commonly as bacteraemia (Skirrow et al., 1993) and rarely as cholecystitis, pancreatitis, cystitis, meningitis and endocarditis (Peterson, 1994). Irritable Bowel Syndrome and Reactive Arthritis are the most common sequelae associated with infection, occurring in 25% and 1-7% of cases respectively (Spiller et al., 2000; Hannu et al., 2002). Less common but more serious, approximately one in 5000 cases develop Guillain-Barré Syndrome – an acute demyelinating neuropathy, requiring months of intensive therapy (Tam et al., 2006b).

Campylobacter-associated mortality is considered to be rare, but is relatively poorly described in the literature. Scandinavian registry studies have demonstrated excess one year mortality following *Campylobacter* infection, suggesting that the long term impact of campylobacteriosis is underestimated. The same studies estimate case-fatality rates of 0.23% and 0.19% respectively (Helms et al., 2003; Ternhag et al., 2005). To examine Campylobacter-associated mortality in England and Wales, mortality data from the Office for National Statistics were obtained and analysed (Appendix 2). *Campylobacter* infection was recorded as the underlying cause of death in 45 instances between 1993 and 2006, representing a case fatality rate of 0.007%. However, when all causes of death were considered, campylobacters were implicated in 153 deaths (case fatality rate 0.02%), suggesting that the role of campylobacters in UK national mortality statistics is underestimated by a factor greater than three. Most patients who died

were elderly or had a pre-existing underlying condition. Over a quarter fulfilling both criteria. Deaths were age and season-dependent, with mortality increasing in patients over 60 years and in the winter months. Campylobacter-associated mortality was most likely to be underestimated when the patient was very old (≥80 years) or had an underlying condition.

4. Campylobacter epidemiology: theory and practice.

Despite the significant public health burden posed by campylobacters, our understanding of the epidemiology of *Campylobacter* infection is limited. This deficiency relates to a combination of the natural history of the microorganism, the high disease incidence which exists and the epidemiological tools applicable to its study.

4.1 Outbreaks

When conducted properly, the investigation of outbreaks of infection attributed to a specific pathogen can inform greatly on the epidemiology of disease caused by that pathogen (O'Brien et al., 2006). Outbreaks are often defined as “an incident in which two or more people, thought to have a common exposure, experience a similar illness or proven infection (at least one of them being ill)” (Kessel et al., 2001). Dissecting this definition into its component parts, it is clear why outbreaks of *Campylobacter* infection are rarely identified. The long and variable incubation period for illness means that establishing accurately exposure amongst individuals and linking these exposures to those in others is problematic. The low infective dose means that cross contamination plays an important role in disease transmission, hence the vehicle of infection may differ greatly from the source, and may not be recalled by the unaware victim. The spectrum of illness caused by campylobacters and its effect on healthcare usage means that epidemiological links between community and laboratory-confirmed cases will rarely be established as the former will often be unknown to public health practitioners. The lack of suitable routine laboratory subtyping methods for campylobacters means that the usual laboratory diagnosis of “*Campylobacter* species” lacks the sensitivity or specificity to identify microbiologically-linked cases from the background of sporadic cases. Finally, the sheer number of infections reported mean that local investigators, who have only limited resources, do not follow up cases of *Campylobacter* infection as diligently as

they would for other bacterial gastrointestinal pathogens (Rooney et al., 2000).

4.2 Case-control studies

Case-control studies are observational studies used frequently in infectious disease epidemiology. They are relatively simple to plan and execute, and are particularly useful for rare diseases or those where other epidemiological approaches would be prohibitively expensive (e.g. cohort studies) or unethical (e.g. randomised control trials to investigate the potentially toxic effects of chemicals). Fundamental to the case-control study is the establishment of an outcome of interest (e.g. confirmed infection, hospital admission, death etc) which distinguishes 'cases' from 'controls' within a particular study population. Exposure information leading up to this outcome is then sought (either retrospectively or prospectively) for both cases and controls and appropriate statistical comparisons of these data are undertaken to identify factors particular to cases i.e. 'risk factors' for the outcome of interest.

Case-control studies are, however, subject to a number of biases which limit their effectiveness and have the potential to distort their findings. Firstly, because they are identified through surveillance, cases usually include laboratory-confirmed infections who are selected non-randomly. Infants, children and people with more severe/prolonged disease are more likely to present to and be seen by a primary care physician, and they may be more likely to submit a sample for laboratory testing. Furthermore, laboratory-confirmed cases might be more willing to participate in a study depending on their exposures, outcomes or both. For example, patients who experienced a more severe illness might be more inclined to participate in a study than patients with milder infections, or they might be more assiduous in their responses to study questions. Alternatively, patients who believe that they contracted their illness at a restaurant might be more willing to participate if they think that it might facilitate compensation claims against the

establishment. Conversely controls, who represent the observed prevalence of exposure in the population if there was no association between that exposure and the outcome of interest, are selected at random from the population from which the cases arose, and hence are not subject to the same constraints. These differences, termed selection bias, may alter the findings of the study. Differential recall bias may be introduced if cases (who have a 'vested interest') are more conscientious in their responses than controls, and observer bias might be introduced if investigators, aware of the hypothesis under investigation, ask questions differently of cases and controls. A major problem with case-control studies that use recruitment of laboratory-confirmed cases as their starting point is that the exposure window for cases might have been more than a month ago, whereas controls tend to answer questions about their exposure in the week or so prior to interview. Thus cases and controls are answering questions about exposure in completely different time periods.

In order to assess the role of case-control studies in our understanding of *Campylobacter* infection, an analytical review of the scientific literature was undertaken (Appendix 3). Analysis of the titles and abstracts of 1734 manuscripts, identified through interrogation of the PubMed database, revealed 36 potential case-control studies on sporadic human *Campylobacter* infection undertaken in developed countries (Murray, 1986; Deming et al., 1987; Southern, Smith, & Palmer, 1990; Hudson et al., 1990; Lighton, Kaczmarski, & Jones, 1991; Hudson et al., 1991; Kapperud et al., 1992; McElroy & Smyth, 1993; Ikram et al., 1994; Schorr et al., 1994; Neal & Slack, 1995; Adak et al., 1995; Neal et al., 1996; Eberhart-Phillips et al., 1997; Neal & Slack, 1997; Svenungsson et al., 2000; Studahl & Andersson, 2000; Effler et al., 2001; Rodrigues et al., 2001; Tenkate & Stafford, 2001; Smith et al., 2002; Neimann et al., 2003; Kapperud et al., 2003; Potter, Kaneene, & Hall, 2003; Evans, Ribeiro, & Salmon, 2003; Cameron et al., 2004; Friedman et al., 2004; Engberg et al., 2004; Schonberg-Norio et al., 2004; Michaud, Menard, & Arbeit, 2004; Carrique-Mas et al., 2005; Olesen et al., 2005; Baker et al., 2005; Ethelberg et al., 2005; Wingstrand et al., 2006; Fullerton et al., 2007), with a further 27 articles identified through the reference lists of these

papers (Pearson et al., 1977; Bruce, Zochowski, & Ferguson, 1977; Blaser & Reller, 1981; Norkrans & Svedhem, 1982; Kist, 1982; Severin, 1982; Taylor et al., 1983; Hopkins & Scott, 1983; Blaser, Taylor, & Feldman, 1983; Santosham et al., 1983; Potter et al., 1983; Kist, 1983; Oosterom et al., 1983; Hopkins, Olmsted, & Istre, 1984; Oosterom et al., 1984; Engleberg et al., 1984; Nolan, Harris, & Canova, 1984; Hopkins & Olmsted, 1985; Kist & Rossner, 1985b; Harris, Weiss, & Nolan, 1986; Harris et al., 1986; Harris, Weiss, & Thompson, 1986; Salfield & Pugh, 1987; Schmid et al., 1987; Harris et al., 1987; Saeed, Harris, & DiGiacomo, 1993; Kassenborg et al., 2004). Further scrutiny revealed eight were not case-control studies (Pearson et al., 1977; Bruce, Zochowski, & Ferguson, 1977; Norkrans & Svedhem, 1982; Hopkins & Olmsted, 1985; Hudson et al., 1990; Svenungsson et al., 2000; Engberg et al., 2004; Olesen et al., 2005), four were case-case comparisons (Murray, 1986; Neal & Slack, 1995; Evans, Ribeiro, & Salmon, 2003; Kassenborg et al., 2004), three were non-exposure case-control studies (Neal et al., 1996; Smith et al., 2002; Ethelberg et al., 2005), three provided insufficient detail (Santosham et al., 1983; Kist, 1983; Baker et al., 2005), two were review articles (Blaser & Reller, 1981; Blaser, Taylor, & Feldman, 1983), two described outbreaks of *Campylobacter* infection (Potter et al., 1983; Harris et al., 1987), two were reports which went onto peer-reviewed publications which were included already (Oosterom et al., 1983; Nolan, Harris, & Canova, 1984) and one focussed on protective factors for *Campylobacter* infection (Cameron et al., 2004). One manuscript (Harris, Weiss, & Thompson, 1986) cited in the reference list of another (Saeed, Harris, & DiGiacomo, 1993) did not exist. These papers were excluded, and three papers (Harris, Weiss, & Nolan, 1986; Harris et al., 1986; Saeed, Harris, & DiGiacomo, 1993) reporting different aspects of the same study were combined into a single record, leaving 35 studies.

Twelve studies were published in the 1980s, ten in the 1990s and thirteen to date this decade, with most studies conducted in North America, the United Kingdom (UK) and the rest of Europe in each of these decades respectively (table 1).

Table 1. Trends in the design and outcome of reported case-control studies of sporadic *Campylobacter* infection.

Factor	Decade (N)			Total
	80s (12)	90s (10)	00s (13)	
Publication area (%)				
N America	58	0	38	34
Rest of Europe	33	20	46	34
UK	8	60	8	23
Australasia	0	20	8	9
Study population				
All	75	80	77	77
Adults	17	20	0	11
Infants & children	8	0	23	11
Percentage indigenous	9	40	62	38
Mean study length (months)	14	7	12	11
Mean sample size	326	456	565	452
Mean number of variables	19	32	106	55
Mean exposure period	7	10	10	9
Mean interview lag	10	10	14	11
Percentage matching	83	100	100	94
Percentage multivariate analysis	17	50	92	54
Foreign travel[†]				
% enquiry	60	83	100	76
% risk factor	33	33	50	39
Poultry variables				
% enquiry – any	75	80	85	80
% enquiry – ch*	58	70	77	69
Mean no. variables – any	4	9	10	8
Mean no. variables – ch*	4	6	8	6
% risk factor – any	89	63	73	75
% risk factor – ch*	86	43	50	58
Other (non-poultry) meats				
% enquiry	42	70	92	69
Mean no. variables	8	5	6	6
% risk factor	40	29	42	38
Dairy				
% enquiry	40	100	100	80
% risk factor	80	51	31	46
Water				
% enquiry	42	60	77	60
% risk factor	80	33	40	48
Animal contact				
% enquiry	42	60	77	60
% risk factor	80	33	40	48
Total risk factors identified	44	41	55	140
Mean risk factors identified	4	4	4	4

[†], Excludes indigenous-only studies; *, chicken

Studies were most frequently conducted over twelve months on subjects from all age groups, but some were restricted to adults or infants/children. The average number of study participants increased over the surveillance period, with the number of parameters under investigation increasing commensurately. Studies increasingly focused on indigenously-acquired infections, employed matching in control selection and utilised multivariate statistical techniques in analysis. Surprisingly, the period of exposure for which information was sought did not vary greatly, averaging nine days.

Based on the information reported, most studies asked participants about recent exposure to poultry (especially chicken) or dairy produce, as well as foreign travel and contact with animals and the wider environment. A disproportionately high number of questions on poultry and/or chicken consumption were included compared with other meat types, and the number of poultry-related questions posed increased over the surveillance period. The number of questions on selected epidemiological parameters, reported in each study, is provided in table A3.2 of Appendix 3.

General poultry consumption was the most commonly identified risk factor, with three quarters (75%) of studies reporting this exposure where it was investigated, followed by animal contact (48%), water consumption (48%), dairy consumption (46%) and foreign travel (non-indigenous studies; 44%). Where investigated, chicken consumption was the most commonly identified specific exposure (58%), and the number of specific chicken risk factors reported (26) was exactly double the second most commonly reported specific risk factor (contact with animals other than dogs; 13; Appendix 3; table A3.3). Where Population Attributable Fractions (an estimate of the proportion of disease in the general population that is attributable to a particular risk factor) were reported (seven studies), chicken accounted for between 0 and 24% of campylobacter cases, and an average of 12% of cases. Other important specific risk factors identified included the consumption of unpasteurised milk (47%), barbecued food (44%) or raw water (44%), and contact with dogs (42%). No case-control studies identified beef or lamb as a risk factor for *Campylobacter* infection.

On average, four risk factors were identified in each study, with the number of factors ranging from one to twenty. Single variable Poisson regression analysis revealed that the number of risk factors identified in studies was unaffected by the decade in which it was undertaken, the area covered, or the duration of the study (Appendix 3; table A3.5). Limiting studies to indigenous cases, altering the exposure period, or applying multivariate statistical techniques in analysis also had no effect. However, the number of reported risk factors identified in studies was positively influenced by the number of cases or controls included in the study (and hence the overall study size), and the number of variables considered. Multivariable analysis controlling for study year demonstrated that only the number of controls included (Relative Risk (RR) 1.42; 95% Confidence Interval (CI) 1.03-1.94; P=0.031) and the number of variables investigated (RR 1.33; 95%CI 1.00-1.77; P=0.048) were independently associated with the number of risk factors identified.

There are two possible explanations for each of these associations. It is possible that an increase in the number of controls in the studies has increased the statistical power, making it possible to detect true risk differences which exist between cases and controls which had hitherto remained unidentified. However, if this was the case one would expect a synergistic effect with the number of cases in studies, but this was not observed, although it was noted that the case and control variables were highly correlated (coefficient 0.86; $p<0.001$) but not collinear. Alternatively, each control in a case-control study carries with them an inherent amount of bias, hence studies with more controls are reflecting increased bias between cases and controls rather than true differences in risk. Similarly, the inclusion of more questions might result in more answers, especially if the number of variables increases with study size. However, the number of variables and the study population were not strongly correlated (coefficient 0.37; $p=0.07$), suggesting the alternative explanation, that increasing the number of variables increases the occurrence of chance associations.

The content of peer-reviewed publications are influenced by editorial restrictions and researchers' perceptions of the most important aspects of their studies, and these factors might influence the analysis of data derived from published case-control studies. Nevertheless, the body of evidence available in the literature suggests that case-control studies of *Campylobacter* infection are increasing in size and complexity without the corresponding improvement in our understanding of disease transmission. If anything, the move towards larger studies is perhaps magnifying the biases inherent in the methodology. Furthermore, they appear to be influenced heavily by investigator and reporter bias, as evidenced by the disproportionate pursuit of the poultry hypothesis, which continues to explain only a fraction of cases.

4.3 Case-case comparisons

Case-case comparisons have been suggested as an alternative to case-control studies for studying the epidemiology of infectious diseases (McCarthy & Giesecke, 1999). These rely on comparing the exposures of one set of cases with those from another similar, but suitably different, set of cases. These studies have a number of advantages. Firstly, as the name suggests, there is no need to enrol healthy controls for comparison as the study consists wholly of cases. This means that studies are not only easier to conduct (control selection and recruitment is often problematic and labour-intensive) but there is also no need (in most instances) to obtain ethical approval if these studies are conducted within a primary surveillance framework. Indeed, this is a prerequisite in most instances, otherwise selection bias might occur. Second, case-case studies have the potential to use all (or most) of the cases within a study population, meaning that any findings relate to the entire study population. This does not usually occur in case-control studies, where only a small proportion of cases within a study population are used and the findings are (rightly or wrongly) extrapolated to the entire population. Thirdly, assuming suitable groups of cases are

selected for comparison, it is unlikely that recall bias would differ between these groups, therefore differential recall bias will be minimised or removed.

Case-case studies also have disadvantages. By definition, ill cases are not compared with healthy controls and therefore differences in exposure identified through such studies cannot be considered 'risk factors' for infection in the classical sense. Thus case-case comparisons can generate hypotheses for infection which require confirmation or refutation elsewhere. Similarly, it is not possible to make statements about the direction or magnitude of population risk based solely on the findings of case-case comparisons. In a hypothetical example, both case group A and case group B reported exposure to X, and the level of exposure in group A was significantly higher than for group B, all other factors being equal. The first impression is that exposure X was positively associated with group A. However, it might be equally possible that group B were significantly less likely to report exposure X than the 'norm', hence the inflated association. Finally, case-case comparisons will not detect risk exposures common to the two groups of cases under comparison.

4.4 Disease determinant analysis.

A causal pathway is a theoretical depiction of the relationship between different factors which, alone or in combination, act to alter disease risk for an individual or population. The term 'pathway' is a misnomer to an extent, as it suggests a straightforward route 'from a to b', whereas in reality causal pathways tend to exist more as frameworks, with some factors having a direct, or 'proximal' effect, some having an intermediary effect and some have a more distant, or 'distal' effect. In an infectious disease context, a rather simplified example of such a pathway would be people of lower socio-economic status (distal) within a particular developing country residing in poorer standard of housing (intermediary), hence having less access to treated water (proximal), which increases their risk of gastrointestinal

infection. An approximation of the likely distal and proximal factors applicable to *Campylobacter* infection in this study are shown in figure 2 below.

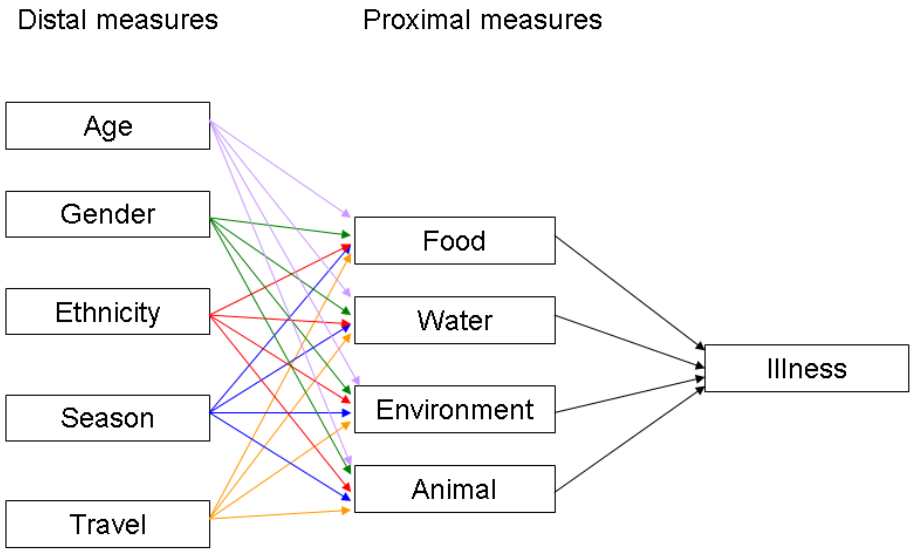

Figure 2. Distal and proximal factors applicable to *Campylobacter* infection applicable to this study (illustrative rather than comprehensive).

The assessment of the roles of different distal factors, or determinants, for a particular outcome is important in epidemiology, as the potential exists to exert control on that outcome further up the causal pathway. To do so, a population with a particular outcome of interest (the numerator) must be observed and the distribution of the determinants measured, and this distribution compared with that for the underlying population (the denominator) from which the cases arose. As with all epidemiological studies, such comparisons are prone to bias and must therefore be diligently designed and executed. Central to this is the establishment of a population where all individuals with a particular outcome of interest would be easily identifiable, accessible and amenable to measurement, and where the population is sufficiently well-defined in that baseline measurements of suitable deterministic factors has already taken place.

5. Study aims and objectives.

Given the sustained and significant public health impact of *Campylobacter* infection in England and Wales, the unsatisfactory understanding of its causes and consequences, and the apparent imperfections of the epidemiological tools thus far applied to its study, there was clearly a need for a new approach to the study of *Campylobacter* epidemiology.

Reference typing methods for campylobacters were developed by the Public Health Laboratory Service (the forerunner to the Health Protection Agency) Campylobacter Reference Unit (CRU) between 1995 and 1997 and were piloted in the North West region and in Wales between 1998 and 1998. However, these areas were not representative of England and Wales as a whole and therefore a sentinel surveillance approach was required.

The Campylobacter Sentinel Surveillance Scheme (CSSS) was conceived in 1998, established in 1999 and ran from May 2000 until April 2003. It was designed with three things in mind. Firstly, that the data accrued would be representative as described above. Secondly, that it would be of sufficient size to allow in-depth epidemiological analysis. Thirdly, that it would be designed around well defined populations to allow the calculation of robust incidence estimates. Twenty-two health authorities, representing all NHS regions in England and in Wales and with a population of over 12 million people, participated in the study, which aimed to capture data on 15% of all campylobacters reported annually (figure 3, overleaf).

The study had two overall aims: to gain a better understanding of the epidemiology of *Campylobacter* infection and to generate systematically new hypotheses for potential vehicles of infection or transmission pathways for campylobacteriosis. Both were to be achieved through the integration of standardised epidemiological and microbiological data generated through the scheme, and by the application of case-case methodology and disease determinant analysis to these data. By its very nature, it was not possible to be more prescriptive about the aims of the study, as in order to generate new

hypotheses a ‘blank canvas’ approach was necessary. If aims were set based on existing knowledge then generating new hypotheses would have been problematic if not impossible.

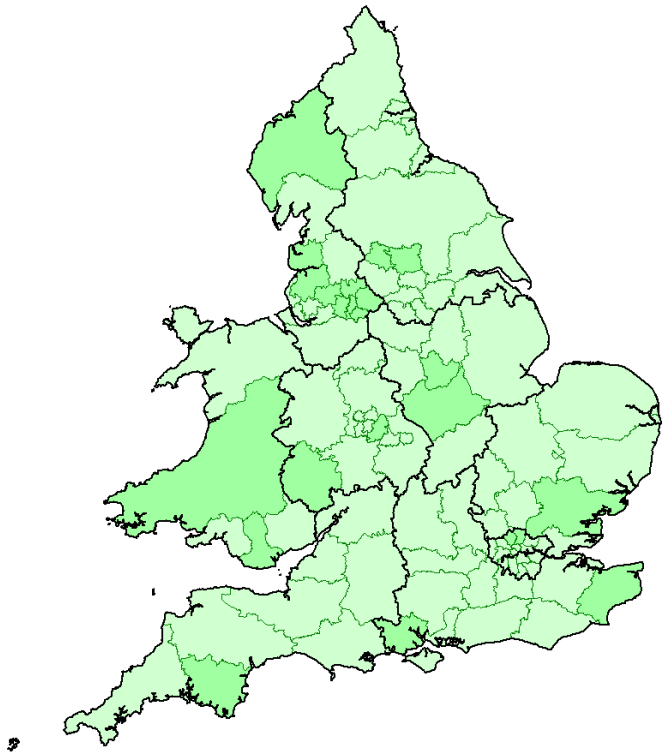

Figure 3. The health authorities (darker green) in England and Wales participating in the Campylobacter Sentinel Surveillance Scheme, by NHS region (black line).

In order to accomplish these aims the following study objectives would need to be met:

- To establish a working group for the project, including epidemiologists, microbiologists and statisticians, as well as representation from public/environmental health.

- To develop a single study protocol, covering the epidemiological and microbiological aspects of the study and including sample size calculations.

- To recruit successfully Health Authorities in each of the NHS regions in England at that time (the Yorkshire and the Humber region has subsequently been split into two regions only one of which is represented) with a total population of approximately 12 million people.

- To design a standard structured surveillance questionnaire amenable to use for a large number of cases over a three year period and to reach consensus on its content through dialogue with participants.

- To set up a meeting with all participants to make them aware of what was expected for the project, to facilitate the smooth running of the scheme and to identify and solve potential difficulties prior to the start.

- To design a database for the entry of data collected on the questionnaires and for the integration of the microbiological data. The database had to be robust enough to cope with the large amount of data which would be accrued and designed in such a way as to minimise the potential for error during the data entry process.

- To design an analytical strategy and to apply this to data on a regular basis. To compile monthly, quarterly and annual surveillance reports, including assessments of response to the scheme by health authority as necessary.

- To prepare articles for submission to peer-reviewed journals and to present findings at local, national and international conferences.

6. Materials and methods.

Regional epidemiologists in England, and public health colleagues in Wales, were contacted in Autumn 1999 and invited to participate in the Campylobacter Sentinel Surveillance Scheme, which was due to commence in April of the following year. This invitation was disseminated to Health Authority-based Consultants in Disease Control, who then agreed or declined to participate. The following health authorities agreed to participate:

- Yorkshire and the Humber
  - Bradford; Leeds
- North West
  - Bury and Rochdale; Manchester; North Cumbria; North West Lancashire; Salford and Trafford; South Lancashire; Stockport; West Pennine; Wigan and Bolton
- West Midlands
  - Birmingham; Herefordshire
- East Midlands
  - Leicestershire; Nottingham
- Eastern England
  - North Essex
- London
  - Barnet, Enfield and Haringey
- South East
  - East Kent; Southampton and South West Hampshire
- South West
  - South and West Devon
- Wales
  - Bro Taf; Dyfed Powys

Each NHS region in England at that time was represented, although a greater proportion of health authorities in the north of the country were represented. The sentinel population was broadly representative of England and Wales as a whole (table 2, overleaf). The only major difference between health authorities which participated and those which did not was the degree of urbanisation, where a greater proportion of the sentinel population resided in less sparse urban areas. Indian and Pakistani communities were also slightly over-represented.

Table 2. Health Authorities participating in the Campylobacter Sentinel Surveillance Scheme population in relation to those in England and Wales as a whole.

Parameter	Percent of population (unless stated otherwise)		
	Sentinel*	E&W†	Diff.
Population	12.1 million‡	52.0 million‡	-
Age group			
0-4	6	6	0
5-9	6	6	0
10-19	13	13	0
20-29	13	13	0
30-59	40	41	-1
60-64	5	5	0
65+	16	16	0
Ethnic group			
White	89	91	-2
Black	2	2	0
Indian	3	2	1
Pakistani	3	1	2
Bangladeshi	1	1	0
Other Asian	0	0	0
Chinese	0	0	0
Mixed	1	1	0
Other	0	0	0
Degree of urbanisation			
Urban > 10K - Less Sparse	86	81	6
Urban > 10K - Sparse	0	0	0
Town and Fringe - Less Sparse	7	9	-2
Town and Fringe - Sparse	0	0	0
Village, Hamlet & Isolated Dwellings – Less Sparse	6	9	-4
Village, Hamlet & Isolated Dwellings – Sparse	1	1	0

*, Sentinel health Authorities; †, England and Wales as a whole; ‡, persons

The scheme was centred around a standard, structured clinical and exposure questionnaire (Appendix 4) was administered to each laboratory-confirmed case of *Campylobacter* infection in participating health authorities by public or environmental health personnel as part of the routine investigation of foodborne infection. The questionnaire captured demographic and clinical information about the case, clinical details with regard to their illness

presentation and severity, foreign and UK travel, food consumption (~20 questions relating to the main food groups), milk and water consumption, recreational water activity, contact with animals and contact with other ill people. Exposures related to the fourteen days prior to the onset of patients' illness.

Collaborators formatted questionnaires as to their local style to encourage participation: the rationale being that individuals would prefer to receive a questionnaire from local teams rather than a national body. They were also permitted to add questions, if inclined, to answer specific research questions of their own, but could not to remove any, therefore maintaining the minimum dataset. Questionnaires were administered according to existing public or environmental practice, in that cases were contacted by post, by telephone or by personal visit depending on what method was currently in place. The study was piloted in two health authorities for one month prior to the start of the study and the effectiveness of the questionnaire as a surveillance tool was assessed at this time.

Concurrently, campylobacter isolates from clinical microbiology laboratories within the health authority catchment areas were referred to the CRU for confirmation and characterisation (speciation (Bolton et al., 1992), serotyping (Frost et al., 1998), phage typing (Frost, Kramer, & Gillanders, 1999) and antimicrobial resistance testing (Thwaites & Frost, 1999).

Electronic epidemiological and microbiological data were merged in Microsoft Access. The two datasets were linked initially using patient's surname and dates of birth. The forename, region and onset/specimen dates for linked cases were then compared in both datasets to ensure that the linkage was correct. For unlinked records a number of strategies were employed to identify the respective record in the other dataset. Searches of first name, date of birth and postcode were undertaken and the person details of potential matches compared. The first few letters of surnames and first names were analysed in the same way. Finally, for each case, the other

dataset was restricted to all cases of the same age, gender and region and the data were scanned to identify a potential match. The data were then classified in preparation for analysis.

In each of the case-case comparison analyses, the effect of the exposures on the particular outcome of interest was investigated by single risk variable analysis using Stata statistical software (Stata Corporation, 1999). Two by two tables (larger for categorical variables) were constructed and Mantel-Haenszel Odds Ratios (OR) were calculated along with confidence intervals and chi-squared significance tests. Exposures associated with the outcome of interest at a significance level greater than 90% (i.e. $P<0.1$ on chi-squared test) were selected for further investigation using multiple variable analysis. Initially, all variables were included in a single logistic regression model to obtain maximum likelihood estimates of the effect of each variable on the outcome of interest whilst controlling for the potential confounding effect of the other variables. The model was then simplified by stepwise exclusion: variables were removed sequentially from the model in order of least significance and tested for significance using the likelihood ratio test. This process was repeated until only significant ($P<0.05$) variables remained in the model.

An analytical strategy for the case-case comparisons was developed through the study period. In the early work (**papers 1** (Gillespie et al., 2003)**, 2** (Gillespie et al., 2003) and **4** (Campylobacter Sentinel Surveillance Scheme Collaborators, 2002)), binary variables created to represent the different strata within distal factors were included in analyses with proximal factors. With hindsight this was far from ideal as the former, by definition, act indirectly on disease risk. Distal factors were ignored altogether in the sixth study (**paper 6** (Gillespie et al., 2005)) and in the seventh study (**paper 7** (Gillespie et al., 2006)) a semi-hierarchical approach, as described by Victora and colleagues (Victora et al., 1997), was employed. This involved examining initially the effect of the distal measures on the outcome of interest, followed by separate analyses of the proximal measures from different transmission pathways (e.g. all the dairy variables together; all the water variables

together, etc). The results of the separate proximal analyses were then combined in a single logistic regression model which contained and retained the variables from the final distal model

For the disease determinant analysis, appropriate denominator data were obtained from the Office for National Statistics (ONS). Case data were than classified according to the particular classification schemes employed by the ONS and incidence calculated by comparing the case numerator with the population denominator for the different strata within the particular categories under investigation. Relative risks with accompanying 95% confidence intervals and significance tests were calculated where required using Stata. Proportions and categorical proportions were compared using the chi-squared test and the chi squared test for trend respectively, which were calculated using Epi Info (Dean et al., 1996).

Further methodological considerations, particular to each study, are described in the following chapter.

7. Results.

Study response rates.

Between 1st May 2000 and 30th April 2003 28,730 isolates were referred for typing from 36 laboratories within the sentinel catchment area. For 1468 isolates (5%) the bacterium referred was not *Campylobacter* spp. and for 389 isolates (1%) it was not possible to resuscitate the referred bacterial culture. Additionally, during the spring peak of the second year of the study, reference laboratory workload was such that isolates were only typed if a questionnaire was received and therefore 176 isolates (0.6%) were not typed at this time. Therefore, 26,697 were available for study.

During the same time period, 20,387 questionnaires were received from 21 health authorities in England and Wales, giving an overall response rate of 76% (table 3, overleaf). This response rate varied over the study period (74, 86 and 69% respectively), with the best response observed in the second year of the study and a lower level in the final year. This feature is commonplace in studies of this kind, as there a lag whilst some health authorities/laboratories come on board at the start of a study and drop off towards the end of the study.

Response rates also varied by health authority and within health authority by study year. This is partly a reflection of the phenomenon described above (East Kent being a good example here, where it took a year to convince the laboratories serving the population to participate), but also relates to the fact that health authorities and laboratories are not necessarily co-terminus, in that the referral of specimens for testing by general practitioners often relates more to economics than it does to geography. Therefore isolates from non-sentinel health authority residents will have been referred and specimens from sentinel health authority residents will have been referred to non-participating laboratories for testing. Whilst every effort was made to monitor

and improve response during the study period, this latter effect was beyond control.

Table 3. Response rates by health authority over the surveillance period.

Health Authority	Question-naires	Isolates	Response (%)*	Response by study year		
				1	2	3
Barnet Enfield and Haringey	510	206	248	95	270	470
Birmingham	2007	2829	71	74	71	67
Bradford	1079	200	540	214	∞	∞
Bro Taf	537	1245	43	0	108	50
North Cumbria	0	682	0	0	0	0
Dyfed Powys	104	587	18	31	16	0
East Kent	684	1082	63	9800	40	32
Hereford	386	150	257	86	∞	∞
Lancashire†	1264	2669	47	40	56	50
Leeds	2084	3307	63	67	64	57
Leicester	1255	1464	86	109	87	62
Manchester‡	4780	4613	104	89	122	112
North Devon	1027	1823	56	59	66	42
North Essex	1181	1506	78	69	92	75
Nottingham	1872	2541	74	73	85	62
Southampton and south west Hampshire	1617	1793	90	102	108	54
Total	20387	26697	76	74	86	69

*, Questionnaires received as a percentage of isolates referred; †,North West and South Lancashire health authorities; ‡, Bury and Rochdale, Manchester, Salford and Trafford, Stockport, West Pennine & Wigan and Bolton health authorities.

Figure 4 overleaf shows the age distribution of cases where isolates were received and questionnaires referred. Whilst the two datasets appear to be generally comparable, some subtle differences are apparent. Young adults were under represented amongst the questionnaire data and the opposite is true for older adults and the elderly. The latter reflects the fact that this age group is notoriously difficult to recruit into epidemiological studies. At the other end of the spectrum, older people may be retired and therefore have more free time to complete and return questionnaires.

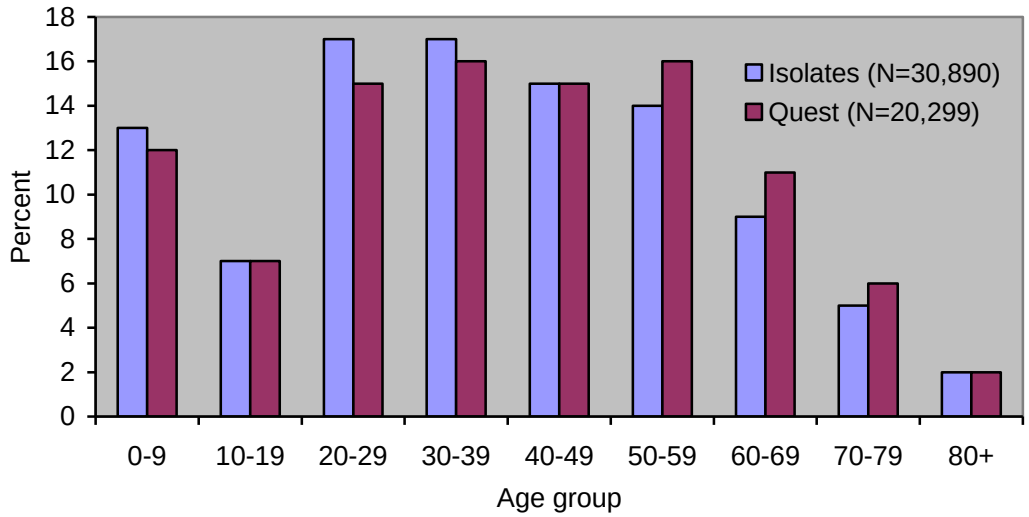

Figure 4. The age distribution of cases where isolates were received and questionnaires referred.

Linkage.

Of 20,387 cases where a questionnaire was received it was possible to integrate typing data in 14,383 instances (71%). Linkage was done in this direction as the questionnaires could be guaranteed to be from residents of the sentinel health authorities. Closer scrutiny of these data, however, revealed that in 116 instances (0.6%) the linked individuals were not identical (different spellings of first names; different postcodes etc) and in 382 instances (1.9%) the two records were not coincident in time (for 82 cases the specimen date occurred before the onset date and for 300 cases the specimen data was more than 28 days after the onset date). These records were considered unlinked in analyses involving linked data.

Cases with linked data were no different to unlinked cases in terms of age (mean 39.4 years in both groups) or gender (68 and 69% linkage in males and females respectively) and linkage did not differ greatly across ethnic groups. The only exception to this was cases who described their ethnicity as ‘Other Asian’ or ‘Other’, where linkage was 65 and 50% respectively compared to 68% in other ethnic groups. These cases only accounted for 2% of all cases however.

The published work.

7.1 Epidemiological distinctions between cases of Campylobacter jejuni *and* Campylobacter coli *infection.*

Standard isolation methods for campylobacters currently used by clinical microbiology laboratories in England and Wales do not differentiate the species within the *Campylobacter* genus. This is achieved through additional serological and biochemical testing, which is beyond the remit of routine public health microbiology. Campylobacters are therefore generally reported to national surveillance as '*Campylobacter* species' and, as a result, are often considered by investigators to be a single disease. This militates against understanding the epidemiology of individual *Campylobacter* species, as species-specific risk factors for infection might be obscured in an epidemiological study conducted at the genera level i.e. if a 'risk factor' for one species is a 'protective factor' for another.

In order to assess this assumption, the exposures of 272 cases infected with *C. coli* (the second most common *Campylobacter* species, accounting for ~8% of isolations or an estimated 3700 laboratory-confirmed cases reported annually) and 3489 cases infected with *C. jejuni* (the most common species, accounting for ~90% of isolations, or an estimated 41,600 laboratory-confirmed cases reported annually) were therefore compared to identify epidemiological differences between the two species and to inform case definitions for future studies (**paper 1** (Gillespie et al., 2002)).

Although cases were similar clinically, a number of epidemiological differences were identified. Cases infected with *C. coli* tended to be older than those with *C. jejuni* and were more likely to be of Asian ethnicity. Travel abroad was important for infection with *C. coli*, as was the consumption of certain meats and bottled water. A number of interactions between variables were observed, giving an indication of the complexity of the epidemiology in different demographic groups and at different times of the year.

This study demonstrated for the first time that the epidemiology of *C. coli* infection in humans differed significantly from *C. jejuni* infection. A major implication was that future epidemiological studies of *Campylobacter* infection should be undertaken at the species level. This also meant that subsequent case-case studies within the CSSS would also have to be restricted in this manner.

7.2 Outbreak underascertainment in Campylobacter jejuni *infection and hypotheses for their cause.*

As described above, despite a high disease incidence, outbreaks of *Campylobacter* infection are rare. For example, of 297,511 laboratory-confirmed cases of *Campylobacter* infection reported in England & Wales between 2000 and 2005 only 280 were reported as part of outbreaks (0.1%) (Health Protection Agency, unpublished data). This compares with 6% for *Salmonella* infection and 12% for Vero cytotoxin-producing *Escherichia coli* O157 infection for the same period.

In addition to capturing data on the patient, the CSSS questionnaire also enquired about other known individuals, either in the cases' household or in the surrounding community, who experienced similar symptoms at the same time as the index case. These data were examined to investigate whether apparent family or community outbreaks of *C. jejuni* infection occur more frequently than is currently recognised, and to identify factors which might instigate them (**paper 2** (Gillespie et al., 2003)).

Seventeen percent (509/3489) of *C. jejuni* infection cases reported other illness in the household and 10% (333/3489) reported other illness in the community. The primary cases in these groups were 465 and 323 respectively, emphasising the comparatively low level of secondary transmission observed in campylobacteriosis (Friedman et al., 2000). Household illness was more common amongst cases reporting contact with diarrhoeal pets, visiting farms and consuming organic meats, whilst

community illness was more common amongst patients reporting the consumption of unpasteurised milk or foods from restaurants.

A limitation in this study was that household or community illness was not confirmed microbiologically and so these episodes might have been unconnected to cases' illness, leading to 'false positive' clusters. Alternatively, cases might have been part of genuine clusters but were unaware of this, resulting in 'false negatives'. With these caveats in mind, however, this study demonstrated that point source outbreaks of *Campylobacter* infection might be more common than previously thought and that better methods for outbreak detection are required. Until suitable subtyping methods applicable to all campylobacters are developed, this might best be achieved through web-based collection of a standardised minimum surveillance dataset for all cases, allowing rapid identification and communication of clusters to local public/environmental health staff for further investigation.

7.3 Destination-specific risk in travel-associated Campylobacter *infection.*

Foreign travel is a major risk factor for gastrointestinal infection as a whole, and *Campylobacter* infection is no exception (Kist & Rossner, 1985b; Neal & Slack, 1997; Wingstrand et al., 2006). However, foreign travel is greatly underestimated by laboratory surveillance, making it difficult to establish the true burden of travel-associated infections in the UK. This is important from a food safety policy perspective, as Governments need to be able to distinguish imported infections from those preventable through measures taken in their own countries. Furthermore, booking a holiday or trip abroad does not alter disease risk in itself: activities undertaken whilst travelling have this effect. At the most basic level, the choice of destination can have a major effect on disease risk, and the identification of high risk travel destinations is therefore important for providing appropriate travel advice and for establishing an evidence base for policy development.

Travel destinations for cases reporting recent travel outside the UK were therefore classified according the ONS International Passenger Survey and destination-specific risks were calculated (**paper 3** (Campylobacter Sentinel Surveillance Scheme Collaborators, 2003b)). In order to assess the effect of travel within the UK, the destinations for cases reporting within-UK travel were coded according to the ONS UK tourism survey and analysed in the same manner.

In the first year of the study a fifth of campylobacter cases reported recent foreign travel (1444/7360; 20%), a smaller proportion (951; 13%) reported UK travel and 94 cases (1%) reported both. Travel to the Indian subcontinent, to other parts of Asia and to the Pacific islands posed the greatest risk of infection, although in terms of impact, the increased risk associated with travel to Spain was of concern due to the large number of UK travellers to this destination. Linked epidemiological and microbiological data demonstrated that *C. coli* infection was more often associated with foreign travel than infection with *C. jejuni*, and that travel to the Indian subcontinent posed a particular risk for this pathogen, perhaps explaining the association between *C. coli* and Asian ethnicity described previously (**paper 1** (Gillespie et al., 2002)). The risk of campylobacteriosis associated with travel within the UK was comparable with travel to a number of northern European destinations, although travel to Cumbria appeared to double the risk compared to other UK destinations.

This study confirmed that foreign travel is an important determinant for *Campylobacter* infection and that the travel destination is also important. However, just as buying an airline ticket does not confer *Campylobacter* infection on an individual, nor does arriving at a particular destination, hence additional studies are required to quantify the within-country risk. Given the adverse effect of negative publicity accompanying ‘holidays from hell’, the high level of accessibility to both ill and well travellers and the legal responsibility for passenger safety, such studies should perhaps be the responsibility of the tourist industry. The increased risk associated with travel to Cumbria might be an artefact of the large number of study collaborators in

north west England and in Yorkshire, and underlies the importance of obtaining appropriate denominator data for this type of analysis. However, UK travel data were only available for the whole of England and Wales at the time of the study.

7.4 Factors associated with the acquisition of ciprofloxacin-resistance **Campylobacter jejuni** *infection at home and abroad.*

Like most gastrointestinal pathogens, illness with campylobacters is usually self limiting. Symptoms resolve usually without specific medical intervention other than fluid replacement and electrolyte balance. However, there are instances (for example, for patients with high fever, bloody diarrhoea or prolonged illness) where antimicrobial chemotherapy is indicated and erythromycin is usually the drug of choice. The introduction of fluoroquinolones provided a useful alternative for adults with gastrointestinal illness, due to its activity against most enteric pathogens and its lack of side-effects compared with erythromycin. However, the emergence of fluoroquinolone resistance is a major public health problem worldwide (Bowler & Day, 1992; Piddock, 1995; Endtz et al., 1991).

Exposure data for cases infected with ciprofloxacin-resistant strains of *C. jejuni* were therefore compared with those from cases with sensitive strains in order to identify factors which might lead to acquisition of ciprofloxacin-resistant strains (**paper 4** (Campylobacter Sentinel Surveillance Scheme Collaborators, 2002)). An initial analysis demonstrated that cases who had travelled abroad were over five times more likely to be infected with ciprofloxacin-resistant strains than patients who had not travelled abroad. Since this difference was unlikely to have occurred by chance, foreign travel appeared to be an important risk factor for ciprofloxacin resistance, and hence analysis were restricted by foreign travel status.

Amongst travel-associated cases (N=653), those infected with ciprofloxacin-resistant strains were more likely to have travelled to specific destinations

(the Iberian peninsula and Cyprus) and were more likely to have eaten chicken or drunk bottled water than cases infected with fully sensitive strains. In cases who acquired their infection in the UK, ciprofloxacin resistance was more common amongst cases reporting the consumption of cold meats.

This study has several important implications. Firstly, if clinicians wish to treat a case of *Campylobacter* infection empirically with antibiotics it is important to obtain a travel history, since ciprofloxacin might be ineffective for patients returning from certain foreign destinations. Secondly, self treatment of traveller's diarrhoea with over-the-counter ciprofloxacin might be unsuccessful. This study also reinforced the confounding effect of foreign travel, so that future analyses within the scheme should be restricted by travel status. Finally, the fact that the epidemiology differed with foreign travel status has implications for control.

7.5 The role of ethnicity in Campylobacter *infection.*

The major recognised drivers for *Campylobacter* infection at the time of the CSSS were age, gender, season and degree of urbanisation (Skirrow, 1987; Tam, 2001). The role of ethnic origin in *Campylobacter* infection, however, had not been previously investigated, despite observed relationships between ethnicity and other communicable and non-communicable diseases in the UK. In order to assess the role of ethnic origin as a determinant for *Campylobacter* infection in England and Wales, the distribution of the main ethnic groups amongst 5180 non travel-associated cases was compared with denominator data specific to the participating sentinel health authorities (**paper 5** (Campylobacter Sentinel Surveillance Scheme Collaborators, 2003a)). Accompanying exposure data was also analysed in an attempt to further quantify the risk.

Resident Pakistanis were at greater risk of *Campylobacter* infection compared with the resident White population, whilst the resident Black and Indian populations were at decreased risk. The risk in the Chinese

community was no different from other recognised ethnic groups, although the number of cases in this group was small. Pakistani cases tended to be male and under five year olds were over-represented . Pakistani cases older than one year were more likely to experience a longer illness and more often required hospital treatment than their White counterparts. The seasonality of infection also differed amongst resident Pakistanis, with more illness at the beginning and end of the calendar year. A number of exposure differences between resident Pakistani and White cases were apparent.

This study identified a distinct pattern of infection for Pakistanis resident in England and Wales which could not be explained by recent foreign travel to high-incidence destinations as described previously (**paper 3** (Campylobacter Sentinel Surveillance Scheme Collaborators, 2003b)). Indeed, a developing country pattern of disease was observed amongst Pakistanis resident in a developed country, with high incidence in infants and young children and little disease in adulthood. This suggests community-specific routes of transmission and accompanying disease burden, necessitating studies to identify risk factors for infection specific to this community, or to assess alternative explanations for these observations (e.g. use of healthcare facilities, prior immunity in older children, adults etc).

Several methodological issues were identified in this study which warrant comment. Firstly, data from the 2001 census was unavailable at the time of the study, so ethnicity-specific denominator data from the 1991 census was used, and therefore the numerator and denominator differed by eleven years. It is possible, therefore, that the observed differences in risk might relate to changes in underlying population structure in the intervening period. This was considered unlikely as such changes would not explain the clinical, demographic, seasonal and exposure characteristics distinct to Pakistani cases. Secondly, we elected to ask patients to describe their ethnic origin rather than providing a choice of categories, meaning that for over a tenth of patients a description was not provided or was not classifiable. This could have skewed our findings if certain ethnic groups were more or less likely to

proffer a description of their ethnic origin. Future studies should take such potential shortfalls into consideration.

7.6 Patient exposure history in relation to the weekly periodicity of **Campylobacter jejuni** *infection.*

The seasonality of *Campylobacter* infection in the UK is well described and is noted for the annual sharp increase in incidence which occurs consistently in late spring/early summer. The pattern of infection over shorter time periods had not been investigated previously. Accordingly, the day of onset for 5606 UK-acquired cases of *C. jejuni* infection reported in the first two years of the study was calculated and examined (**paper 6** (Gillespie et al., 2005)).

Disease incidence was greatest on the days during or immediately following the weekend and cases who were ill at this time (N=3438) were more likely to have consumed Halal meats, offal, restaurant food or water from a private supply than cases whose illness onset occurred later in the week (N=2168). Furthermore, compared with those who had not eaten in restaurants, cases with a 'weekend illness' were more likely to have consumed foods from takeaway kebab shops and Indian restaurants.

It is tempting to conclude that, given the usual incubation period for *Campylobacter* infection, cases with illness onset at the weekend or soon after would have been exposed towards the end of the previous week. However, the incubation period for *Campylobacter* infection is thought to be inversely proportional to dose, and therefore the consumption of potentially heavily contaminated (e.g. offal or Halal meats) foods or untreated or poorly treated water might precipitate illness soon after. To our knowledge this is the first time that the weekly periodicity of an infection has been studied. The findings suggest that individuals undertake activities at the weekends which affect their risk of *Campylobacter* infection. Such potential daily differences in exposure should be considered when designing case-control studies of *Campylobacter* infection, as interviewing cases and controls on different days will increase the likelihood of differential recall bias. This method could also

provide useful insights into the epidemiology of other infections, and not just those causing gastrointestinal illness.

7.7 Host susceptibility and exposure history in relation to clinical presentation for indigenously-acquired Campylobacter jejuni *infection.*

Human infection with campylobacter presents usually as an acute enteritis. Diarrhoea, malaise, fever and abdominal pain are the most commonly reported symptoms. However, whilst nausea is common with *Campylobacter* infection, vomiting is less so. A case-case comparison was undertaken to examine host, microbiological and environmental factors which might give rise to this particular clinical manifestation in UK-acquired cases of *C. jejuni* infection (**paper 7** (Gillespie et al., 2006)). Bloody diarrhoea was studied in the same way as it was reported at a similar frequency as vomiting.

Initially, UK-acquired cases from the entire study who reported vomiting (N=3346; 35.8%) and bloody diarrhoea (N=2661; 28.5%) were compared separately with cases who reported neither symptom (N=3335). However, it became apparent that these two manifestations were linked, since cases who reported one were more likely to experience the other. Separate analyses revealed similar levels of morbidity (length of illness and hospital admission) and a similar risk exposure profile, hence cases who reported either symptom (N=4043) were compared with those who reported neither. Cases who did not respond to one or both of these symptom questions (N=1972) were excluded from the analysis.

Cases who reported vomiting and/or bloody diarrhoea were more likely to experience a longer illness and to be admitted to hospital than cases who reported neither. Self-reported vomiting and/or bloody diarrhoea was more common amongst females but decreased with age. It was more commonly reported by cases who reported the consumption of poultry other than chicken, pre-packed sandwiches or sausages, or amongst cases who reported engineering work on, or supply problems with, their water supply.

Similarly those who reported an increasing daily consumption of unboiled tap water were more likely to present with diarrhoea and vomiting. Eating salads, cheese and fish/shellfish was reported less commonly by cases reporting vomiting and/or bloody diarrhoea, and few associations with infecting *C. jejuni* serotype were observed.

This study suggests that for *Campylobacter* infection, vomiting and bloody diarrhoea share a similar aetiology, represent the more severe end of the disease spectrum and might relate to host susceptibility and/or infective dose. These findings have important implications for case-control studies of laboratory-confirmed *Campylobacter* infection. If heavily contaminated ("high dose") foods lead to severe disease then it follows that 'normal' doses will lead to 'normal' disease, 'lower' doses will lead to mild symptoms that might be dismissed as disease and the lowest doses will lead to sub-clinical infections. Some people will not be exposed at all (figure 5, below).

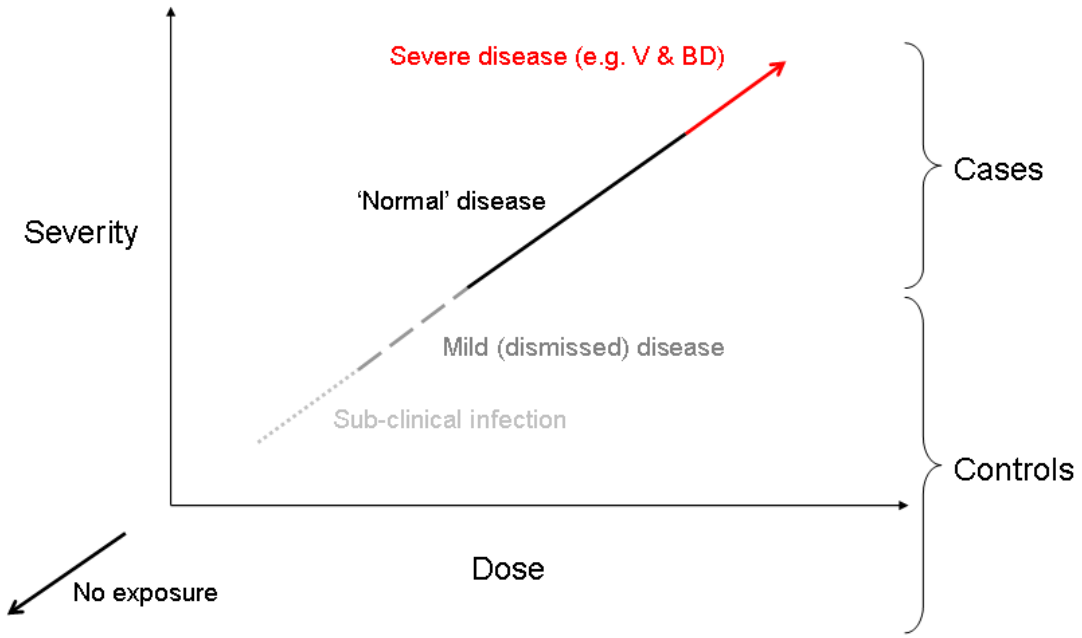

Figure 5. An extension of the dose response model for *Campylobacter* infection and its hypothesised effect of case and control classification in case-control studies.

Cases in case-control studies of laboratory-confirmed infection will therefore consist of normal and severe infection (normal and high dose) whilst healthy controls will comprise individuals with very mild clinical (lower dose) or sub-clinical (lowest dose) infections and those who were not exposed (no dose). Thus, case-control studies might be biased towards detecting high-dose foods. An accurate assessment of the epidemiology of *Campylobacter* infection can therefore only be achieved whilst controlling for previous exposure to campylobacters in the control population.

7.8 Demographic determinants for Campylobacter infection in England & Wales.

In the final year of the study (May 2002 to April 2003), data from the 2001 UK census became available. This provided an opportunity to address some of the methodological limitations experienced previously (**paper 5** (Campylobacter Sentinel Surveillance Scheme Collaborators, 2003a)), and to examine in detail the role of other demographic determinants in *Campylobacter* infection in England and Wales (**paper 8** (Gillespie et al., 2008)). Cases who reported no history of foreign travel in the two weeks preceding their illness were studied (N=15,907). Cases' descriptions of their ethnic origins and occupations were classified according to the UK census classification and Standard Occupational Classification (SOC) 2000 classification respectively.

Overall, incidence was highest in infants, decreased from two to thirteen years, increased from 14 to 22 years and remained relatively stable from 22 to 69 years before declining from 70 years. This pattern varied with gender. Incidence was higher in males than females from birth to 17 years and this difference was most noticeable between 13 and 15 years. Gender-specific incidence then switched, with females at greater risk from 20 to 36 years. Greater variability was observed further up the age spectrum although overall, incidence was higher in males. Analysis by ethnic group confirmed and extended earlier findings, demonstrating that the increased incidence in resident Pakistanis was not an artefact of dated denominator data, and that

the incidence in male Pakistani children under five years greatly exceeded that in female Pakistanis in the same age group, and in all other children in that age group, regardless of gender. White-collar workers were at marginally greater risk of infection than blue-collar workers, and incidence by socioeconomic status varied greatly with age and gender.

This study has reemphasized that age and gender are major determinants for *Campylobacter* infection in England and Wales and has also demonstrated that ethnicity, occupation and socioeconomic status are important. Epidemiological studies on *Campylobacter* infection need to take all these factors into consideration at either the design or the analysis stage if meaningful findings are to be obtained, and this is likely to increase either their size (larger single studies) or complexity (numerous smaller studies), with obvious financial implications. Some important hypotheses concerning the role of host susceptibility in disease transmission were also generated, in that we suggest that endogenous or exogenous hormones, present at elevated levels in different genders at different stages of life, might affect the growth characteristics of any campylobacters present in vivo, altering disease risk accordingly.

8. Discussion.

The research carried out by the candidate and documented in the aforedescribed publications which form this body of work demonstrate that the aims and objectives of this project have been met. The candidate has successfully improved current understanding of *Campylobacter* infection and generated new hypotheses for infection.

The candidate has demonstrated that age, gender, ethnicity, occupation and socioeconomic status are major determinants for *Campylobacter* infection in England and Wales, and that variation in behaviour throughout the week also has a bearing on risk. The candidate has shown that campylobacteriosis cannot be considered a single disease, as exposure differences exist in cases infected with different *Campylobacter* species or subspecies, and these differences can be confounded by foreign travel status. The fact that disease incidence amongst foreign travellers is country-specific suggests that the above exposure differences will be confounded further by travel destination. The candidate has shown that outbreaks of campylobacteriosis occur more commonly than described previously, suggesting that an opportunity for furthering our understanding of infection is being missed. Finally, the candidate has examined the dose-response relationship for *Campylobacter* infection.

A good marker for the significance of scientific work is its acceptance by peers. In addition to passing the peer-review process in journals with an average impact factor of 2.76, the publications which form this submission have been cited on sixty-six occasions by colleagues worldwide (table 4). In addition, the data generated from the study has been used to answer over 50 documented and many more undocumented information requests from Government, industry and academia. It has contributed to at least three Government-funded research projects, has been used to inform World Health Organisation strategy on campylobacteriosis and has been presented at local, national and international meetings.

Table 4. Subsequent citation of the publications in this body of work (excludes self-citation).

Paper	Citation
1	Tam et al., 2003; Evans, Ribeiro, & Salmon, 2003; Best et al., 2003; Altekruse & Tollefson, 2003; Hopkins et al., 2004; Best et al., 2004; Siemer et al. 2004; Mangen, Havelaar, & de Wit, 2004; Miller et al., 2004; Nichols, 2005; Bae et al., 2005; French et al., 2005; Siemer, Nielsen, & On, 2005; Gurtler et al., 2005; Miller et al., 2005; Kolackova & Karpiskova, 2005; Smole Možina & Uzunovic-Kamberovic, 2005; Wilson, 2005; Miller et al., 2006; Tam et al., 2006a; Gilpin et al., 2006; Tam, O'Brien, & Rodrigues, 2006; Black, Kirk, & Millard, 2006; Pennington, 2006; Workman et al., 2006; Samie et al., 2007; D'lima et al., 2007; Litrup, Torpdahl, & Nielsen, 2007; O'Brien & Halder, 2007; Karenlampi et al., 2007; Horrocks et al., 2007; Stafford et al., 2007; Best et al., 2007; Chan et al., 2007; Blanco et al., 2007; Strachan et al., 2007
2	Adak et al.. 2005; Cheng, McDonald, & Thielman., 2005; Gurtler et al., 2005; Wilson, 2005; Alter & Scherer, 2006; Heaton & Jones, 2007; Álvarez, Estrada Lorenzo, & Pérez, 2007; Fussing et al., 2007; Evers, Horneman, & Doorduyn, 2007; Luquero Alcalde et al., 2007; Best et al., 2007
3	Sopwith et al., 2006
4	Osterlund, Hermann, & Kahlmeter, 2003; French et al., 2005; Humphrey et al., 2005; Uzoigwe, 2005; Rosenbaum, 2005; Wassenaar, Kist, & de Jong, 2007; Johnson et al., 2007; O'Brien & Halder, 2007; Vicente et al., 2008
5	-
6	Nelson & Harris, 2006; Hanel & Atanassova, 2007
7	Yip, 2007
8	N/A in press

The sentinel health authorities were chosen for their geographical representativeness, with the hope that representation from each of the NHS regions in existence at the time would provide a study population broadly representative of England and Wales as a whole. A number of subtle differences were identified above, however, and these should be considered in terms of their potential bearing on the published findings. The sentinel health authorities contained a greater proportion of dense urban areas than England and Wales as a whole. It is probable that this contributed to the slight excess of Indian and Pakistani communities in the study population, as large cities often have greater populations of individuals from ethnic minorities. These variations in distal measurements would have little effect on the results of case-case analyses, however, as these focus on the effect of proximal measurements on disease risk. Furthermore they would have no effect on the disease determinant analyses, as the denominator used was particular to the sentinel health authorities and so controlled for any underlying population differences. Conversely, the observed variations in response to the questionnaire by age group (slightly lower in young adults; slightly higher in older adults and the elderly) had the potential to affect the findings of **paper 8** (Gillespie et al., 2008) in that incidence estimates by age would be biased downwards and upwards respectively for these age groups. This is based on the assumption, however, that all the isolates referred were from sentinel health authority residents, and this is unlikely for the reasons outlined previously.

A critique of the suitability of the methods chosen for analysis and their application is also necessary, as is discussion of alternative strategies and their suitability. Exposure information for the fourteen day period prior to patients' onset of illness was captured, despite a mean incubation period for *Campylobacter* infection of three days and an upper range of approximately eight days. This period was chosen to ensure that all potential disease exposure events for as many patients as possible were captured, as the potential existed for exposures at the outer limit of the incubation period to be important, or for the incubation period to be underestimated. In doing so the prevalence of exposure to the proximal variables under investigation will

have been increased, necessitating additional statistical power to identify true differences which might have existed. However, data were captured on almost 20,000 cases of *Campylobacter* infection and therefore statistical power will have been adequate.

The choice of denominator data in disease determinant analysis is important in ensuring that incidence estimates are not skewed. This is best illustrated in **paper 3** (Campylobacter Sentinel Surveillance Scheme Collaborators, 2003b), where the risk of campylobacteriosis associated with travel to Cumbria was inflated potentially by increased access to this area of the country by a number of participating health authorities situated in north or north west England. This was unavoidable, as health authority-specific denominator data was unavailable. It is important to bring such caveats to the attention of the reader so as to keep the findings in context.

In **paper 5** (Campylobacter Sentinel Surveillance Scheme Collaborators, 2003a) and **paper 8** (Gillespie et al., 2008) we were unable to control for all the factors under investigation in a single analysis, increasing the likelihood of uncontrolled confounding. This was especially apparent in the latter, where age, gender, ethnicity and socio-economic status were all investigated. This potential drawback could have been overcome by applying, for example, multivariate log-linked Poisson regression techniques to the data, which would also have allowed for the highly seasonal pattern of infection to be examined. Such techniques require denominator data stratified by all factors under investigation, however, and these were unavailable.

Bearing in mind its advantages and disadvantages, case-case methodology is applicable to any data where an outcome is readily identifiable and exposure data are available, from whence they follow case-control study methodology. That is not to say however, that the analytical methods employed in the publications described were not improved over the course of the study. The changing analytical strategy with regard to the case-case comparisons, described previously, is a case in point. However, there is no suggestion that the findings of the earlier studies are necessarily

fundamentally flawed. Since the application of case-case methodology to infectious disease epidemiology is in its infancy, no consensus on a gold-standard method for analysis exists currently. It is hoped that the methodological advances detailed in these studies will inform future case-case studies.

Case-crossover studies are an alternative approach which could have been applied at the outset of this study (McCarthy & Giesecke, 1999). These involve capturing information on patients exposures in the incubation period for a particular disease and comparing these to exposures from a time outside the incubation period. They therefore employ 'control times' rather than 'control persons' with the patient perfectly matched to themselves. They obviate the need for ethical approval if conducted within a primary surveillance framework and are relatively simple to conduct. Ideal in theory.

They assume, however, that the individual has done something 'out of the ordinary' which has resulted in their disease episode and this assumption is debatable for *Campylobacter* infection. Whilst there are documented instances where a 'change from the norm' has resulted in campylobacteriosis (e.g. household illness following the introduction of a puppy) it is equally possible that infection occurs as a result of indirect actions in everyday life (e.g. buying a contaminated sandwich from a sandwich shop where one routinely buys the same sandwich which has not previously been contaminated). Furthermore, the incubation period for *Campylobacter* infection would impact on the suitability of this study design. Firstly, it is long and therefore the control period would have to be some time prior to onset, increasing the likelihood of recall bias for the 'control' over the 'case' period. Secondly, it is variable, and therefore if the chosen control period is too recent then it is possible that the illness-causing exposure could be included in the control period and hence the case would be misclassified as a control.

In the absence of a control group, descriptive studies can only tell us so much about the role of particular exposures in disease, and policy makers and public health practitioners generally require a higher level of evidence for

action. In the absence of improvements in the detection of outbreaks of *Campylobacter* infection, it is likely that case-control studies will remain the epidemiological tool of choice for the foreseeable future. Perhaps the greatest contribution of this body of work, therefore, is that it informs greatly on the conduct of future case-control studies of *Campylobacter* infection. Unless travel-associated infection is under investigation, studies should be restricted to domestically-acquired cases and consideration should be given to restricting further to cases who have not travelled within the UK prior to illness. Studies should be conducted at the *Campylobacter* species level, or better still sub-species level. Studies should be restricted to, or matched on, age, gender, social and ethnic group, and these factors should also be investigated during analysis. Perhaps most fundamentally, the exposure status of controls needs to be measured immunogenically to determine if they are in fact controls, or merely unidentified cases. Controls should also be interviewed on the same day of the week as the case's onset date and with the minimum delay between case and control interviews (i.e. a week). Finally, investigators must approach studies with open minds, rather than focussing on chicken as a source of infection.

For these requirements to be met, case-control studies of *Campylobacter* infection will need to be larger and more complex, with obvious financial implications. Policy makers should bear this in mind when commissioning research into the study of risk factors for *Campylobacter* infection. The provision of greater resources for either larger or more focused studies should result in more accurate findings, leading to the opportunity for more evidence-based policy development. In the immediate term, policy makers should commission research to investigate the high disease incidence in the resident UK Pakistani community.

The body of work also identifies additional areas for research. A rapid and non-invasive method of assessing accurately previous exposure to campylobacters amongst healthy controls is a research priority as it will enable researchers to distinguish true controls from undiagnosed cases, leading to increased specificity when defining the study outcome in case-

control studies. The potential role of drinking water (both bottled and municipal) in campylobacteriosis was highlighted in a number of the published works, and therefore research is required to improve the methods for the isolation of campylobacters from water, leading to a detailed assessment of the prevalence of, and hence the potential risk from, campylobacters in drinking waters. Outbreaks of campylobacteriosis appear to be underascertained and therefore a system should be developed which routinely detects and reports clusters of infection to local investigators. This would require not only the agreement of a minimum dataset (onset date, postcode and foreign travel status (for exclusion purposes) should suffice) to define clusters in time and space, but also a change to current public/environmental health practice, as the data collected would need to be entered into a single database for analysis. Finally, work should continue into the development of typing methods which are sufficiently robust so as to form epidemiologically-meaningful organism groups, whilst not being overly cumbersome or prohibitively expensive and hence are applicable to all campylobacters.

In conclusion, campylobacters are a common cause of gastrointestinal disease in developed countries worldwide. The disease is not trivial and a number of sequelae add to the substantial disease burden. Campylobacteriosis-associated death, whilst rare, appears to be underestimated. An improved understanding of the complex epidemiology of *Campylobacter* infection is therefore an essential first step in informing on prevention strategies. This study has demonstrated that the systematic collection of standardised epidemiological information on all cases of *Campylobacter* infection, reported from large, well defined populations over prolonged periods, coupled with detailed strain characterisation, can achieve this, leading to public health gains.

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The published work

A Case-Case Comparison of *Campylobacter coli* and *Campylobacter jejuni* Infection: A Tool for Generating Hypotheses

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Preventing campylobacteriosis depends on a thorough understanding of its epidemiology. We used case-case analysis to compare cases of *Campylobacter coli* infection with cases of *C. jejuni* infection, to generate hypotheses for infection from standardized, population-based sentinel surveillance information in England and Wales. Persons with *C. coli* infection were more likely to have drunk bottled water than were those with *C. jejuni* infection and, in general, were more likely to have eaten pâté. Important differences in exposures were identified for these two *Campylobacter* species. Exposures that are a risk for infection for both comparison groups might not be identified or might be underestimated by case-case analysis. Similarly, the magnitude or direction of population risk cannot be assessed accurately. Nevertheless, our findings suggest that case-control studies should be conducted at the species level.

Campylobacters are the most commonly reported bacterial cause of acute gastroenteritis in the industrialized world (1). In the United Kingdom (UK), laboratory reports of campylobacter have increased steadily since surveillance began in 1977; in 1999, >60,000 cases were reported (incidence rate 103.7 per 100,000). However, the true population burden of campylobacter infection is thought to be much higher. For every laboratory-confirmed case reported to national surveillance in England, an additional eight cases may be unrecognized (2). This estimate suggests that in 1999, approximately half a million people in the UK became ill with campylobacter enteritis. The cost to the nation of a case of campylobacter infection has been estimated as £314.00 (at 1994–95 prices) (3); in 1999 campylobacter infection probably cost the nation >£150 million (US$ 225 million). The clinical complications of campylobacter infection include toxic megacolon, hemolytic uremic syndrome, Reiter's syndrome, and Guillain Barré syndrome, the most common cause of acute neuromuscular paralysis in the industrialized world (4).

Although campylobacters were recognized as important pathogens >20 years ago, their epidemiology is still poorly understood (5–8). Eating poultry has long been a leading hypothesis for spread of campylobacter infection, but few case-control studies have identified it as a major risk factor except in a commercial context (9–11). An estimated 20% to 40% of sporadic disease might result from eating chicken (12,13). Although a variety of food vehicles and other risk factors have been reported in several case-control studies, most cases in these studies remain unexplained by the risk factors identified (5–11).

A difficulty, until recently, has been the lack of routine microbiologic characterization of clinical strains (14), which has militated against systematic study of the epidemiology of the different species and subtypes of campylobacter. Control and prevention strategies cannot be developed and implemented without proper understanding of the epidemiology of campylobacter infection. On May 1, 2000, an active, population-based sentinel surveillance scheme for campylobacter infections was initiated in England and Wales (15). Its aim is to generate hypotheses for human campylobacter infection by using a systematic, integrated epidemiologic and microbiologic approach. Twenty-two district health authorities are collaborating in the scheme, working with their hospital microbiology and local environmental health departments

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(Figure 1). The sentinel system covers a population of approximately 12.5 million and captures standardized information on approximately 15% of all laboratory-confirmed campylobacter infections in England and Wales. The health authorities are broadly representative of England and Wales as a whole.

We have used case-case comparisons, an adaptation of conventional case-control methods, as suggested by McCarthy and Giesecke (16), to generate hypotheses concerning risk factors for campylobacter infection. We report results from the first year of the study and discuss the strengths and weaknesses of case-case analysis.

Methods

Campylobacters isolated by National Health Service and Public Health Laboratory Service (PHLS) laboratories within the catchment area were referred to the Campylobacter Reference Unit of the PHLS Laboratory of Enteric Pathogens for speciation, serotyping, phage typing, and antibiotic resistance testing (17–20). A standard, structured clinical and exposure questionnaire was administered to each patient by the health or local authority as part of the routine investigation of foodborne infection. The questionnaire, which can be completed by the patient, captured demographic and clinical data, as well as travel history (foreign and domestic), food history (>20 exposures), milk (3 exposures) and water (8 exposures) consumption, recreational water activity, animal contacts, and other illness (either in the household or the community) during the 2 weeks before the onset of illness. Epidemiologic exposure data and microbiologic typing information were then collated centrally by the Gastrointestinal Diseases Division of the PHLS Communicable Disease Surveillance Centre.

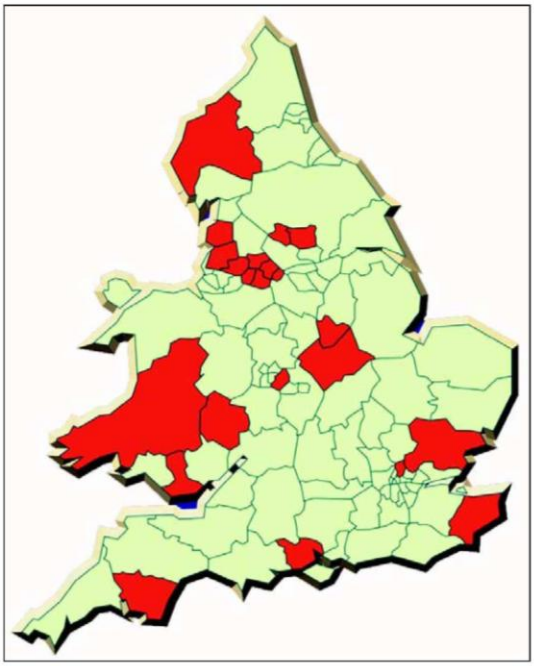

Figure 1. The health authorities in England and Wales participating in the sentinel surveillance scheme for Campylobacter.

The combined epidemiologic and microbiologic dataset, generated through the sentinel scheme, was analyzed by Stata version seven (Stata Corporation, College Station, TX). For the case-case analysis, illness in patients infected with *C. coli* was designated a "case;" patients infected with *C. jejuni* were designated as controls. Differences in demographic and clinical data were assessed by using Pearson's chi-square test and the Student t test. Cases were excluded from analysis if a patient was infected with more than one campylobacter subtype (133 cases) or was confirmed as infected with *C. lari* (two patients) or *C. fetus* (one patient).

The date of onset of illness for cases was used to define the month of onset and approximations of the four seasons (spring, March–May; summer, June–August; autumn, September–November; winter, December–February) were calculated. Socioeconomic group, based on occupation, was determined by standard occupational classification (21). Additional categories were generated for persons who described their occupation as unemployed, preschool child, school child, student, homemaker, retired, or part time, and for those who were unable to work because of disabilities or long-term illness. Food exposures were coded to compare those who had eaten a particular food in the 2 weeks before onset of illness (once or more than once) with those who had not. Daily water consumption was coded to differentiate no exposure from 1–4, 5–9, and >10 glasses of water drunk. Patient age was classified in 10-year age groups. Persons with missing data were omitted from the analyses using those data.

Initially, comparisons between *C. coli* and *C. jejuni* cases were performed by single-risk variable analyses. Mantel-Haenszel odds ratios (OR) were calculated for each explanatory variable. Logistic regression was applied to obtain maximum likelihood estimates of the effect of exposures on the species-specific outcome, while the data were controlled for potential confounders. Variables with a p value <0.1 from the single-risk variable analysis were included initially. Stepwise exclusion was used to simplify the model: variables were removed one at a time and tested for significance by the likelihood ratio (LR) test. Potential interactions (among the main effects included in the initial logistic regression model and age, sex, and season) were also examined by using the LR chi-square test.

Results

Epidemiologic data have been gathered for 7,360 laboratory-confirmed cases of campylobacter infection during the first year of the study (response rate 7,360 [76%] of 9,655). The median delay between onset of symptoms and completion of a questionnaire was 16 days. Case-patients ranged from <1 month to 99 years of age (Figure 2), and the overall sex distribution

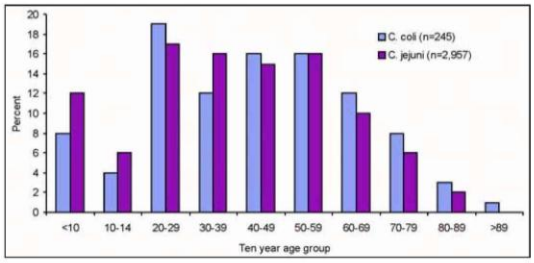

Figure 2. Age distribution of *Campylobacter coli* and *C. jejuni* cases reported to the sentinel surveillance scheme.

was even. Diarrhea (95%), abdominal pain (85%), and fever (78%) were the most commonly reported symptoms, with vomiting (35%) and bloody diarrhea (27%) reported less frequently. A total of 6,948 case-patients amassed 79,090 days of illness (mean 11), and 10% were hospitalized for an average of 5 days (range 1–42 days). Six hundred fifty-nine patients accumulated 3,048 hospital days. Five thousand one hundred seven patients reported absence from work or an inability to undertake normal activities for a total of 38,769 days (mean 8 days).

Linked epidemiologic and microbiologic data are available for 3,764 cases. *C. jejuni* accounted for 3,489 (93%) of the cases, with 272 *C. coli* (7%), 2 *C. lari* (<1%), and 1 *C. fetus* (<1%) also reported. Case-patients with *C. coli* and *C. jejuni* infection did not differ with regard to sex, clinical symptoms, or duration of illness (Table 1). However, case-patients infected with *C. coli* tended to be older (mean 42.9 years) than patients with *C. jejuni* (mean 38.5 years) (p=0.001).

Patients with *C. coli* infection were more likely to describe their ethnicity as Asian and to have traveled abroad in the 2 weeks before the onset of symptoms (single-risk variable analysis; Table 2). Patients with *C. coli* were also more likely to report having eaten specific types of meats (Halal meat [meat slaughtered according to Islamic law], meat pies, offal [organ meats], and pâté) and bottled water. They were less likely to have had contact with animals than were patients with *C. jejuni* infection. Persons with *C. coli* and those with *C. jejuni* infection did not differ with regard to eating chicken (89.8% vs. 90.8%; odds ratio [OR] 0.89; 95% confidence interval [CI] 0.58 to 1.36; chi square 0.59) or other types of poultry (23.6% vs. 19.7%; OR 1.26; 95% CI 0.91 to 1.74; chi square 0.16) in the 2 weeks before onset of illness.

Patients with *C. coli* infection were more likely to have drunk bottled water than persons with *C. jejuni* infection and, in general, were more likely to have eaten pâté (logistic regression analysis; Table 3). Retired persons who ate meat pies were more likely to be infected with *C. coli* than *C. jejuni*, as were Asians who had traveled abroad in the 2 weeks before illness. Case-patients with *C. coli* infection were, in general, less likely to be ill in the summer, and men who traveled abroad in the 2 weeks before illness were more likely to be infected with *C. jejuni* infection.

Discussion

To our knowledge, this population-based sentinel surveillance system for campylobacter infection is unique because we have successfully linked detailed epidemiologic exposure information with detailed microbiologic strain characterization for a large sentinel population. Campylobacters are widely distributed in the environment, and this genus is adapted to a wide range of ecologic niches throughout the food chain (22). Microbiologic data show that the prevalence of different campylobacter species and subtypes varies between different potential sources of infection, including different animal species, foods, and water (23–27). Although *C. coli* infection accounts for a small proportion of laboratory-confirmed human campylobacter cases in England and Wales, the potential for prevention is substantial if the true population burden is much higher (3). Most case-control studies have so far sought to determine risk factors for sporadic infection with campylobacter and have not sought to differentiate between species (5–

Table 1. Demographics, clinical symptoms, and severity of infections with *Campylobacter coli* and *C. jejuni*

	Campylobacter species (%)			
Variable	*C. coli* (n=272)	*C. jejuni* (n=3,489)	χ^2	p value
Mean age	42.9	38.5	-	0.001
Male	123 (45)	1,734 (50)	2.02	0.16
Female	149 (55)	1,755 (50)		
Mean length of illness	11.4	11.3	-	0.92
Diarrhea				
Yes	253 (96)	3,355 (98)	3.11	0.08
No	10 (4)	73 (2)		
Bloody stools				
Yes	73 (35)	964 (34)	0.07	0.79
No	134 (65)	1843 (66)		
Vomiting				
Yes	87 (37)	1249 (40)	1.00	0.32
No	151 (63)	1885 (60)		
Abdominal pain				
Yes	236 (93)	3,013 (92)	0.13	0.72
No	19 (7)	265 (8)		
Fever				
Yes	206 (84)	2,812 (86)	1.44	0.23
No	40 (16)	440 (14)		
Seeking advice from a doctor				
Yes	260 (97)	3,345 (98)	0.65	0.42
No	8 (3)	76 (2)		
Hospitalized				
Yes	23 (9)	358 (10)	0.97	0.32
No	245 (91)	3,055 (90)		
Mean days off work/normal activities	6.7	7.6	-	0.05

Table 2. Risk exposures for *Campylobacter coli* infection, by single-risk variable analysis

Exposure	No. exposed (%)		Odds ratio	p value[a]	95% Confidence intervals
	C. coli (n=272)	*C. jejuni* (n=3,489)			
Summer	75 (27.6)	1,206 (34.6)	0.72	0.02	0.55 to 0.95
Dyfed Powys Health Authority	5 (1.8)	24 (0.70)	2.7	0.04	1.02 to 7.15
10-year age group (increasing)	-	-	1.10[b]	0.001[c]	1.04 to 1.17
Members of the armed forces	1 (0.37)	2 (0.06)	6.43	0.08	0.58 to 71.27
Retired persons	61 (22.4)	580 (16.6)	1.45	0.01	1.07 to 1.95
Preschool-aged children	14 (5.2)	288 (8.3)	0.60	0.07	0.35 to 1.05
Homemakers	16 (5.9)	131 (3.8)	1.60	0.08	0.94 to 2.73
South Asian ethnicity	21 (9.1)	168 (5.8)	1.63	0.04	1.01 to 2.61
European ethnicity	4 (1.7)	118 (4.1)	0.42	0.08	0.15 to 1.14
Travel abroad	76 (28.3)	653 (19.0)	1.68	0.0002	1.27 to 2.22
Halal meats	23 (10.7)	216 (7.3)	1.52	0.07	0.96 to 2.39
Meat pies	78 (33.9)	856 (27.9)	1.32	0.049	1.00 to 1.76
Offal (organ meat)	19 (8.7)	170 (5.6)	1.60	0.06	0.97 to 2.62
Pâté	42 (18.7)	397 (13.2)	1.51	0.02	1.06 to 2.14
Bottled water	150 (63.6)	1,646 (53.7)	1.51	0.003	1.14 to 1.98
Contact with animals	138 (51.7)	1,989 (57.8)	0.78	0.049	0.61 to 1.00

[a]Exposures where p<0.1 shown.
[b]Approximation to the odds ratio for a one-unit increase in 10-year age group.
[c]Derived from score test for trend of odds

7). This distinction is important if *C. coli* and *C. jejuni* differ in their etiology or if the contribution of similar risk factors differs between the two species. If exposures are aggregated for different pathogenic campylobacter species, the contribution of risk factors unique to or predominantly associated with *C. coli* will be masked by the predominance of *C. jejuni* (in the study population: *C. jejuni*: *C. coli* approximately 10:1). This source of bias can be overcome by comparing the exposure characteristics of cases with *C. coli* infection with those of cases with *C. jejuni* infection. The data for cases with *C. jejuni* infection are then used to contrast with, rather than dilute, any observations for *C. coli* infection. Therefore, in generating hypotheses for infection, we identified potential species differences by adopting case-case analysis.

Hypothesis: Bottled Water

Case-patients with *C. coli* infection were more likely to report bottled water consumption than were those with *C. jejuni* infection. This observation is biologically plausible. Raw water can be contaminated with *C. coli* (28,29) and, while European legislation governing the marketing of natural mineral water makes it a condition that it be free from parasites and pathogenic organisms (30), testing for campylobacters is rarely undertaken (31). As the bottled water industry is large ($35 billion a year worldwide [32]) and expanding rapidly (consumption in the United States, which was 5 billion gallons in 2000, is predicted to increase to 7.3 billion gallons in 2005 [32]), an accurate assessment of the risk associated with these products is required. Our hypothesis-generating questionnaire did not distinguish between types of bottled water (e.g., spring or mineral, carbonated, or still), but these issues merit further investigation by case-control study.

Hypothesis: Pâté

The finding that having eaten pâté was more likely to be reported by case-patients with *C. coli* infection than those with *C. jejuni* infection is also biologically plausible. Pork is often the main constituent of pâté, and *C. coli* is found in pigs (33). In a recent study of the occurrence of campylobacters in 400 freshly eviscerated porcine liver samples, 6% were infected with *Campylobacter* spp; most (67%) were *C. coli* (34). Pâté is a perishable comminuted meat product containing nitrite, and possibly nitrate, ascorbate, or both (35). While the use of such preservatives might deter the growth of spoilage microorganisms (assuming adequate storage conditions are maintained), vegetative pathogens might not be destroyed; therefore, the ultimate critical control point during production is likely to be effective heat treatment.

Hypothesis: Meat Pies

The fact that retired people with *C. coli* infection were more likely to report having eaten meat pies is interesting. The types of meat in the pie fillings are not known, but the finding might point to the use of cheaper cuts of meat in these products.

Table 3. Independent risk exposures for *Campylobacter coli* infection: final logistic regression model[a]

Exposure	Odds ratio	p value	95% Confidence intervals
Summer	0.64	0.029	0.42 to 0.95
Summer (for participants 50–60 y of age)	3.10	0.013	1.27 to 7.59
South Asians who traveled abroad	9.70	0.006	1.89 to 49.73
Pâté	1.85	0.006	1.19 to 2.88
Pâté (for participants 50–60 y of age)	0.21	0.050	0.05 to 1.00
Meat pies eaten by retired persons	3.41	0.005	1.45 to 8.01
Bottled water	1.45	0.042	1.01 to 2.08
Men who traveled abroad	0.42	0.028	0.19 to 0.91
Male	1.05	0.804	0.72 to 1.53
Age (y)	1.00	0.586	0.99 to 1.02

[a] Main effects not shown if p>0.05; data were controlled for a priori confounders of age and sex.

Hypothesis: Foreign Travel

Persons from a South Asian ethnic background who had traveled abroad in the 2 weeks before onset of symptoms were more likely to have acquired a *C. coli* infection, but the reverse was true for men. This finding probably reflects the fact that travel abroad is simply a marker for activities or behavior while abroad, and a further study of the "travel cohort," generated through the surveillance scheme, might provide a better indication of where the risks lie.

Hypothesis: Seasonality

Campylobacter infection has marked seasonality, and case-patients infected with *C. coli* were less likely to be ill in the summer than those infected with *C. jejuni*. As data accumulate, generating season-specific hypotheses might be possible, which may have implications for the time period over which analytic studies are performed.

Sources of Bias

In interpreting the results from the sentinel surveillance system, likely sources of bias should be considered. Selection bias has been minimized by including all laboratory-confirmed cases of campylobacter infection identified by PHLS and National Health Service laboratories in the participating districts. Furthermore, both groups in the case-case comparison have been subjected to the same selection process, so selection bias should not influence our analysis.

The effect of time delays in reaching the patient, and hence recall bias for reported exposures, should be limited by close collaboration between the various participants in the scheme. While the time delay reported in this study introduces some recall bias, there is no reason to believe that recall is operating differently among patients infected with different species or among exposure groups, so that recall bias should not influence the case-case comparison.

Interpreting Case-Case Analyses

A detailed account of the pros and cons of case-case analysis is provided by McCarthy and Giesecke (16), but two important points influence the interpretation of this type of study. The first is that exposures that are a risk for infection for both comparison groups will not be identified or might be underestimated. By using patients with campylobacter infection, albeit with a different species, as "controls," we may obscure an association with the infection of interest because the controls might share some of the risk exposures with the cases. Thus, exposures common to both infections are controlled for by the study design.

The second is that traditionally controls are selected to provide an estimate of the exposure prevalence that would be seen in the cases if there were no association between the exposure and disease. Since our controls have been differentially selected by factors that are related to certain exposures, they might not be representative of the exposure prevalence of the population group from which the cases originated. We cannot, therefore, use comparisons between our cases and controls to make statements about the magnitude or direction of population risk.

Conclusion

Our work has shown that important differences in exposures might exist for these two campylobacter species. This finding is not necessarily surprising. For example, nontyphoidal salmonellosis is well recognized to represent a large group of serotypes, each with its own distinctive epidemiology (36). Given this knowledge, conducting a case-control study with a case definition comprising *Salmonella* spp. is inconceivable. Why should the same not be true for *Campylobacter* spp.? The implications for analytic study design are that researchers should not aggregate different species, which may mask important species-specific risk factors. Thus, the comparison of two organisms thought to represent one disease with a common cause has provided new avenues for the epidemiologic investigation of human disease. Focused analytical studies, based on systematically generated hypotheses, determining etiologic fractions for the risk factors identified, will allow informed prevention strategies for human infection.

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Point source outbreaks of *Campylobacter jejuni* infection – are they more common than we think and what might cause them?

THE *CAMPYLOBACTER* SENTINEL SURVEILLANCE SCHEME COLLABORATORS*

(*Accepted 7 January 2003*)

SUMMARY

Despite being the commonest bacterial cause of infectious intestinal disease (IID) in England and Wales, outbreaks of campylobacter infection are rarely reported. However, data from the *Campylobacter* Sentinel Surveillance Scheme suggested that outbreaks might be more common than was previously suspected, since a high proportion of cases reported other illness in the home or in the community at the same time as their illness. To identify factors that might lead to these apparent outbreaks, the exposures of cases of *Campylobacter jejuni* infection reporting other illness, either in the home or the community, were compared with those for cases not reporting other illness using case–case methodology. Illness in the home was associated with consuming organic meats in the winter, having contact with a pet suffering from diarrhoea or visiting a farm in the 2 weeks before the onset of symptoms. Illness in the community was associated with the consumption of foods in restaurants or drinking unpasteurized milk. Prevention of campylobacter infection requires that better methods of outbreak detection and investigation are developed, which in turn should lead to a better understanding of risk factors.

INTRODUCTION

Campylobacters are the commonest bacterial cause of infectious intestinal disease (IID) in England and Wales [1]. Laboratory reports of faecal isolates have exceeded 50 000 cases annually for the past 5 years [1], and these cases represent a fraction of those cases thought to occur in the community at large [2]. Despite this, outbreaks of campylobacter infection are rarely reported, with only 2% of all outbreaks of IID reported to the Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre (CDSC) between 1992 and 1999 being attributed to this pathogen [3, 4].

Outbreaks of campylobacter infection might go unrecognized for several reasons. Firstly, the long incubation period [5] means that cases might not recall certain common exposures, or that exposure might have occurred outside the period of enquiry. Secondly, investigators might have insufficient resources to investigate such large numbers of individual cases [6]. Finally, having identified a cluster of cases in space and time, investigators have not, until relatively recently, had a central reference facility to add microbiological typing evidence to epidemiological information, which is often needed in the recognition or confirmation of outbreaks [4].

The epidemiological and microbiological evidence gained from outbreak investigations provides valuable data on the sources and vehicles of infection [7]. The lack of recognized outbreaks means that risk factors for campylobacter infection are not easily identified, and this hampers the identification, implementation and monitoring of intervention strategies.

The *Campylobacter* Sentinel Surveillance Scheme, which was launched in May 2000, aims to generate new hypotheses for campylobacter infection through

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the integration of standardized epidemiological and microbiological typing data [8]. Data from the first year of the scheme suggested that point source outbreaks of campylobacter infection might be more common than was previously suspected, with a high proportion of cases reporting concurrent illness in the home or in the community [9, 10].

The aim of this study was to determine what factors, if any, might lead to these apparent outbreaks, by comparing the exposures of cases reporting other illness, either in the home or the community, with those cases who did not, using case–case methodology [11].

METHODS

Epidemiological information for all laboratory-confirmed campylobacter cases in the participating health authorities was collected using a standard, structured questionnaire. Demographic and clinical information was captured, in addition to the patients' travel history and exposures to food, water, the environment and animals in the 2 weeks prior to illness. Completed questionnaires were forwarded to the Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre (CDSC) for data entry. Laboratory isolates were referred to the *Campylobacter* Reference Unit of the PHLS Laboratory of Enteric Pathogens for speciation [12], serotyping [13], phage typing [14] and antimicrobial resistance testing [15].

The epidemiological and typing datasets were combined using the patients' surnames and dates of birth, and analysed using Stata version seven (Stata Corporation, College Station, TX, USA). The date of onset was used to define the season in which illness commenced. 'Spring' was defined as March to May, 'summer' from June to August, 'autumn' from September to November and 'winter' from December to February. Standard occupational classification was employed to determine cases' socio-economic group [16]. Additional categories were created for individuals who described their occupation as unemployed, pre-school child, school child, student, homemaker, retired, part time, and for those who were unable to work due to disabilities or long-term illness. Food exposures were coded to compare those who had eaten a particular food in the 2 weeks prior to onset (once or more than once) with those who had not. Contact with raw meat was coded to compare no contact with 1, 2–5, 6–10 and more than 11 times. Daily water consumption was coded to differentiate no exposure from 1 to 4, 5 to 9 and 10 or more glasses of water drunk.

Patient age was stratified into 10-year age groups. Household size was recorded to compare those households with 1–4 (adults or children), with 5–9 and with 10 or more members. Individuals with missing data were omitted from the analyses using those data items.

For the case–case comparison, cases of *C. jejuni* infection who reported individuals with similar symptoms at the same time (either in their home or in the community) were considered 'cases'. The epidemiological data for these 'cases' were scrutinized, and where other individual or individuals were infected with a different pathogen (confirmed, other than campylobacter), or where the onset of illness was greater than 7 days from that of the 'case', that 'case' was excluded. 'Controls' were those cases of *C. jejuni* infection who did not report other illness in either the home or the community. For the analysis of household illness, all cases who reported living alone were excluded from the analysis.

Demographic and clinical differences were assessed using Pearson's χ^2 test and the Student's t test. Initial comparisons were undertaken using single risk variable analyses. Mantel–Haenszel odds ratios (OR) were calculated for each explanatory variable. Logistic regression was then applied to obtain maximum-likelihood estimates of the effect of exposures on the outcome of interest whilst controlling for confounding. Variables with a $P<0{\cdot}1$ from the single risk variable analysis were included initially and the model was simplified using the likelihood ratio (LR) test. Potential interactions (between the main effects included in the initial logistic regression model and age, gender and season) were also examined using this method.

RESULTS

Linked data were available for 3489 cases of *C. jejuni* infection reported during the first year of the surveillance scheme. Cases ranged from less than 1 month to 94 years in age (mean 39) and the gender distribution was even. Diarrhoea (96%), abdominal pain (86%) and fever (81%) were the most commonly reported symptoms, and over a quarter (28%) of cases reported bloody diarrhoea. Cases amassed 37386 days of illness (range 0–701 days) and 358 cases (10%) were admitted to hospital for at least 1400 days.

Table 1. *Risk exposures for illness in the home – single risk variable analysis (exposures with a* P *<0·1 are shown)*

Exposure	Percent exposed		OR*	*P*	95% CI†	
	'Cases'	'Controls'			Lower	Upper
Increasing 10 year age group	—	—	0·85	<0·001	0·81	0·89
Skilled manual workers	3·7	6·7	0·53	0·02	0·32	0·90
Unemployed workers	0·5	1·8	0·25	0·04	0·06	1·04
School children	10·4	4·9	2·28	<0·001	1·59	3·28
Pre-school children	20·0	8·0	2·86	<0·001	2·16	3·79
British ethnicity	82·5	88·6	0·61	<0·001	0·45	0·82
Asian ethnicity	10·5	5·6	1·98	<0·001	1·36	2·89
Travel abroad	26·6	18·5	1·59	<0·001	1·26	2·00
Baby food	8·9	4·2	2·26	<0·001	1·48	3·44
Barbecued food	22·1	18·4	1·26	0·08	0·97	1·62
Beef (incl. roast, mince, steak)	68·6	72·5	0·82	0·09	0·83	0·10
Cold meats (pre-cooked)	63·5	73·9	0·61	<0·001	0·49	0·77
Halal meats	9·4	7·0	1·39	0·08	0·96	2·00
Organic meats	6·0	3·9	1·56	0·06	0·98	2·50
Pork, ham or bacon	74·5	80·7	0·70	0·003	0·55	0·89
Pre-packed sandwiches	33·8	44·4	0·64	<0·001	0·51	0·80
Handling raw meat (increasing frequency)	—	—	0·83	<0·001	0·76	0·91
Unpasteurized milk	10·7	7·6	1·45	0·03	1·03	2·04
Engineering work or supply problems (water)	9·7	5·0	2·07	<0·001	1·43	2·98
Swimming	28·6	19·2	1·69	<0·001	1·35	2·12
Sailing	3·88	1·66	2·39	0·002	1·34	4·28
Contact with a pet horse	2·2	1·0	2·18	0·04	1·00	4·74
Contact with a pet rodent	7·5	4·4	1·76	0·008	1·15	2·69
Contact with a pet with diarrhoea	11·8	6·5	1·93	0·005	1·21	3·10
Visiting a farm	15·9	9·6	1·79	0·001	1·25	2·55
Increasing number of household members	—	—	1·08	<0·001	1·03	1·13

* Odds ratio; † exact confidence interval.

Other illness in the household

Of the 3070 cases of *C. jejuni* infection who did not live alone, 509 cases (17%) reported another individual or individuals within the household with similar symptoms at the same time (66 cases did not respond to the question). Of the 509 cases reporting other persons with similar illness, 41 cases reported that the other ill individual or individuals had a date of onset greater than 1 week from the case and three individuals were confirmed as being infected with another gastrointestinal pathogen. These cases were excluded, leaving 465 'cases' and 2495 'controls'.

Cases tended to be younger (mean age 30·2 years) than controls (mean age 37·5) (*t* test, $P<0·001$) and were more likely to report vomiting (44·7 *vs.* 39·4%; $P=0·04$) and abdominal pain (94·5 *vs.* 92·0%; $P=0·04$). There were no differences in gender (51·6 *vs.* 50·5% male), length of illness (11·4 days each) or admission to hospital (9·5 *vs.* 10·5%).

Exposures in the fortnight prior to illness (Single risk variable analysis)

Cases were more likely to be school children or pre-school children than controls and were more likely to be Asian (Table 1). They were more likely to have travelled outside the United Kingdom in the 2 weeks before illness and to report the consumption of certain foods, engineering work or problems with their water supply, or recreational exposure to water. They were more likely to have had contact with certain animals, or to have visited a farm in the 2 weeks prior to the onset of symptoms.

Independent exposures in the fortnight prior to illness (logistic regression analysis)

Cases were more likely to be pre-school or school children than controls (Table 2). They were more likely to have consumed organic meats in the winter, to have had contact with a pet suffering from

Table 2. *Independent risk exposures for illness in the home (logistic regression model controlling for age and gender)*

Exposure	OR*	*P*	95% CI†	
			Lower	Upper
Organic meats in the winter	6·86	0·014	1·49	31·69
School children	2·18	0·022	1·12	4·26
Pre-school children	2·32	0·022	1·13	4·77
Contact with pets with diarrhoea	2·19	0·005	1·27	3·77
Visiting a farm	2·05	0·03	1·07	3·93
Visiting a farm in summertime	0·24	0·03	0·07	0·87
The winter	0·49	0·012	0·28	0·85
Summertime	1·01	0·94	0·70	1·48
Organic meats	1·14	0·76	0·49	2·68
Age	0·99	0·229	0·98	1·01
Gender	1·32	0·106	0·94	1·85

* Odds ratio; † exact confidence interval.

diarrhoea or to have visited a farm in the 2 weeks before the onset of symptoms.

Other illness in the community

Of the 3489 cases of *C. jejuni* infection reported in the first year of the study, 333 (10% reported knowledge of an individual outside the household with a similar illness. Of these, 10 cases (10/333) reported that the other ill individual or individuals had a date of onset greater than 1 week from the case. These cases were excluded, leaving 323 'cases' and 3048 'controls'.

Cases were, on average, younger (mean 32·5 years) than controls (mean 39 years) (*t* test, $P<0·001$) and were more likely to be female (56·7 *vs.* 49·5%; χ^2 $P=0·01$). There was no difference between these groups of cases with regard to length of illness (mean 11 days each; *t* test, $P=0·9$) or admission to hospital (10·8 *vs.* 10·5%; χ^2 $P=0·8$).

Exposures in the fortnight prior to illness (single risk variable analysis)

Cases were more likely to be intermediate non-manual workers (e.g. teachers, nurses, etc.) and farmers than controls (Table 3). They were more likely to be female and were more likely to have travelled outside or within the United Kingdom in the 2 weeks before illness. They were more likely to report the consumption of organic vegetables, vegetarian foods, food in restaurants, unpasteurized milk or bottled water. They were more likely to report swimming, sailing or contact with animals.

Independent exposures in the fortnight prior to illness (logistic regression analysis)

Cases tended to be younger than controls and were more likely to be intermediate non-manual workers (Table 4). They were more likely to report eating in restaurants and consuming unpasteurized milk.

DISCUSSION

Data from the first year of a large, population-based sentinel surveillance scheme suggests that point source outbreaks of *C. jejuni* infection in England and Wales, either in the home or in the community, might be more common than was previously thought. Case–case comparisons have allowed us to identify independent factors which might expose several individuals to campylobacter infection at the same time.

In the majority of instances, we were unable to determine the aetiological agent responsible for illness in other individuals reported to be symptomatic at the same time as the cases. This could have implications for the specificity of our case definition, since in some instances other illness reported by cases in the home or the community might not have been acquired from a common point source or might have been aetiologically unrelated. We examined extensively the available epidemiological data and excluded those cases where the illness might have been secondary or aetiologically unconnected in order to minimize false positivity. Conversely, some cases might have represented true clusters while not necessarily being aware of other related illness. However, our questionnaire

Table 3. *Risk exposures for illness in the community – single risk variable analysis (exposures with a* P *<0·1 are shown)*

Exposure	Percent exposed		OR*	*P*	95% CI†	
	'Cases'	'Controls'			Lower	Upper
South and West Devon District Health Authority	1·2	3·3	0·36	0·04	0·13	0·99
Increasing 10-year age group	—	—	0·86	<0·001	0·81	0·91
Intermediate non-manual workers	4·6	6·3	1·76	<0·001	1·30	2·37
Farmers (employers and managers)	0·7	0·1	9·52	0·006	1·33	68·0
Retired individuals	8·3	18·5	0·40	<0·001	0·26	0·61
Asian ethnicity	2·9	6·0	0·47	0·03	0·23	0·96
Travel abroad	23·8	18·5	1·37	0·02	1·04	1·80
Travel in the UK	18·6	14·2	1·38	0·04	1·01	1·88
Barbecued food	24·6	17·5	1·53	0·004	1·15	2·04
Lamb	37·1	44·3	0·74	0·02	0·58	0·95
Meat pies	19·4	29·0	0·59	<0·001	0·43	0·80
Organic vegetables	19·1	14·9	1·34	0·07	0·97	1·85
Vegetarian food	24·1	19·1	1·34	0·04	1·01	1·79
Eating in restaurants	65·7	53·4	1·67	<0·001	1·31	2·13
Unpasteurized milk	11·6	7·8	1·55	0·02	1·06	2·27
Bottled water	62·0	52·7	1·46	0·002	1·14	1·86
Swimming	27·7	18·8	1·65	<0·001	1·28	2·15
Sailing	3·6	1·7	2·08	0·03	1·07	4·05
Contact with animals	64·0	57·3	1·32	0·02	1·04	1·68
Contact with pet rodents	6·6	4·1	1·63	0·06	0·97	2·73

* Odds ratio; † exact confidence interval.

Table 4. *Independent risk exposures for illness in the community (logistic regression model controlling for age, gender and season)*

Exposure	OR*	*P*	95% CI†	
			Lower	Upper
Farmers (employers and managers)	$3{\cdot}89 \times 10^{9}$	—	—	—
Unpasteurized milk	2·15	0·002	1·33	3·49
Intermediate non-manual workers	1·49	0·045	1·01	2·19
Restaurants	1·40	0·036	1·02	1·92
Asian ethnicity	0·28	0·01	0·11	0·74
Meat pies	0·56	0·003	0·38	0·82
Age group (increasing)	0·82	<0·001	0·75	0·89
Male gender	0·75	0·059	0·55	1·01
Season	0·95	0·528	0·82	1·10

* Odds ratio; † exact confidence interval.

contained specific questions about other individuals with similar symptoms at the same time, and we would expect that most cases would be aware of other concurrent illness resulting from point source exposures, particularly among individuals in their own home.

Other illness in the household

Concurrent illness within the household setting might be less important than in the community in public health terms as the numbers affected will tend to be

smaller. However, there are still issues with regard to treatment and prevention, and our data suggest that simultaneous *C. jejuni* infection occurs more frequently in the household setting than in the community.

An association between the consumption of organic meats in the winter and other illness in the household might relate to a higher prevalence of *C. jejuni* in organic meats. In a study of *Campylobacter* spp. in 160 broiler flocks in Denmark, 100% of organic broiler flocks were positive, compared with 37% of conventional broiler flocks and 49% of extensive indoor broiler flocks [17]. The prevalence of exposure to organic meats was low, and the increased risk in the winter might relate to greater consumption of meat dishes, such as roasts, at this time of year [18]. We did not ask about the type of organic meat consumed. However, an accurate assessment of the risks associated with organic meats is needed, especially as the production [19] and consumption [20] of organic produce has increased dramatically in the United Kingdom recently.

The associations between pre-school and school children and other illness within the household might indicate selection bias. Individuals in households often share meals and activities, therefore it is possible that several members may become infected by a single contamination event. However, whilst symptomatic adults might not present to general practitioners (GPs), it is more likely that symptomatic children would be taken to their GP [21].

Contact with pets with diarrhoea was suspected as a source of campylobacter infection in man before campylobacters were recognized as important human pathogens [22]. Campylobacters have been isolated from a variety of domestic animals [23–27] and contact with animals has been implicated in several epidemiological studies of campylobacter infection [28–32]. Pets are often regarded as members of the household, and close contact with them increases the likelihood of disease transmission [33]. Owners, and possibly more importantly the children of owners [30], need to be made aware that pets might be an important source of campylobacter and other enteric infections. This might best be achieved at the pet shop or veterinarian level.

The role of farm visits as a source of enteric disease has been highlighted by outbreaks and incidents of Vero cytotoxin-producing *Escherichia coli* (VTEC) O157 infection. Like VTEC O157 [34–36], campylobacters are shed intermittently by symptomatic [37] and asymptomatic [38] farm animals and the infective dose for humans is low [5, 39]. Poor hygiene following contact with the farm environment might therefore lead to infection. Recent guidelines for the control of infection with VTEC O157 provide specific information for farms open to the public [36], and this advice applies equally to avoidance of campylobacter infection.

Other illness in the community

The consumption of unpasteurized milk has been associated with outbreaks of campylobacter infection in England and Wales [40–45]. Its inclusion here is therefore unsurprising, but it might add weight to other observed associations. Raw milk for drinking remains on sale despite overwhelming scientific evidence [46–49] about the risks associated with its consumption. Those who drink it believe that the health benefits outweigh the risks, although these have not been demonstrated [50]. Under current UK legislation [51] raw milk for drinking should be free from pathogenic micro-organisms. Enforcement, through inspection and testing by food authorities, is done at a frequency considered necessary to ensure that the requirements of the regulations are complied with. If raw milk for drinking is to remain on sale (several attempts by the Government to ban its sale have been unsuccessful [52]) then this frequency needs to be increased.

The association between eating in restaurants and other illness in the community might relate to poor hygiene in the commercial catering environment. Outbreaks of campylobacter infection have been shown to be associated with commercial catering premises [3, 4] and epidemiological studies of sporadic disease have linked chicken prepared by or eaten in a commercial food establishment with infection [53–55]. Caterers need to be made aware that contamination of the hands and the environment with campylobacters can occur whilst preparing raw meat dishes [56, 57], and this contamination can be spread to ready-to-eat foods. An assessment of the risks involved in each step of the food preparation process, based on the principles of Hazard Analysis and Critical Control Points and in line with UK food safety legislation [58], is recommended if infection associated with, and poor consumer confidence in [59], these premises is to be avoided.

Older cases of *C. jejuni* infection were less likely to report other illness in the community. This might

be artefactual. The questionnaires for infants and younger children are answered by their parents who might be aware of other illness through playgroups, schools, etc.

The independent inverse associations identified in this study might point towards poor outbreak recognition rather than sources of sporadic infection. Laboratory reports underestimate the true incidence of infection by a factor of eight [2], therefore a large number of people must be infected from the same source for that source to be identified amongst laboratory-confirmed cases.

Finally, a note should be made on the independence of subjects included in this analysis. Ideally, each true cluster of disease would be represented by a single case. It is possible that some cases were, in fact, part of the same clusters, and this could have led to an over-estimation of effects due to factors related with those clusters.

CONCLUSION

Concurrent illness in the home and/or the community occurred more frequently than might have been expected, based on previous publications. The results of these analyses are plausible in that they highlight exposures which would have affected more than one member of a family or a community at the same time. Prevention of campylobacter infection requires that better methods of outbreak detection are developed, which in turn should lead to a better understanding of risk factors.

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Foreign and Domestic Travel and the Risk of *Campylobacter* Infection: Results from a Population-based Sentinel Surveillance Scheme

The Campylobacter Sentinel Surveillance Scheme Collaborators

The United Kingdom Food Standards Agency aims to reduce foodborne illness by 20% in 5 years from April 2001,[1] and similar initiatives are in place around the globe.[2] Key to achieving this will be reducing campylobacter infections. Policymakers need to be able to differentiate cases preventable through measures taken by their own countries from travel-associated cases. As routine surveillance underestimates this proportion, the reduction in infection acquired in the home country cannot be assessed accurately. In broader health protection terms, identifying risks for acquiring campylobacter infection amongst travelers is also important, so as to reduce the risk where practical. Using data from a large population-based sentinel surveillance scheme,[3] we aimed to assess the impact of travel away from home within or outside the United Kingdom on the overall burden of campylobacter infection.

Methods

Isolates from laboratory-confirmed cases of campylobacter infection were referred to the Public Health Laboratory Service Laboratory of Enteric Pathogens for speciation and sub-typing.[3] Epidemiologic information, covering exposures in the 2 weeks preceding illness, were collected by postal questionnaire or telephone interview. Destination-specific risks for the acquisition of campylobacter infection were calculated using denominator data from the Office for National Statistics International Passenger Survey[4] or the UK Tourism Survey.[5] Exact 95% confidence intervals (CI) and risk ratios (RR) were calculated using *Stata* version seven (Stata Corporation. College Station, Texas).

Results

During the first year ending April 30, 2001, epidemiologic information was gained from 7,360 of 9,655 (76%) cases of campylobacter infection. Recent foreign travel was reported in one-fifth of cases (1,444 of 7,360; 20%) and domestic travel was reported in 951 cases (13%). Ninety-four cases (1%) had done both.

This study was initially presented at the 11th Conference on Campylobacter, Helicobacter, and Related Organisms (CHRO2001), Freiburg, Germany, September 1-5, 2001.

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Table 1 Destination-Specific Risk of *Campylobacter* Infection among Foreign Travelers

Foreign Travel				*95% CI§*	
Destination	*Cases**	*Travelers†*	*Risk‡*	*Lower*	*Upper*
Africa	93	873,221	10.7	8.6	13.1
Australia	10	289,986	3.4	1.7	6.3
Austria	6	417,329	1.4	0.5	3.1
Bangladesh	9	45,017	20.0	9.1	38.0
Belgium	14	1,435,931	1.0	0.5	1.6
Canada	7	507,556	1.4	0.6	2.8
Caribbean	19	533,928	3.6	2.1	5.6
Central, Eastern Europe	19	528,118	3.6	2.2	5.6
Channel Islands	7	-	-	-	-
China	2	61,144	3.3	0.4	11.8
Cruise	4	204,733	2.0	0.5	5.0
Cyprus	42	711,277	5.9	4.3	8.0
Denmark	1	249,416	0.4	0.01	2.2
Egypt	7	218,267	3.2	1.3	6.6
France	113	10,219,595	1.1	0.9	1.3
Germany	25	1,917,695	1.3	0.8	1.9
Greece	53	1,461,181	3.6	2.7	4.7
Hong Kong	7	154,078	4.5	1.8	9.4
India	78	415,459	18.8	14.8	23.4
Ireland	34	3,168,502	1.1	0.7	1.5
Italy	19	1,568,861	1.2	0.7	1.9
Luxembourg	1	33,205	3.0	0.01	16.8
Malta	12	395,111	3.0	1.6	5.3
Mexico	7	86,453	8.1	3.3	16.7
Middle East	13	241,821	5.4	2.9	9.2
The Netherlands	10	1,543,305	0.6	0.3	1.2
New Zealand	3	89,639	3.3	0.7	9.8
Other Asia‖	80	299,694	26.4	21.2	33.2
Other Pacific#	28	4,900	591.8	380.0	824.8
Pakistan	69	176,003	39.2	30.5	49.6
Portugal	84	1,105,619	7.6	6.1	9.4
South & Central America	19	119,509	15.9	9.6	24.8
Spain	546	75,54,377	7.2	6.6	7.9
States of the Former USSR	4	126,443	3.2	0.9	8.1
Sweden	2	282,221	0.7	0.01	2.6
Switzerland	5	514,301	1.0	0.3	2.3
Turkey	38	1,032,715	3.7	2.6	5.1
USA	17	3,089,399	0.6	0.3	0.9
Unknown/ unclassified	11	-	-	-	-
All foreign destinations	1518	41,676,009	3.6	3.5	3.8

*Single visits by cases and visits by cases as part of multiple travel destinations.
†Based on the ONS international passenger survey.[4]
‡Per 100,000 visits.
§Exact 95% confidence intervals.
‖Thailand, Nepal, Sri Lanka, Malaysia, etc.
#Indonesia/Bali, Singapore, The Philippines.

Table 2 Destination-Specific Risk of *Campylobacter* Infection among Domestic Travelers

Foreign Travel				*95% CI§*	
Destination	*Cases**	*Travelers†*	*Risk‡*	*Lower*	*Upper*
				Lower	Upper
Cumbria	45	3,600,000	1.3	0.9	1.7
East of England	53	16,300,000	0.3	0.2	0.4
Greater London	104	14,800,000	0.7	0.6	0.9
Heart of England	112	19,700,000	0.6	0.5	0.7
North West	85	10,800,000	0.8	0.6	1.0
Northumbria	9	5,100,000	0.2	0.001	0.3
South East	91	13,500,000	0.7	0.5	0.8
Southern	45	12,200,000	0.4	0.3	0.5
South West	99	19,100,000	0.5	0.4	0.6
Yorkshire	78	10,400,000	0.8	0.6	0.9
Scotland	51	10,500,000	0.5	0.4	0.6
Wales	78	10,900,000	0.7	0.6	0.9
Northern Ireland	2	-	-	-	-
Mix	68	-	-	-	-
Unknown	31	-	-	-	-
All UK destinations	951	146,900,000	0.6	0.6	0.7

*Single visits by cases and visits by cases as part of multiple travel destinations.
†Based on the UK tourism survey.[5]
‡Per 100,000 visits.
§Exact 95% confidence intervals.

The risk associated with domestic travel in the United Kingdom was comparable to that for travel to Scandinavia, The Netherlands, and the United States (Table 1). Travel to Cumbria (a rural area in the North West of England) appeared to increase risk of campylobacter infection compared with other UK destinations (RR 2.0; 95% CI 1.5-2.7; $p < .001$)(Table 2).

Linked microbiologic and epidemiologic data are currently available for 3,764 cases. *Campylobacter coli* represented 10% (78 of 753) of travel-associated cases compared with 6% (198 of 3,084) of indigenous cases (RR 1.6; 95%CI 1.3–2.1; $p < .001$). The risk of acquiring a *C. coli* infection amongst travelers to the Indian subcontinent was greater than for other destinations (0.22 vs. 0.09; RR 2.6; 95%CI 1.6–4.0; $p < .001$).

Discussion

Foreign travel remains an important risk factor for campylobacter infection in England and Wales, with one-fifth of laboratory-confirmed cases acquired abroad.

The risk of infection in many Northern European and North American countries was similar to that in the United Kingdom, but high risks were identified for several popular travel destinations. Further work is required by the tourism industry to identify and address these hazards in line with European Union directives.[6] Appropriate advice to travelers on reducing the risk when abroad remains important.

Travel abroad, and to the Indian subcontinent in particular, was associated with *C. coli* infection. This might relate to water consumption. *C. coli* is commonly found in untreated water.[7] Further analysis of the foreign travel cohort might allow us to identify factors that appear to increase (or decrease) the risk in specific destinations.

The perceived risk associated with travel to Cumbria might be artefactual, as several participating health authorities are situated in the North West of England. Similarly, the popularity of destinations, such as Bali, among back-packers might have increased since 1996, hence inflating the estimate of risk.

In terms of a foodborne disease target, there is a need to be able to adjust for foreign travel which, at least for campylobacter infection, comprises a considerable proportion of the cases. As the numbers of people traveling abroad increases, and destinations become more exotic, a real decline in indigenous infections might be hidden in an increase in travel-associated cases. Effective surveillance is therefore essential.

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Ciprofloxacin resistance in *Campylobacter jejuni*: case–case analysis as a tool for elucidating risks at home and abroad

The Campylobacter Sentinel Surveillance Scheme Collaborators*†

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***Objective*: To determine factors independently associated with the acquisition of a ciprofloxacin-resistant *Campylobacter jejuni* infection.**

***Methods*: Self-completion questionnaires were used to collect clinical, demographic and exposure data from cases of campylobacter infection reported to a sentinel surveillance scheme in England and Wales. Isolates from those cases were referred to the Public Health Laboratory Service Campylobacter Reference Unit for speciation, subtyping and antimicrobial resistance testing. Cases infected with a ciprofloxacin-resistant *C. jejuni* were compared with cases infected with a sensitive strain using case–case analysis. Single risk variable analysis and logistic regression analysis were employed. The analysis was restricted by travel status to control for the confounding effect of foreign travel.**

***Results and conclusion*: Over half (55%) of the campylobacter infections acquired abroad were resistant to ciprofloxacin, compared with 10% of UK-acquired strains [relative risk 5.23; 95% confidence interval (CI) 4.58–5.96]. For travel-associated cases, ciprofloxacin-resistant infections were independently associated with travel to Spain [odds ratio (OR) 6.87; 95% CI 3.52–13.38], Portugal (OR 22.40; 95% CI 4.36–114.99) or Cyprus (OR 11.74; 95% CI 1.28–108.02), and the consumption of chicken (OR 4.95; 95% CI 2.12–11.56) or bottled water (OR 3.70; 95% CI 1.69–8.10). Indigenous cases infected with a ciprofloxacin-resistant strain were more likely to report the consumption of pre-cooked cold meats (OR 2.13; 95% CI 1.44–3.13). The risk of acquiring a ciprofloxacin-resistant campylobacter infection was strongly associated with foreign travel. Restricting the analyses by travel status revealed different sets of risk exposures for acquiring a resistant *C. jejuni* strain, suggesting that different intervention strategies will be required.**

Introduction

Campylobacters are the most commonly reported bacterial cause of acute gastrointestinal infection in England and Wales.[1] Annual reports of laboratory-confirmed campylobacter infection rose steadily throughout the 1980s and 1990s, culminating in a peak of 58 059 cases in 1998 (incidence rate 111 per 100 000[2]). The true population burden of campylobacter infection is ~10 times higher, as most campylobacter cases are unrecognized by national laboratory-based surveillance.[3] Despite this important public health impact, the epidemiology of campylobacter infection is still poorly understood, with the majority of infections remaining unexplained by recognized risk factors.[4]

Campylobacter enteritis is usually an unpleasant but self-limiting disease where treatment is often limited to fluid and electrolyte replacement.[5] Where antimicrobial therapy is indicated (for patients with high fever, bloody diarrhoea or more than eight stools a day; for patients whose symptoms have not lessened or are worsening at the time of diagnosis; or patients whose symptoms have persisted for more than a week[6]), the treatment of choice has tended to be erythromycin.[7,8]

The introduction of fluoroquinolones provided a suitable therapeutic alternative to erythromycin for adults with gastro-

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intestinal symptoms because of their activity against most enteric pathogens.[9] However, the emergence of resistance to fluoroquinolones has become a major public health problem worldwide.[10–14]

The Campylobacter Sentinel Surveillance Scheme was launched on 1 May 2000.[15] The overall aim of the scheme is to generate hypotheses for campylobacter infection systematically by the integration of standardized epidemiological and typing data. Twenty-two District Health Authorities, with a population of ~12.5 million people, are collaborating in the scheme, which aims to capture standardized information on ~15% of all laboratory-confirmed campylobacter infections in England and Wales. The health authorities are broadly representative of England and Wales as a whole.

This study focuses on data generated during the first year of the scheme, and aims to determine factors affecting the acquisition of a ciprofloxacin-resistant *Campylobacter jejuni* infection.

Materials and methods

Campylobacter isolates were referred from Public Health Laboratory Service (PHLS) and National Health Service (NHS) laboratories within the sentinel catchment area to the PHLS Laboratory of Enteric Pathogens. Speciation,[16] serotyping[17] and phage typing[18] were undertaken, and antimicrobial resistance (to ampicillin, chloramphenicol, ciprofloxacin, nalidixic acid, gentamicin, kanamycin, neomycin, erythromycin, furazolidone and tetracycline) was determined by an agar dilution method, with breakpoints for ciprofloxacin at 1 mg/L and erythromycin at 4 mg/L.[19] Epidemiological data were captured on a standardized patient questionnaire (available as Supplementary data at www.jac.oupjournals.org) administered by local public health or environmental health departments. Demographic and clinical information was sought, in addition to the patients' travel history and exposures to food, water, the environment and animals in the 2 weeks prior to the onset of illness. Completed questionnaires were forwarded to the Gastrointestinal Diseases Division at the Communicable Disease Surveillance Centre (CDSC) for data entry. The electronic epidemiological and microbiological data sets were then linked using the patient's surname and date of birth.

The combined data set was analysed using Stata version seven (Stata Corporation). Date of onset was used to define the season in which infection took place. 'Spring' was defined as March to May, 'summer' as June to August, 'autumn' as September to November and 'winter' as December to February. Standard occupational classification was employed to determine cases' socio-economic group.[20] Additional categories were created for individuals who described their occupation as unemployed, pre-school child, school child, student, homemaker, retired, part time, and for those who were unable to work because of disability or long-term illness. Food exposures were coded to compare those who had eaten a particular food in the 2 weeks prior to onset (once or more than once) with those who had not. Daily water consumption was coded to differentiate no exposure from one to four, five to nine and >10 glasses of water drunk. Patient age was arranged in 10 year age groups. Individuals with missing data were omitted from the analyses using those data.

For the case–case comparison, cases with a ciprofloxacin-resistant *C. jejuni* infection were designated a 'case', whereas those infected with a sensitive strain were designated a 'control'. In order to control for the confounding effect of foreign travel,[21,22] analysis was restricted to those cases who travelled abroad in the 2 weeks before illness and those who did not. For each data set, demographic and clinical differences were assessed using Pearson's χ^2 test and Student's t-test. Initial comparisons were undertaken using single risk variable analyses. Mantel–Haenszel odds ratios (ORs) were calculated for each explanatory variable. Logistic regression was then applied to obtain maximum likelihood estimates of the effect of exposures on the outcome of interest whilst controlling for potential confounders. Variables with a P value of <0.1 from the single risk variable analysis were included initially. Step-wise exclusion was used to simplify the model: variables were removed one at a time and tested for significance using the likelihood ratio (LR) test. Potential interactions (between the main effects included in the initial logistic regression model and age, sex and season) were also examined using the LR χ^2 test.

Results

Between 1 April 2000 and 31 May 2001, linked microbiological and epidemiological data were obtained from 3489 patients infected with *C. jejuni*. One thousand seven hundred and forty-eight cases (50%) were infected with a strain that was resistant to at least one antimicrobial agent, and 260 cases (8%) were infected with a multiresistant strain (resistant to four or more unrelated antimicrobials). Almost a fifth (19%) of cases were infected with a ciprofloxacin-resistant strain, whereas only 1% of cases were infected with an erythromycin-resistant strain.

Six hundred and fifty-three cases of *C. jejuni* infection (19%) reported travel outside the UK in the 2 weeks before the onset of illness, 2783 cases (80%) did not, and for 53 cases (2%) this information was not recorded. Cases of *C. jejuni* infection who reported foreign travel in the 2 weeks before the onset of symptoms were more likely to be infected with a ciprofloxacin-resistant strain (347/653; 53%) compared with those who did not (283/2783; 10%) [risk ratio (RR) 5.23; 95% confidence interval (CI) 4.58–5.96; $P < 0.001$]. This relationship was not observed with resistance to erythromycin (0.6% versus 0.7%; RR 0.81, 95% CI 0.28–2.36; $P = 0.7$).

Travel-associated C. jejuni cases

Over half (347; 53%) of the 653 travel-associated cases of *C. jejuni* were infected with a ciprofloxacin-resistant strain. One hundred and forty-eight (23%) were infected with a strain sensitive to all antimicrobials, and a further 158 cases (24%) were infected with a *C. jejuni* strain that was sensitive to ciprofloxacin but resistant to at least one other antimicrobial agent. The latter group of cases was excluded from further analysis. There was no difference between cases infected with ciprofloxacin-resistant strains and strains sensitive to all antimicrobials with regard to mean age (39.0 versus 38.0; *t*-test $P = 0.57$), gender (47% versus 49% male; χ^2 $P = 0.37$), mean length of illness (12.7 versus 13.5 days; *t*-test $P = 0.56$) or admission to hospital (both 6%; χ^2 $P = 0.9$).

Exposures associated with ciprofloxacin-resistant strains amongst travel-associated C. jejuni cases—single risk variable analysis (Table 1). Travel-associated cases who were infected with a ciprofloxacin-resistant strain of *C. jejuni* were more likely to have travelled to Spain or Portugal in the 2 weeks before illness than cases infected with a strain sensitive to all antimicrobials. They were also more likely to report the consumption of chicken, sausages or bottled water. They were less likely to have travelled to France or Africa, to report the consumption of baby food or mains water, and they were less likely to have had contact with animals.

Exposures independently associated with ciprofloxacin-resistant strains amongst travel-associated C. jejuni cases—logistic regression analysis (Table 2). Cases infected with a ciprofloxacin-resistant strain of *C. jejuni* were more likely to have travelled to Spain, Portugal or Cyprus in the 2 weeks prior to illness than those cases infected with strains sensitive to all antimicrobials. They were more likely to report the consumption of chicken and bottled water. They were less likely to have consumed mains water, to have had contact with a pet bird or to have travelled to Africa.

Indigenous C. jejuni cases

Amongst the 2783 cases who acquired their *C. jejuni* infection in the UK, 291 (10%) were infected with a ciprofloxacin-resistant strain and 1593 (56%) were infected with a strain sensitive to all antimicrobials. A further 952 cases were infected with a *C. jejuni* strain that was sensitive to ciprofloxacin but resistant to at least one other antimicrobial. These cases were excluded from further analysis. There was no dif-

Table 1. Risk exposures for the acquisition of a travel-associated ciprofloxacin-resistant *C. jejuni* infection—single risk variable analysis (exposures with a *P* value of <0.1 are shown)

	Percentage exposed				95% CI	
Exposure	cases[a]	controls[b]	OR	*P* value	lower	upper
Spain (versus other countries)	48	16	4.79	<0.001	2.88	7.98
Cyprus (versus other countries)	5	1	3.53	0.0764	0.80	15.64
Portugal (versus other countries)	8	3	3.04	0.0329	1.04	8.89
Turkey (versus other countries)	3	6	0.41	0.058	0.16	1.06
France (versus other countries)	4	11	0.35	0.0039	0.16	0.74
Africa[c] (versus other countries)	3	13	0.24	0.0001	0.11	0.52
Chicken	92	82	2.33	0.0039	1.29	4.22
Bottled water	90	80	2.28	0.0031	1.30	4.00
Sausage	56	46	1.51	0.0484	1.00	2.29
Filter jug water	11	18	0.56	0.0539	0.31	1.02
Mains water	60	80	0.38	<0.001	0.23	0.62
Baby food	1	5	0.14	0.0069	0.03	0.74
Swimming	59	49	1.47	0.0531	0.99	2.17
Contact with animals	48	64	0.52	0.0011	0.34	0.77
Contact with a pet dog	20	27	0.65	0.0883	0.39	1.07
Contact with a pet bird	1	6	0.21	0.0078	0.06	0.75
Contact with a pet rodent	2	5	0.38	0.0864	0.12	1.20
Contact with a pet hamster	<1	4	0.10	0.0106	0.01	0.90

[a]Cases with a ciprofloxacin-resistant *C. jejuni* infection ($n = 347$).
[b]Cases with a sensitive *C. jejuni* infection ($n = 148$).
[c]Morocco (55%); Tunisia (19%); South Africa (10%); Kenya (6%); Mauritius (6%); Tanzania (3%).

Table 2. Independent risk exposures for the acquisition of a travel-associated ciprofloxacin-resistant *C. jejuni* infection—logistic regression analysis

Exposure	OR	*P* value	95% CI lower	95% CI upper
Portugal (versus other destinations)	22.40	<0.001	4.36	114.99
Cyprus (versus other destinations)	11.74	0.03	1.28	108.02
Spain (versus other destinations)	6.87	<0.001	3.52	13.38
Africa (versus other destinations)	0.11	0.019	0.02	0.70
Chicken	4.95	<0.001	2.12	11.56
Bottled water	3.70	0.001	1.69	8.10
Mains water	0.24	<0.001	0.12	0.50
Contact with a pet bird	0.11	0.009	0.02	0.58
Interactions				
mains water × travel to Africa	9.17	0.044	1.06	79.67
Age	1.00	0.739	0.98	1.01
Gender	1.01	0.971	0.57	1.80

ference between cases infected with ciprofloxacin-resistant strains and strains sensitive to all antimicrobials with regard to mean age (40.1 versus 37.9; *t*-test $P = 0.12$), gender (48% versus 50% male; χ^2 $P = 0.62$), mean length of illness (11.8 versus 11.2 days; *t*-test $P = 0.66$) or admission to hospital (14% versus 12%; χ^2 $P = 0.39$).

Exposures associated with ciprofloxacin-resistant strains amongst indigenous C. jejuni cases—single risk variable analysis (Table 3). Indigenous cases with a ciprofloxacin-resistant *C. jejuni* infection were more likely to be ill in the autumn or winter than cases infected with a strain sensitive to all antimicrobials, and were less likely to be ill in the summer. They were more likely to report the consumption of pre-cooked cold meats in the 2 weeks before illness and were less likely to have drunk water from a private supply.

Exposures independently associated with ciprofloxacin-resistant strains amongst indigenous C. jejuni cases—logistic regression analysis (Table 4). Cases with a ciprofloxacin-resistant *C. jejuni* infection were more likely to report the consumption of pre-cooked cold meats in the 2 weeks prior to illness than those cases infected with strains sensitive to all antimicrobials. They were less likely to be ill in the summer or to report the consumption of water from a private supply.

Discussion

The aim of this study was to determine factors independently associated with the acquisition of a ciprofloxacin-resistant *C. jejuni* infection. The case–case comparison method employed here, although not without its limitations,[23] is an effective method for achieving this. Traditional case–control methodologies, comparing the exposures of ill 'cases' with well 'controls', will only identify risk factors for illness and not necessarily for the acquisition of a resistant strain.

Foreign travel remains an important risk factor for antimicrobial resistance,[21,22] and travel to Spain, Portugal or Cyprus was independently associated with the acquisition of a ciprofloxacin-resistant strain. These findings have two implications. The first is that general practitioners need to ensure that they obtain accurate travel histories since, if antimicrobial treatment is necessary, ciprofloxacin would not now appear to be the treatment of choice in travellers returning from these countries. The second is that travellers to these destinations who might buy ciprofloxacin over the counter, such as at commercial travel clinic, for the treatment of travellers' diarrhoea cannot be guaranteed that such treatment will work.

Foreign travel is a marker both for activities undertaken whilst abroad, and for differences in the incidence of resistance between countries. Restricting our analyses by travel status revealed different sets of risk exposures for acquiring a resistant *C. jejuni* strain at home and abroad, suggesting that different intervention strategies might be required.

The apparent association between the consumption of chicken and the acquisition of a ciprofloxacin-resistant *C. jejuni* infection amongst foreign travellers might point to the use of enrofloxacin in veterinary medicine and animal husbandry. Enrofloxacin has been used extensively in the broiler industry in the first week of life to reduce vaccination problems or in the third or fourth week of life to combat res-

Table 3. Risk exposures for the acquisition of an indigenous ciprofloxacin-resistant *C. jejuni* infection—single risk variable analysis (exposures with a *P* value of <0.1 are shown)

	Percent exposed				95% CI	
Exposure	cases[a]	controls[b]	OR	*P* value	lower	upper
Winter (versus other seasons)	25	17	1.67	0.0007	1.24	2.26
Autumn (versus other seasons)	32	23	1.60	0.0008	1.21	2.12
Summer (versus other seasons)	22	38	0.44	<0.001	0.32	0.60
Semi-skilled manual workers	6	3	1.71	0.06	0.96	3.04
Retired individuals	22	17	1.32	0.08	0.96	1.80
School children	2	5	0.47	0.05	0.22	1.03
Cold meats (pre-cooked)	80	71	1.59	0.004	1.16	2.21
Pâté	14	10	1.44	0.09	0.96	2.17
Organic vegetables	18	14	1.37	0.09	0.95	1.96
Fish and shellfish	63	57	1.29	0.07	0.98	1.69
Eating in restaurants	52	46	1.25	0.09	0.97	1.62
Barbecued food	11	15	0.68	0.08	0.44	1.06
Baby food	3	6	0.47	0.08	0.20	1.10
Private water supplies	4	8	0.45	0.03	0.22	0.94
Contact with a pet guinea pig	1	3	0.21	0.09	0.03	1.57

[a]Cases with a ciprofloxacin-resistant *C. jejuni* infection ($n = 291$).
[b]Cases with a sensitive *C. jejuni* infection ($n = 1593$).

piratory problems due to *Escherichia coli*.[14] Its introduction into veterinary medicine in the Netherlands in 1987 was followed by the emergence of ciprofloxacin-resistant campylobacters in poultry products (14%) and man (11%) by 1989,[13] and similar patterns have been observed in Spain[24] and the USA.[22] Rapid development and persistence of ciprofloxacin resistance in *C. jejuni*, with MICs increasing from 0.25 to 32 mg/L within the 5 day treatment time, has been shown following fluoroquinolone (sarafloxacin or enrofloxacin) treatment of broiler chickens.[25] Enrofloxacin (and sarafloxacin) belongs to the same class of antimicrobials as ciprofloxacin, and selection of resistance to one drug leads to cross-resistance to the other.[26] The lack of a similar association amongst home-acquired cases of *C. jejuni* infection might reflect the more stringent controls on the veterinary use of antimicrobials that exist in the UK compared with some other countries.[27] Since the majority of poultry consumed in the UK is home produced[28] the opportunity for human exposure to resistant campylobacters might be reduced.

The association between bottled water and the acquisition of a ciprofloxacin-resistant *C. jejuni* infection amongst travel-associated cases is striking. No interactions between this variable and age group, gender, season or any other variables included in the initial logistic regression model were observed. This, in conjunction with the relatively narrow CI surrounding the estimate of the OR, suggests that the effect is real. Current advice to overseas travellers states that bottled water (preferably carbonated with gas) in sealed containers should be used if the individual is in any doubt about the local water quality.[29] We did not ask specific questions about the type of water drunk (sparkling or still) or whether it was consumed with or without ice, and therefore this hypothesis merits further investigation to assess whether this advice might require refinement.

An alternative explanation of the above finding is that the consumption of bottled water reduces the risk of acquiring a sensitive strain of *C. jejuni*. Those who routinely drink bottled water would be expected to have lower levels of exposure to

Table 4. Independent risk exposures for the acquisition of an indigenous ciprofloxacin-resistant *C. jejuni* infection—logistic regression analysis

			95% CI	
Exposure	OR	*P* value	lower	upper
Summer	0.46	<0.001	0.33	0.65
Cold meats (pre-cooked)	2.13	<0.001	1.44	3.13
Private water supplies	0.38	0.018	0.17	0.85
Age	1.00	0.861	0.99	1.01
Gender	1.02	0.88	0.76	1.38

pathogens found in mains water, and sensitive strains of *C. jejuni* were more commonly isolated from individuals who reported the consumption of mains water while abroad compared with those who did not.

Drinking mains water abroad or water from a private supply in England and Wales appeared to favour infection with sensitive *C. jejuni* strains, implying that many environmental campylobacters have not yet acquired resistance. In a study of 96 *C. jejuni* isolates from farm animals and the environment in the north west of England, most isolates exhibited a higher level of resistance than a National Collection of Type Cultures (NCTC) strain, but none had the high MICs of ciprofloxacin and erythromycin typically associated with clinical resistance.[30] This reinforces the need for an agreed susceptibility testing method in order to make meaningful comparisons between microbiological results and their clinical significance. Furthermore, the question of the proportion of campylobacter infection attributable to water consumption, regardless of antimicrobial susceptibility, needs further study.

The consumption of pre-cooked cold meats amongst home-acquired cases of *C. jejuni* infection was independently associated with the acquisition of a ciprofloxacin-resistant strain. Cold cooked meats have been implicated in a recent epidemiological study of campylobacter infection in the USA.[31] The researchers found that cases were more likely to report the recent consumption of chicken luncheon meat and ham than controls. However, there is no evidence in the literature to support the association between the consumption of cooked meats and a ciprofloxacin-resistant *C. jejuni* infection yet. As we did not ask specific questions about the types of meat consumed, or their country of origin, then this hypothesis warrants further investigation.

Antimicrobial prescribing in human medicine has probably contributed the most to the development of resistant bacteria.[27] A limitation of our study is that our questionnaire did not include a question on current or recent treatment with antimicrobials. It is possible, therefore, that uncontrolled confounding might have occurred. However, our experience with self-completion questionnaires is that questions on treatment are often poorly answered, so the addition of this data would be of little benefit.

The exclusion of those cases infected with a *C. jejuni* strain that was sensitive to ciprofloxacin but resistant to at least one other unrelated antimicrobial merits further discussion. Since ciprofloxacin resistance is chromosomal[11] the exclusion of these cases might be considered a waste of valuable data. However, it was deemed to be necessary to account for uncontrolled confounding.

The relationship between particular *C. jejuni* subtypes and ciprofloxacin resistance is beyond the scope of this paper. Investigations into the relationships between resistance, exposures and subtypes would have been prohibitively complicated because of the potential for chance interactions between exposure and subtype variables. A study investigating the relationships between resistance and *Campylobacter* subtype, based on the laboratory data collected through the surveillance scheme, is currently underway.

Case–case analysis proved a useful tool for generating hypotheses for acquisition of a ciprofloxacin-resistant *C. jejuni* infection. Restricting the analysis by foreign travel identified different potential risks both at home and abroad, leading to the possibility of risk reduction by targeted prevention. Similar analyses, based on other resistance markers, are planned, and these might add to our knowledge of sources or vehicles of antimicrobial-resistant infections. Determining the contributions of human and veterinary clinical practice, animal husbandry and environmental sources (including food) requires complementary public health surveillance activities across the entire spectrum.

Supplementary data

Supplementary data for this paper are available at www.jac.oupjournals.org.

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Ethnicity and Campylobacter infection: a population-based questionnaire survey

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KEYWORDS
Campylobacter;
Epidemiology; Ethnicity;
Risk; Food

Summary *Objectives*. Population based-studies on Campylobacter infection have focused on age, gender, season and the level of urbanisation. The aim of this study was to determine the risk of infection in different ethnic groups resident in England.

Methods. Ethnicity-specific risk for Campylobacter infection were calculated using data on 6585 laboratory-confirmed cases from 18 health authorities in England.

Results. The Pakistani community was at greater risk of Campylobacter infection than the White community (Risk Ratio (RR) 1.71; exact 95% confidence interval (CI) 1.45–2.01). The Indian (RR 0.38; 95% CI 0.28–0.52) and Black (RR 0.30; 95% CI 0.21–0.44) communities were at lower risk than the White community. The risk in the Chinese community was no different from other ethnic groups (RR 1.21; 95% CI 0.74–1.98). Epidemiological differences between Pakistani and White cases were identified.

Conclusions. The epidemiology of Campylobacter infection in England differs according to ethnic origin, and some ethnic groups appear to be at greater risk of infection than others. This has important implications for the development of effective disease control strategies and the design of epidemiological studies. Failure to take ethnicity into consideration might mask important risk factors for infection and limit understanding of disease transmission processes, enhancing inequality of access to preventative measures.

Introduction

Campylobacter is the commonest bacterial cause of infective gastroenteritis in the developed world, and frequently causes foodborne illness. In 2000, Campylobacter accounted for an estimated 359,466 cases of indigenous foodborne disease, with 16,946 hospital admissions and 86 deaths in England and Wales.[1] Despite intensive study, the bulk of human infection remains inexplicable by risk factors identified through case-control studies.[2]

Demographic features affecting the incidence of Campylobacter infection at population level include age, gender, season and the level of urbanisation.[3] The effect of ethnic origin on disease incidence has not been studied in detail,[4] despite observed relationships between ethnicity and other communicable[5–8] and non-communicable diseases.[9–11]

Patterns of Campylobacter infection in the developed and developing worlds are known to be different.[12] What is not known is whether or not these differences persist when people with different ethnic backgrounds reside in the United Kingdom. Cultural differences, including diet and behaviour might influence the risk of Campylobacter infection.

Using data generated through population-based

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Table 1 Classification of ethnic origin.

ONS[a] classification	Cases' description of their ethnic origin[b]
White	White, British, English, Caucasian, Church of England, United Kingdom, Anglo Saxon, Welsh, Scottish
Asian Pakistani	Pakistani, Asian Pakistani
Asian Indian	Indian
Asian other	Asian
Asian Bangladeshi	Bangladeshi
Black Caribbean	Afro Caribbean
Black African	Black African
Black other	Black
Chinese	Chinese
Others	Non-British nationals, Mixed race, European, Muslim, Jewish, Hindu, Sikh, other religions

[a] Office for National Statistics.
[b] Descriptions used by more than five cases shown.

sentinel surveillance in England and Wales,[13] the aims of this study were twofold. The first was to examine the risk of Campylobacter infection in different ethnic groups resident in England, who had not recently travelled abroad. The second was to identify factors that might influence the risk of infection within selected ethnic groups resident in England.

Materials and methods

Between May 2000 and April 2001, standardised clinical, demographic and risk exposure data were collected through a structured, self-completion questionnaire from all laboratory-confirmed cases of Campylobacter infection within 18 sentinel health authorities in England (population ~10.5 million) as part of their routine surveillance. The geographical distribution of these health authorities has been described previously.[13] Questions on age, gender, illness onset, symptoms, duration (patients were asked how long their illness lasted) and severity, food, water and recreational exposures in the two weeks before illness were included. An open question asking the case to describe their ethnic origin was also incorporated.

All Campylobacter isolates from cases in the study area were referred to the Public Health Laboratory Service Laboratory of Enteric Pathogens for further characterisation.[13] The questionnaire information was combined with the typing data in a Microsoft Access database.

Data were analysed using Microsoft Excel 2000, Epi Info version 6.04d and Stata version 7. Ethnic origin was classified according to the 1991 census.[14] Denominator data for each sentinel health authority were obtained from the Public Health Common Data Set 1998.[15] Risks, with accompanying exact 95% confidence intervals (CI), and risk ratios (RR) were calculated using Stata version 7. Differences in proportions were compared using the chi-squared test. For smaller samples Fisher exact test was used. Differences in means were

Table 2 The risk of home-acquired Campylobacter infection in England by ethnic origin.

ONS[a] ethnic group	Number of cases	Population[b]	Risk[c]	Exact 95% CI[d]	
				Lower	Upper
Whites	4294	8,994,617	48	46	49
South Asian	258	475,942	54	48	61
Pakistani	153	187,552	82	69	96
Indian	40	218,060	18	13	25
Bangladeshi	11	39,330	28	14	50
Other	54	31,000	174	131	227
Blacks	27	188,453	14	9	21
Caribbean	22	119,599	18	12	28
African	2	29,513	7	0.8	24
Other	3	39,341	8	2	22
Chinese	16	27,782	58	33	94
Other	72	58,284	124	97	156
Unknown	513	-	-	-	-
Total	5180	9,745,078	53	52	55

[a] Office for National Statistics.
[b] Within the sentinel health authorities.
[c] Per 100,000.
[d] Confidence interval.

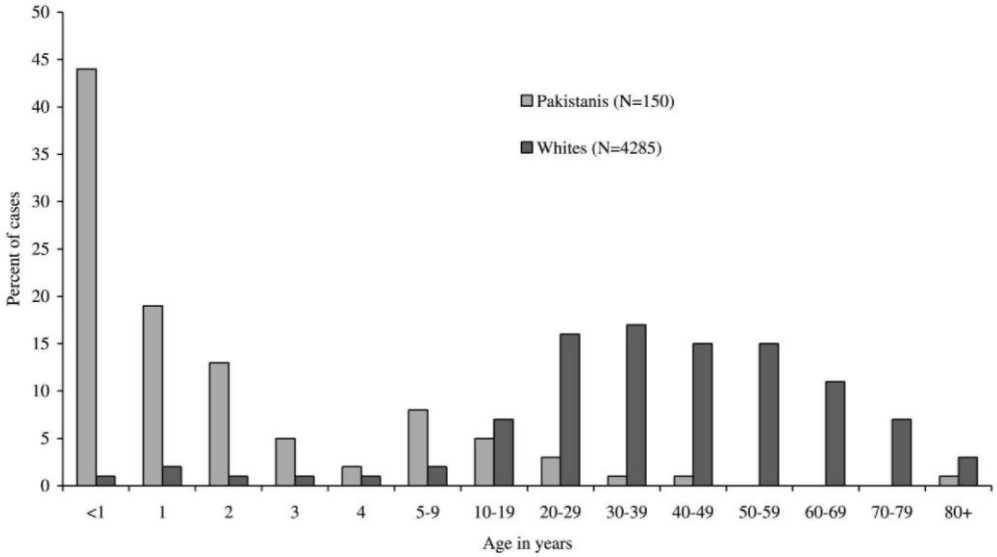

Figure 1 Age distribution of home-acquired Campylobacter infection amongst Pakistani and White cases.

compared using the Student's *t* test. Analyses were restricted to those cases who did not report foreign travel in the two weeks before illness.

Results

During the study period, 6585 questionnaires were returned (response rate = 6585/8520; 77%). Seventy-nine percent of cases had not travelled abroad in the previous fortnight (5180/6585).

Classification

Where cases' ethnic origin was described (4667/5180; 90%), most cases (4294; 92%) described their ethnic origin as White ('White cases') (Table 1). South Asians ('South Asian cases') accounted for the majority (258/301; 86%) of the remainder. For 72 cases (2%) it was not possible to classify the description provided. There was no difference in age (mean 38.5 yrs vs. 39.8 yrs; *t* test $P = 0.08$) or gender (50% male vs. 49% male; $\chi^2 = 0.1; P = 0.9$) between cases who recorded their ethnic origin and those who did not. Cases classified as 'White cases', who described their ethnicity as something other than White (e.g. British, English), tended to be older than those who described their ethnicity as White (mean age 44.5 vs. 37.3 years, *t* test $P < 0.001$).

Risks

The Pakistani community in England were at greater risk of Campylobacter infection than the White community (RR = 1.71; 95% CI 1.45-2.01; $\chi^2 = 84.69; P < 0.001$) (Table 2), whilst the Black (RR = 0.30; 95% CI 0.21-0.44; $\chi^2 = 43.79; P < 0.001$) and Indian (RR = 0.38; 95% CI 0.28-0.52; $\chi^2 = 39.1; P < 0.001$) communities were at decreased risk. The risk in the Chinese community was no different from other recognised ethnic groups (Whites, Pakistanis, Indians, Bangladeshis and Black communities; RR = 1.21; 95% CI 0.74-1.98; $\chi^2 = 0.6; P = 0.83$). Subsequent analyses were restricted to compare Pakistani cases with White cases as numbers were sufficiently large to allow comparison.

Gender

More Pakistani cases were male (91/153; 59%) than White cases (2108/4294; 49%)($\chi^2 = 6.4; P = 0.01$).

Age distribution

Pakistani cases were younger (<5 yrs; 123/150; 82%) than White cases (255/4054; 6%) ($\chi^2 = 1013.0; P < 0.001$) (Fig. 1). White cases were more evenly distributed across the age spectrum.

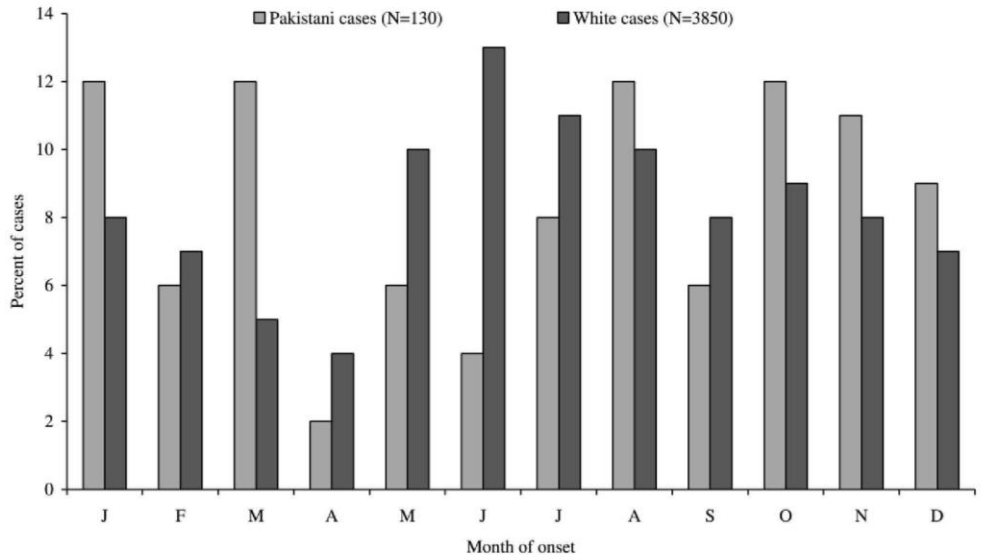

Figure 2 Seasonality of home-acquired Campylobacter infection amongst Pakistani and White cases.

Disease impact

Pakistani and White cases amassed 46,761 days of illness and 459 cases (10%) were admitted to hospital for 2130 days (median 8 days; range 1–42 days). Amongst cases under one, there was no difference between Pakistani and White cases with regard to mean illness duration (11.6 vs. 10.0 days; t test $P = 0.3$) or hospital admission (21/63; 33% vs. 16/49; 33%; $\chi^2 = 0.9$ $P = 0.3$). However, amongst cases over one year of age, Pakistani cases experienced longer illnesses than White cases (mean 20.9 vs. 10.8 days; $P < 0.001$) and were more likely to be admitted to hospital (14/85; 16% vs. 408/4199; 10%; $\chi^2 = 4.3; P = 0.04$).

Seasonality

Disease onset amongst the White cases showed a sharp increase in late spring/early summer followed by a general decline through the year (Fig. 2). Pakistani cases experienced more illness at the beginning and end of the calendar year.

Risk behaviour

Pakistani cases reported fewer meat types (mean 1.7) than White cases (mean 5.0) (t test $P < 0.001$) regardless of age. In general, they were less likely to report the consumption of most individual meat types (including chicken), except for Halal meats and lamb (Table 3).

White cases, aged over one year, were more likely to have drunk bottled water and eaten in restaurants. White cases of all ages, who ate in restaurants were more likely to have consumed foods cooked rare (209/1677; 12%) than those who did not (130/1700; 8%) ($\chi^2 = 21.7; P < 0.001$).

Pakistani cases, aged over one year, were more likely to report the consumption of unpasteurised milk than White cases, but reported less water consumption (mean 1.0 vs. 1.5 exposures) (t test $P < 0.001$). Pakistani cases were no more likely than White cases to report having contact with a pet with diarrhoea or visiting a farm.

Ethnic group and Campylobacter spp

Typing data were available for 71 Pakistani and 2371 White cases. Most cases (2279/2442; 93%) were infected with *C. jejuni*, with most of the remainder (161/163; 99%) infected with *C. coli*. There was no difference between Pakistani cases (68/71; 96%) and White cases (2211/2371; 93%) with regard to the proportion infected with *C. jejuni* (Fisher exact test $P = 0.6$).

Discussion

Analyses of structured sentinel surveillance data in England revealed an epidemiological pattern for Campylobacter infection specific to residents who classified their ethnic origin as Pakistani. This pattern was characterised by a higher risk of infection; longer periods of illness; higher rates of

Table 3 Risk behaviour, stratified by age group, amongst home-acquired White and Pakistani cases of Campylobacter infection.

Exposure	<1 year				≥1 year			
	Percent exposed		χ^2	P	Percent exposed		χ^2	P
	Pakistanis (66[a])	Whites (50)			Pakistanis (84)	Whites (4235)		
Baby food	78	87	1.20	0.27	26	1	F[b]	<0.001
Barbecued food	17	26	1.5	0.22	4	16	7.82	0.005
Beef (inc roast, mince, steak)	5	31	11.05	<0.001	15	77	150.41	<0.001
Cheese	2	50	30.89	<0.001	47	81	50.04	<0.001
Chicken	24	56	10.38	0.001	87	93	4.28	0.04
Cold meats (pre-cooked)	0	21	F	0.0004	3	78	225.34	<0.001
Fish/shellfish	16	30	2.77	0.10	57	61	0.63	0.43
Halal meat	25	3	8.41	0.004	83	4	F	<0.001
Lamb	14	13	0.05	0.83	65	44	12.69	<0.001
Meat pies	15	26	2.09	0.15	0	33	36.5	<0.001
Offal or tripe	0	0	-	-	3	7	2.20	0.14
Other poultry	4	8	F	0.39	8	22	7.80	0.005
Organic meat	15	26	2.09	0.15	1	3	F	0.73
Organic vegetables	5	13	F	0.26	8	14	2.28	0.13
Pâté	15	24	1.44	0.23	0	14	11.78	<0.001
Pork, ham or bacon	0	24	F	<0.001	0	85	368.11	<0.001
Pre-packed sandwiches	15	24	1.44	0.23	18	46	23.51	<0.001
Salads	7	8	F	1.00	71	75	0.49	0.48
Sausages	0	23	F	<0.001	1	63	113.54	<0.001
Vegetarian food	15	13	0.06	0.81	39	15	34.11	<0.001
Foods cooked rare	0	5	F	0.22	3	10	3.09	0.08
Eating food from restaurants	0	7	F	0.09	15	52	42.88	<0.001
Unpasteurised milk	4	6	F	0.66	14	7	7.12	0.007
Bird-pecked milk	2	2	F	1.00	3	1	F	0.29
Mains water	37	42	0.26	0.61	91	87	1.38	0.24
Private water	17	22	0.52	0.47	2	6	F	0.10
Bottled water	7	7	F	1.00	11	48	37.83	<0.001
River, stream or spring water	0	0	-	-	1	2	F	1.00
Filter jug water	4	7	F	0.65	1	11	6.42	0.01
Contact with animals	10	71	45.11	<0.001	18	63	67.96	<0.001
Contact with a pet with diarrhoea	0	6	F	1.00	7	7	F	1.00
Visiting a farm	9	24	F	0.41	6	10	F	1.00

[a] Number of cases.
[b] Fisher's exact test.

hospital admission; a marked skewing of the age distribution towards infants; a higher proportion of males; a reduction in disease levels between April and June; lower levels of chicken, red meat/meat product consumption; lower levels of water consumption; lower levels of contact with animals. These findings are important because they suggest community-specific differences in routes of transmission for Campylobacter infection and the resulting burden of disease. These differences might be mediated through yet to be identified cultural determinants.

In interpreting these findings potential sources of bias introduced through the data used or the methods employed must be assessed.

The sentinel study population includes metropolitan areas in the Midlands, the North West and West Yorkshire, all of which have ethnically diverse populations, potentially affecting the generalisability of the findings. However, by using appropriate denominator data, we should have controlled for population differences, so the results should be broadly representative.

The denominator data used to calculate risks were based on the 1991 census estimations. The distribution of ethnic groups within the sentinel population might have changed since then, but data from the 2001 census were not available.

More than five hundred cases did not record their ethnic origin. Although no underlying differences between those cases providing and not providing ethnic origin was shown, some ethnic groups might have been more disinclined to respond than others, affecting the estimates of risk.

An important assumption was that people who described themselves as British or English were

White. This might have inflated the estimate of risk in this group. However, our analyses suggest that the different descriptions provided arise from age differences within the White cases. Furthermore, we have classified in line with previous publications on ethnicity[16] to facilitate comparison.

Finally, we were unable to control for socio-economic status, which might confound the observed relationships between ethnic origin and the risk of Campylobacter infection. Although data on several markers for social class (e.g. occupation, household size) were collected for adult cases, these data (e.g. parents' occupations) were not sought for cases under the age of 16 years. Hence, we could not determine whether increased rates in children were associated with overcrowding for example. Future studies of this type should address this issue.

Pakistanis experienced a higher risk of infection than members of other ethnic groups, with a risk approaching twice that of Whites and almost five times that of Indians. Accurate population denominators for age by ethnic category were not available so it was not possible to calculate levels of risk to infants by ethnic group. Nevertheless, despite living in the United Kingdom, and not having travelled abroad during the incubation period, Pakistani infants appeared to display a developing world pattern of disease.[12]

Ethnic differences in disease incidence might relate to differences in exposure, usage of healthcare facilities or perhaps to prior immunity. Whilst our work can go some way to identifying differences in exposure between ethnic groups resident in England, which might affect disease risk, we are unable to account for differences in healthcare usage or prior immunity in this study. However, it is unlikely that these factors play a major role here, given the observed differences in risk between the resident Pakistani and Indian communities.

Campylobacter infection gives rise to more prolonged illness and higher rates of hospital admission in infants than adults.[17] The fact that in our study, Pakistani cases older than one year experienced longer illnesses and more hospital admissions than White cases of this age is, therefore, intriguing and merits further investigation.

Religious practices might influence the observed differences in consumption of meat/meat products. Although questions on religion were not specifically included, Pakistan, an Islamic republic, is predominantly Muslim.[18] Therefore, the proportion of practising Muslims, who should only eat Halal food,[19] should be higher among Pakistanis than Whites, explaining why Pakistani cases were more likely to have consumed Halal meat and much less likely to have consumed Haram foods[19] (such as those containing pig meat). However, we acknowledge that Pakistani cases might have reported the consumption of Halal meats rather than individual meat types. Similarly, non-Pakistani cases might have consumed Halal meats without being aware of doing so. That Halal meat might pose a greater risk of Campylobacter infection is borne out by a recent study of 183 raw meat samples from Halal butcher shops, in which 28% were found to contain campylobacters,[20] a level far higher than that (0.6%) observed in 2330 samples from conventional butchers.[21]

Pakistani cases were less likely to be exposed to many of the 'recognised' risk factors for Campylobacter infection including, consumption of chicken,[22] consumption of barbecued food,[23] eating at restaurants[22] and contact with animals.[23] Pakistanis and Whites might acquire Campylobacter infection from distinct, if overlapping, sources. A further indication of this is the contrasting seasonality of infection in the two case groups. The seasonality of infection amongst White cases followed the classical pattern of a spring rise.[24] This was not observed amongst the Pakistani cases. How is the Pakistani community preferentially exposed to sources of infection giving rise to disease in winter whilst being shielded from the sources that give rise to the late spring/early summer peak of infection in the White community?

The finding that the Pakistani community appears to be at greater risk of infection than either the Indian or Bangladeshi communities is interesting. There is considerable variety in dietary, culinary and behavioural practices reflecting religious, climatic, social, economic and geographical diversity across this region of south Asia. More detailed investigation of the epidemiology of disease in these populations appears to be warranted to identify the characteristics that explain distinct patterns of infection in different ethnic groups.

Investigation of the epidemiology of enteric infection in different sub-populations can reveal differences in disease risk and burden. Detailed community studies examining a wide range of dietary, culinary and behavioural factors are needed to develop tailored control measures to ensure equity of access to appropriate health interventions for all our communities.

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SHORT REPORT

Is *Campylobacter jejuni* enteritis a weekend disease?

The Campylobacter Sentinel Surveillance Scheme Collaborators*,†

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Campylobacter is the commonest reported bacterial cause of gastroenteritis in England and Wales, and *Campylobacter jejuni* accounts for almost all infections.[1] The public health impact is compounded by sequelae, such as Guillain-Barré syndrome, toxic megacolon and haemolytic uraemic syndrome,[2] associated with infection. Despite extensive research, spanning a quarter of a century, Campylobacter incidence remains high.[2]

The marked annual seasonality of Campylobacter infection is well known.[2] However, the pattern of infection over smaller time periods has not, to our knowledge, been investigated previously. We examined epidemiological data, captured through sentinel surveillance of Campylobacter infection in England and Wales[1] over a 2-year period from the 1st May 2000, to determine the weekly pattern of *C. jejuni* infection and account for any observed differences throughout the week.

A standard, structured questionnaire, capturing demographic, clinical and exposure data for the 2-week period prior to illness onset, was administered to all laboratory-confirmed cases of Campylobacter infection in 22 participating health authorities (total population ~12 000 000) in England and Wales.[1] Concurrently, Campylobacter isolates from participating laboratories serving the same population were referred for further characterisation.[1] The epidemiological and microbiological datasets were then linked using patients' surnames and dates of birth.

Statistical analyses, restricted to cases of *C. jejuni* infection acquired in the United Kingdom (indigenous cases), were performed using Stata version 7. The day of the week on which illness commenced was derived from onset dates. Differences in medians were assessed using the non-parametric K-sample test on the equality of medians. Differences in disease incidence over the course of the week were examined further by comparing cases' risk exposures. Single risk variable analysis and logistic regression were applied.

Epidemiological data were available for 7471 cases of *C. jejuni* infection reported in the first two years of the study. Cases amassed 78 553 days of illness (range <1-291 days; median 8 days) and 624 cases (8%) required admission to hospital for at least 2789 days (range 1-35 days; median 4 days). Of those cases who reported their travel status (7368; 99%) 5959 (81%) did not travel abroad in the 2 weeks before illness.

The date and therefore the day of onset of illness was available for 5606/5959 (94.1%) indigenous cases of *C. jejuni* infection. Disease incidence was greater on the days during or immediately following the weekend (Fig. 1). The lag period between onset of illness and the completion of a questionnaire ranged from five to 59 days (median 15 days). There was no difference between the median lag period amongst those cases who were ill from Saturday to Tuesday (16 days; range 5-59) compared with those who were ill during the rest of the week (15 days; range 5-59; $\chi^2 = 3.7$; $P = 0.054$).

Cases of *C. jejuni* infection who were ill from

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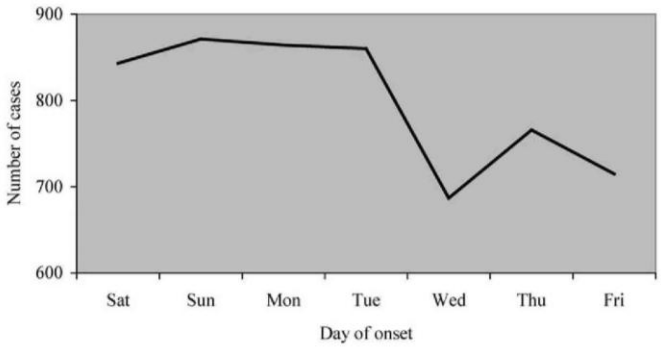

Figure 1 Weekly periodicity of indigenous *C. jejuni* infection in Sentinel Health Authorities in England and Wales ($N = 5606$).

Saturday to Tuesday ($N = 3438$) were more likely to have consumed Halal meats, offal or water from a private supply than cases who were ill on other days ($N = 2168$; Table 1). They were more likely to have eaten foods from restaurants. When different restaurant types were considered, cases who were ill from Saturday to Tuesday were more likely to report having eaten takeaway food from kebab houses or Indian restaurants (restaurants providing traditional Indian dishes) than cases who did not eat any food from restaurants.

The incubation period for Campylobacter is normally two to four days,[2] and therefore the pattern of disease described above does not necessarily suggest a weekend exposure. However, since the incubation period is believed to be inversely proportional to infective dose,[2] the consumption of potentially heavily contaminated foods (such as Halal meats[3] and offal[4]) or untreated or poorly treated water[5] at the weekend might result in illness at this time or soon after.

People tend to eat out more at restaurants in their leisure time, and therefore the observed association between consuming foods from restaurants and weekend illness is unsurprising. However, eating in restaurants (and from certain types of take-away restaurant in particular) appeared to contribute to the increased incidence at and following this time, reinforcing the need for improved standards of food hygiene in the catering sector.

The advantages and disadvantages of case-case studies such as this have been discussed in detail elsewhere.[1] The most important of these in this context is that we cannot make statements about the magnitude or direction of population risk.

Digit preference is a form of information bias where individuals are inclined to report certain numbers (e.g. multiples of 5 or 10), leading to rounding of measurements. Digit preference might have occurred in this study if cases, unsure of their actual date of onset, estimated a date at the weekend or the beginning of the week. However, since the lag periods for both groups are similar it is unlikely that digit preference is operating in this instance.

Table 1 Factors leading to weekend illness amongst cases of *C. jejuni* infection. Final logistic regression model (controlling for age, gender and season)

Exposure	Odds ratio	95% Confidence interval		*P* value
		Lower	Upper	
Halal meats	1.72	1.26	2.34	0.001
Offal	1.47	1.08	2.01	0.015
Didn't eat food from restaurants	1	-	-	-
Eating food from restaurants	1.17	1.02	1.34	0.024
Eating food from take-away Kebab restaurants	2.87	1.37	5.99	0.005
Eating food from take-away Indian restaurants	4.90	1.71	14.04	0.003
Drinking water from a private supply	1.34	1.00	1.80	0.049
Age	1.00	1.00	1.00	0.345
Gender	0.94	0.82	1.07	0.366
Season	0.98	0.92	1.04	0.528

We suggest that individuals in England and Wales undertake activities at the weekend that might affect their risk of Campylobacter infection. The periodicity of infection described here is unlikely to be unique to *C. jejuni*, but to the best of our knowledge such periodicity has not been described for other infectious diseases.

Appendix A. The writing committee (and their contributions)

Iain A. Gillespie (initiating this piece of work, undertaking the analysis, drafting the paper)
Sarah J. O'Brien (discussing the analyses, contributing ideas, drafting the paper)
Keith R. Neal (contributing ideas, drafting the paper)
Jennifer A. Frost (drafting the paper)
John M. Cowden (drafting the paper)
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Appendix B. The Campylobacter Sentinel Surveillance Scheme Steering Committee

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Appendix C. The Campylobacter Sentinel Surveillance Scheme Collaborators

Public health, environmental health and laboratory staff who serve the populations of the following health authorities:

Birmingham, Bradford, Bro Taf, Bury and Rochdale, Dyfed Powys, East Kent, Barnet, Enfield and Haringey, Herefordshire, Leeds, Leicestershire, Manchester, North Cumbria, North Essex, North West Lancashire, Nottingham, Salford and Trafford, South and West Devon, South Lancashire, Southampton and South West Hampshire, Stockport, West Pennine, Wigan and Bolton

In association with:

LEP, Campylobacter Reference Unit
HPA CDSC, Gastrointestinal Diseases Department
HPA Local and Regional Services
HPA Statistics Unit

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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.

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

†The Campylobacter Sentinel Surveillance Scheme Collaborators are public health, environmental health and laboratory staff who serve the populations of the following health authorities: Birmingham, Bradford, Bro Taf, Bury and Rochdale, Dyfed Powys, East Kent, Barnet, Enfield and Haringey, Herefordshire, Leeds, Leicestershire, Manchester, North Cumbria, North Essex, North West Lancashire, Nottingham, Salford and Trafford, South and West Devon, South Lancashire, Southampton and South West Hampshire, Stockport, West Pennine, Wigan and Bolton. In association with: HPA Laboratory of Enteric Pathogens, Campylobacter Reference Unit; HPA Centre for Infections, Environmental and Enteric Diseases Department; HPA Local and Regional Services; HPA Statistics Unit.

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 ($\geqslant 65$ 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 $\geqslant 10$ 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 (Victora *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 (Victora *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		*P* value
	Cases* ($n=4043$)	Controls† ($n=3335$)		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.

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.

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.

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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Demographic determinants for *Campylobacter* infection in England and Wales: implications for future epidemiological studies

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SUMMARY

Despite a significant public health burden the epidemiology of human *Campylobacter* infection remains blurred. The identification of demographic determinants for *Campylobacter* infection is therefore essential for identifying potential areas for intervention. Demographic data from an active, population-based sentinel surveillance system for *Campylobacter* infection (from 2000 until 2003, $n=15\,907$) were compared with appropriate denominator data from the 2001 United Kingdom Census. Incidence was higher in males from birth until the late teens and in females from 20 to 36 years. Age- and gender-specific differences in *Campylobacter* incidence were observed in different ethnic and socioeconomic groups and hence are all major drivers for *Campylobacter* infection. Epidemiological studies on *Campylobacter* infection need to take these factors into consideration during design and analysis. The collation of detailed epidemiological data and its comparison with appropriate denominator data provides a valuable epidemiological tool for studying infection.

INTRODUCTION

Campylobacter spp. are a commonly reported cause of infectious gastroenteritis in developed countries. Whilst the incidence of *Campylobacter* infection in England and Wales has declined in recent years since peaking in 2000, the disease still represents a significant source of morbidity, with over 46 000 laboratory-confirmed cases reported annually [1]. Infection with *Campylobacter* spp. can manifest across a wide clinical spectrum, from asymptomatic carriage to symptoms indicative of appendicitis [2]. This, coupled with the fastidious nature of the micro-organisms [3], results in laboratory-confirmed cases representing the tip of the infection iceberg [4].

Our understanding of the epidemiology of human *Campylobacter* infection in developed countries is derived mainly from the investigation of outbreaks and from case-control studies of sporadic cases [5]. However, the infective dose for *Campylobacter* infection is low [6, 7] and the incubation period long and variable [6], meaning that accurately establishing

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exposure in cases and comparing this with exposure in others is problematic. This, exacerbated by the relatively poor routine follow-up of sporadic cases of human *Campylobacter* infection at the local level [8] and the lack of suitable laboratory subtyping methods applicable to all isolates, means that outbreaks of *Campylobacter* infection are rarely identified [9, 10].

The biases associated with case-control studies are numerous and described elsewhere [11]. They include selection bias when the probability of including cases (and/or controls) is associated with the exposure under investigation; and information bias (both recall and observer bias). It is perhaps for these reasons that risk factors for *Campylobacter* infection identified through case-control studies consistently fail to account for the majority of cases exposed in those studies [12–18]. An additional factor which might have reduced the usefulness of case-control studies on *Campylobacter* infection is that numerous variables, from different transmission routes and various points on the causal pathway, are often considered together. In doing so, bias will often be introduced by inappropriately adjusting for factors that are on the causal pathway. The development of conceptual frameworks for analysis has been suggested as a method of overcoming this [19]. Similarly, studies can be restricted to distinct population groups that might be at particular risk. Both methods, however, require prior knowledge of the social and biological determinants of disease.

The Campylobacter Sentinel Surveillance Scheme was a population-based surveillance scheme for *Campylobacter* infection in England and Wales which aimed to generate new hypotheses for infection [20]. It ran from May 2000 to April 2003 inclusively – a period which coincided with the 10-year Census in the United Kingdom in 2001. This provided a valuable opportunity to compare the demographic characteristics of cases of *Campylobacter* infection with that of the population from which they arose, with an aim of identifying those demographic subgroups in England and Wales at greatest risk of *Campylobacter* infection.

METHODS

The Campylobacter Sentinel Surveillance Scheme comprised 22 health authorities from all National Health Service regions across England and Wales. Participating laboratories within the health authority catchment areas referred *Campylobacter* isolates from all laboratory-confirmed cases to the Public Health Laboratory Service (PHLS) Campylobacter Reference Unit (CRU) for further characterization. A standard, structured clinical, demographic and exposure questionnaire was administered by post or by telephone concurrently to all cases by local public health and environmental health practitioners as part of their routine investigations. Completed questionnaires were forwarded to the Public Health Laboratory Service Communicable Disease Surveillance Centre (now the Health Protection Agency Centre for Infections). Electronic microbiological and epidemiological data were reconciled using patients' surnames and dates of birth.

Data classification was undertaken using Epi-Info version 6.04d [21] and Microsoft Access (Microsoft Corporation, Redmond, WA, USA). Patients' descriptions of their ethnic origin were coded according to the United Kingdom 2001 Census [22]. The occupation descriptions provided by patients of working age (16–74 years) were coded by two contributors (I.A.G., C.P.) according to Standard Occupational Classification [23]. National Statistics Socioeconomic Classification (NS-SEC) was then derived using the self-coded simplified method [24], which was subsequently grouped into analytical class.

In early 2001, health authorities in England and Wales were replaced by Primary Care Trusts (PCTs) and Strategic Health Authorities. Accordingly, age, gender, ethnicity and socioeconomic denominator data for the PCTs which constituted the sentinel health authorities were obtained from Office for National Statistics Standard Tables for health areas. Denominator data for 2001 were used as an approximation of the sentinel population over the entire study period.

Statistical analysis was undertaken using Microsoft Excel (Microsoft Corporation) and Stata version 8.2 [25]. Analysis was restricted to cases that had not travelled abroad in the 2 weeks before illness. Estimates of incidence (cases/100 000 population per year unless stated otherwise) and relative risk (RR), with accompanying 95% confidence intervals (CI) and significance tests were calculated. Changes in proportion for categorical variables were assessed using the χ^2 test for trend.

RESULTS

Between 1 May 2000 and 30 April 2003, questionnaires were received for 20 387 of the 28 510

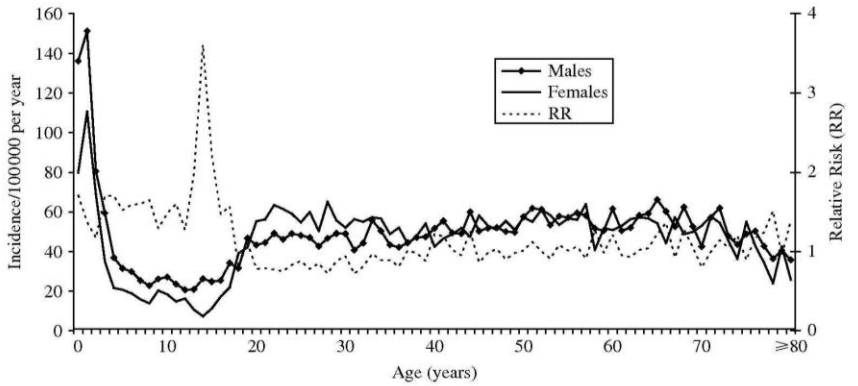

Fig. 1. The incidence by age of *Campylobacter* infection in males and females, and the male to female relative risk, in the Campylobacter Sentinel Surveillance Scheme population ($n=15\,855$), England and Wales, May 2000 to April 2003.

human *Campylobacter* isolates referred to the PHLS CRU (response rate 72%). Of these, 4109 cases (20%) reported recent foreign travel and a further 371 cases (2%) did not report their travel status. These cases were excluded, leaving 15 907 United Kingdom-acquired cases of *Campylobacter* infection from a population of 11 281 065 – an indigenous annual incidence of 47·0 cases/100 000 per year (95% CI 46·3–47·7).

Gender and age

The gender of all cases was known and cases were distributed equally across both genders (7965/15 907 male cases; 50%). However, the incidence in males was slightly higher than in females (risk ratio 1·06, 95% CI 1·03–1·10, $P=0·0001$). Patients' ages were available for 15 855/15 907 cases (99·7%). Overall, incidence was highest in infants (⩽1 year 120·1, 95% CI 112·6–128·0). It decreased for ages 2 to 13 years (from 74·8 to 15·8, χ^2 for trend 263·1, $P<0·001$). The incidence then increased for ages 14 to 22 years (from 16·9 to 56·3, χ^2 for trend 223·3, $P<0·001$) and remained relatively stable for ages 22 to 69 years (52·7, 95% CI 51·7–53·7), before declining for ages ⩾70 years (from 48·1 to 29·0, χ^2 for trend 85·7, $P<0·001$).

The incidence in male and females, and the male to female relative risk of infection for all ages is shown in Figure 1. Overall, incidence in males was higher than in females from birth until the late teens (0–17 years, RR 1·54, 95% CI 1·43–1·66, $P<0·001$). This effect was observed consistently throughout this age group and was especially marked from 13 to 15 years (RR 2·48, 95% CI 1·85–3·30, $P<0·001$). Incidence in females was lowest at 14 years but increased rapidly from this age to 22 years (from 7·3 to 63·4, χ^2 for trend 219·0, $P<0·001$), exceeding that in males at 18 years. Although not significant on a year-on-year basis, incidence in females was higher than in males from 20 to 36 years (RR 1·21, 95% CI 1·14–1·29, $P<0·001$). Incidence varied from 50 years onwards, but was overall higher in males than in females in this age group (RR 1·12, 95% CI 1·06–1·18, $P<0·0001$).

Ethnicity

Accurate descriptions of ethnic origin were provided by 12 970/15 907 cases (80·4%). The incidence in the resident Pakistani population was higher than in the resident white population (RR 1·14, 95% CI 1·03–1·26, $P=0·01$), which in turn was higher than that of the resident Indian (RR 2·74, 95% CI 2·30–3·27, $P<0·001$), Bangladeshi (RR 2·58, 95% CI 1·80–3·69, $P<0·001$), Black (RR 2·49, 95% CI 2·07–3·01, $P<0·001$) and Chinese (RR 1·85, 95% CI 1·31–2·60, $P<0·01$) communities.

Patient age and gender was available for 12 309 of 12 327 cases (99·9%) in the ethic groups (White, Pakistani, Indian and Black) where numbers were sufficient for further analysis (Table 1). The incidence in male Pakistanis aged 0–4 years was higher than in female Pakistanis in this age group and than any of the other age/gender groups in the studied ethnic groups. In white males, the incidence was greater than in females at 0–4 years, 5–9 years and 10–19 years, but not at 20–29 years. In the resident Indian and Black populations no significant differences by age and gender were observed.

Table 1. *The incidence by age and gender of indigenous* Campylobacter *infection in the main ethnic groups resident in the Campylobacter Sentinel Surveillance Scheme population (n = 12 309), England and Wales, May 2000 to April 2003*

	Incidence/100 000 per year (95 % confidence intervals)							
	White		Pakistani		Indian		Black	
Age group (years)	Male	Female	Male	Female	Male	Female	Male	Female
0–4	143·5 (130·0–158·1)	98·1 (86·6–110·6)	957·5 (825·3–1104·6)	661·8 (551·2–788·0)	248·6 (162·5–364·0)	175·5 (102·3–280·8)	125·5 (62·7–224·5)	149·3 (79·5–255·1)
5–9	59·7 (51·4–68·8)	43 (35·9–51·1)	98·9 (57·6–158·4)	36·0 (13·2–78·4)	9·1 (0·2–50·5)	28·5 (5·9–83·3)	43·4 (11·8–111·1)	43·8 (12·0–112·2)
10–19	67·5 (61·3–74·2)	53·1 (47·5–59·1)	43·4 (23·7–72·8)	19·2 (7·0–41·7)	63·2 (36·2–102·7)	23·8 (8·8–51·9)	27 (8·8–63·1)	31·9 (11·7–69·4)
20–29	121·8 (113·3 130·8)	150 (140·7 159·9)	24 (9·6 49·4)	32·3 (15·5 59·4)	45·5 (22·7 81·4)	41 (20·5 73·4)	46 (18·5 94·7)	67·9 (35·1 118·6)
30–39	120·9 (113·1–129·0)	134·8 (126·7–143·2)	19·4 (5·3–49·6)	24·6 (8–57·4)	35·1 (15·2–69·2)	24·3 (8·9–52·8)	46·1 (23·0–82·4)	30 (13·7–57·0)
40–64	141·9 (136·0–147·9)	138·8 (133·0–144·7)	24·6 (9·0–53·6)	24·4 (9·0–53·1)	19·6 (8·5–38·6)	12·0 (3·9–27·9)	38·4 (18·4–70·5)	16·2 (5·3–37·7)
⩾65	122·5 (114·5–130·9)	98·9 (92·9–105·2)	14·4 (0·4–80·2)	0	31·8 (6·6–93·0)	20·1 (2·4–72·4)	100 (48·0–183·9)	32·4 (6·7–94·5)
Total	39·5 (38·5–40·5)	38·0 (37·1–39·0)	52·4 (46·0–59·6)	35·5 (30·1–41·4)	17·1 (13·5–21·5)	11·2 (8·3–14·8)	17·3 (13·2–22·4)	13·9 (10·4–18·2)

Table 2. *The incidence by National Statistics – Socioeconomic Class (NS-SEC) of indigenous* Campylobacter *infection in the Campylobacter Sentinel Surveillance Scheme population (n = 12 309), England and Wales, May 2000 to April 2003*

NS-SEC analytical class	Common occupation descriptions	Cases	Population	Incidence/100 000 per year (95% CI)
Managerial and professional*	Teacher, engineer, nurse, accountant, company director, sales manager	3010	2 052 696	48·9 (47·2–50·7)
Intermediate occupations	Civil servant, secretary, administrator, police officer, clerk	1429	760 039	62·7 (59·5–66·0)
Small employers and own account workers	Joiner, builder, taxi driver, carpenter, bricklayer, child minder	456	558 713	27·2 (24·8–29·8)
Lower supervisory and technical	Electrician, printer, plumber, supervisor, gardener, mechanic	433	566 197	25·5 (23·2–28·0)
Semi-routine	Housewife, chef, shop/sales assistant, receptionist, postman	2133	945 359	75·2 (72·1–78·5)
Routine	Cleaner, factory worker, driver, hairdresser, butcher, bus driver	800	750 475	35·5 (33·1–38·1)
Never worked and long-term unemployed	Unemployed, disabled, medically retired, not working	352	351 844	33·3 (30·0–37·0)
Not classified	Retired, not recorded, student, unknown, self-employed	3775	2 116 276	59·5 (57·6–61·4)
Total		12 388	8 101 599	51·0 (50·1–51·9)

CI, Confidence interval.
* Higher managerial and professional occupations and lower managerial and professional occupations combined.

Socioeconomic classification

A total of 3906 different occupational descriptions were provided by the 12 388 cases aged between 16 and 74 years, and these were classified into NS-SEC Analytical Class ('AC', Table 2). Overall incidence in white-collar workers ('of or relating to work done in an office or other professional environment' [26]) was marginally higher than in blue-collar workers ('of or relating to manual work or workers' [26]; RR 1·06, 95% CI 1·01–1·11, $P=0·01$), although incidence was highest in people working in semi-routine occupations (RR 1·73, 95% CI 1·64–1·81, $P<0·001$).

Age and gender were available for all 8261 cases in the main ACs (Fig. 2*a*, *b*) and incidence differed greatly within and between genders. Although based on small numbers, the incidence in Small Employers and Own Account workers in both gender groups was higher than other ACs in the <20 years age group (RR 2·54, 95% CI 1·34–4·80, $P=0·004$), declined rapidly to 30–34 years (χ^2 for trend 14·1, $P<0·001$) and more gradually further up the age spectrum (χ^2 for trend 2·9, $P=0·09$). In Managerial and Professional (RR 1·17, 95% CI 1·05–1·31, $P=0·01$), Small Employers and Own Account (RR 1·79, 95% CI 1·16–2·76, $P=0·02$), Semi-Routine (RR 1·14, 95% CI 1·02–1·28, $P=0·04$) and Routine (RR 1·37, 95% CI 1·12–1·67, $P=0·007$) workers, the risk in females aged 20–24 years was significantly higher than for males in the same occupational groups. In Intermediate workers the risk of infection increased with increasing age up to 34 years (χ^2 for trend 28·2, $P<0·001$) with no difference in risk between males and females (RR 0·98, 95% CI 0·87–1·11, $P=0·72$). The risk in male Intermediate workers then increased (χ^2 for trend 5·08, $P=0·02$) to a peak in the 50–54 years age group, exceeding the risk in female Intermediate workers (RR 1·44, 95% CI 1·30–1·60, $P<0·001$) and other male workers in the 35–54 years age group (RR 2·13, 95% CI 1·88–2·40, $P<0·001$).

DISCUSSION

The comparison of comprehensive population-based surveillance data with detailed denominator data for the population from which the cases arose has enabled us to gain a valuable insight into the demographic characteristics of *Campylobacter* infection in England and Wales. The population covered by the Campylobacter Sentinel Surveillance Scheme has

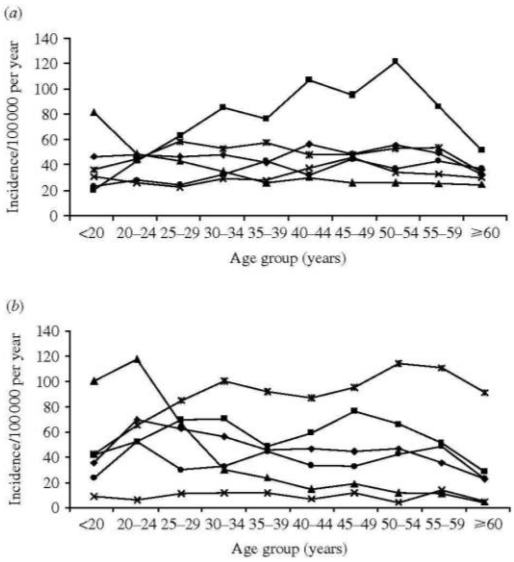

Fig. 2. The incidence by age group and National Statistics – Socioeconomic Class (NS-SEC) of indigenous *Campylobacter jejuni* infection in (*a*) males and (*b*) females in the Campylobacter Sentinel Surveillance Scheme population ($n=8261$), England and Wales, May 2000 to April 2003. –◆–, Managerial and Professional; –■–, Intermediate; –▲–, Small Employers and Own Account; –×–, Lower Supervisory and Technical –✱–, Semi-routine; –●–, Routine.

meant that the dataset generated is large and more geographically representative of the population of England and Wales. The coincidental timing of the study in terms of the United Kingdom 2001 Census has resulted in the availability of highly specific, accurate and relevant denominator data. Our study has re-emphasized that age and gender are major determinants for *Campylobacter* infection in England and Wales and has demonstrated that ethnicity, occupation and socioeconomic status are also important.

Where significant differences within and between demographic groups were identified, additional analyses of accompanying exposure data were undertaken to try to explain the increased risk. The prevalence of exposure was investigated, both between genders within age groups and between age groups within genders. Few differences were identified. This might relate to the fact that our exposure questionnaire is not exhaustive and covers a broad (14-day) exposure period, making differences difficult to detect, or that incidence differences relate to factors not connected with exposure. Our data did not allow us to disentangle these, since suitable control populations were unavailable.

The relationship between age and gender and the incidence of *Campylobacter* infection described in this study has not been described previously in such detail [27]. Infants and young children with infectious intestinal disease are more likely to present to primary-care physicians than older children and adults [28], therefore the observed increased incidence in <2-year-olds is not unusual. It is surprising, however, that within this age group the incidence in males was significantly higher than that in females and that this effect was noted each year from birth to 17 years. Few differences in exposure were noted between males and females in this age group, suggesting that other factors might have a role. The high male to female relative risk between 13 and 15 years is particularly intriguing. This period corresponds to the peak in puberty in males and it is possible that hormonal changes occurring at this time might affect the growth of *Campylobacter* present in the human gut. Hormones have been shown to have a positive effect on the growth of *Campylobacter* spp. *in vitro*, by enhancing their aerotolerance [29]. Recent research suggests that their presence might also increase pathogenicity [30].

The increase in incidence in females from 14 years and the 'switch' in relative risk from males to females from 18 years to 36 years is also remarkable. This period corresponds to the main childbearing age in women, and accompanying hormonal (endogenous or exogenous) changes could affect women's susceptibility to infection. Both oestrogen and progesterone have been shown to positively affect the growth of *C. rectus in vitro* and this is thought to be an important factor in periodontal disease progression in pregnant women [31]. Oral contraceptives will increase the concentrations of one or both of these hormones in the gut. Furthermore, the pattern of oral contraceptive use in the United Kingdom by age correlates well with the incidence of campylobacteriosis in women described in this study [32]. Alternatively, female cases in this age group could represent co-primary or secondary infections if they are exposed at the same time as their children or subsequently infected by them. Furthermore, the age- and gender-specific effects described above may also relate to behavioural differences which exist between males and females in certain age groups (e.g.

greater exposure to the outside environment in males due to football, rugby, etc.) not covered by our questionnaire. Additional work is required to explain the distinct risk profiles in men and women at different ages of life.

The increased incidence in the indigenous Pakistani community in England and Wales has already been described [33]. Previously we were unable to quantify the risk further, as age- and gender-specific denominator data were unavailable. Here we are able to confirm that infants and young children in all the main ethnic groups resident in England and Wales are at increased risk of infection compared with older people in these groups. However, the incidence in Pakistani infants and young children, and in males in particular, far exceeded that in the other main ethnic groups. Further study of this subset of the population is required to identify the causes of this increase.

The pattern of infection in the indigenous adult white population in England and Wales is in contrast to that observed in developed countries [34], where incidence is very high and low in childhood and adulthood respectively. Repeated exposure to multiple *Campylobacter* spp. at an early age in hyperendemic regions probably provides a high level of general immunity, whereas episodes of infection in developed countries arise mainly from single strains, providing little cross-immunity against other subtypes [35]. This does not, however, explain the lack of disease in indigenous adult Indians and Pakistanis in England and Wales in this study, unless immigration or previous travel to endemic regions has played a role.

Consideration of a number of methodological issues is required to contextualize the findings from this study and to inform on future studies of this kind. First, including all cases of *Campylobacter* infection in our study might have masked species-specific demographic factors, as previous research has demonstrated different risk exposures in cases of *C. jejuni* and *C. coli* infection [20]. However, typing data were available for only 63% of cases and therefore the specificity gained would have been at the expense of statistical power. An analysis of the *C. jejuni* subset, which gave similar findings to the ones described in this study and are available on request, confirm this. Furthermore, as 92% of laboratory-confirmed campylobacters in England and Wales are *C. jejuni* our findings are likely to relate more to this species than to others.

Second, providing patients with free text fields to describe their ethnic origin or occupation led to missing or unclassifiable responses, and increased the possibility of misclassification during coding, all of which might have affected our incidence estimates for some ethnic or socioeconomic groups, although this would be difficult to measure. Future studies of this kind should overcome this shortfall by providing categorical responses to the demographic questions posed. Similarly, the two-stage process of deriving socioeconomic status from patients' occupation descriptions could have led to errors in misclassification or transcription, and some occupational descriptions might have been wrongly assigned to NS-SEC by using the simplified derivation method. Classification and transcription was carried out by two contributors, however, and results were compared to minimize error, and the simplified technique for deriving NS-SEC still provides a high level (>83%) of agreement with the full method [24].

Finally, we were unable to control for all the factors under investigation in a single analysis, increasing the possibility of uncontrolled confounding. For example, it is possible (although unlikely, given the age distribution) that part of the observed risk in certain ethnic groups is mediated by their socioeconomic status and/or occupation. This potential drawback could have been overcome by applying multivariate regression techniques to the data, which would also have allowed for the effect of season to be examined. Such techniques require denominator data stratified by all factors under investigation, and these were unavailable. Given the developments in information technology over the last 20 years, national population data should be able available in a more dynamic form in the future.

In conclusion, age, gender, ethnicity and socioeconomic class are all important determinants of *Campylobacter* infection and epidemiological studies which fail to account for these effect modifiers, in design and/or analysis, might mask important risk factors for infection, if factors positively associated with disease in one demographic subset are protective in another. Future epidemiological studies on *Campylobacter* infection need to be of sufficient size to allow subgroup analyses within conceptual frameworks, or are focused on specific high-risk groups. With regard to the latter, there is a clear need to elucidate further the high observed disease incidence in Pakistani children resident in the United Kingdom.

APPENDIX

The Campylobacter Sentinel Surveillance Scheme Steering Committee

Mr A. Charlett (*Head, Statistics, Modelling & Bioinformatics, Health Protection Agency Centre for Infections*); Dr J. M. Cowden (*Consultant Epidemiologist, Health Protection Scotland*); Mrs J. A. Frost (*Welsh Assembly, Cardiff, UK*); Mr I. A. Gillespie (*Clinical Scientist, Environmental and Enteric Diseases Department, Health Protection Agency Centre for Infections*); Ms J. Millward (*Principal Environmental Health Officer, Birmingham City Council*); Dr K. R. Neal (*Clinical Reader in the Epidemiology of Communicable Diseases, Division of Epidemiology and Public Health, University of Nottingham*); Prof. S. J. O'Brien (*Division of Medicine & Neuroscience, University of Manchester, UK*); Dr M. J. Painter (*Consultant in Communicable Disease Control, Manchester Health Authority*); Prof. Q. Syed (*Regional Director, Health Protection Agency North West*); Dr D. Tompkins (*Regional Microbiologist, Health Protection Agency Yorkshire & the Humber*).

The Campylobacter Sentinel Surveillance Scheme Collaborators

Public health, environmental health and laboratory staff who served the populations of the following health authorities:

Birmingham, Bradford, Bro Taf, Bury & Rochdale, Dyfed Powys, East Kent, Barnet, Enfield & Haringey, Herefordshire, Leeds, Leicestershire, Manchester, North Cumbria, North Essex, North West Lancashire, Nottingham, Salford & Trafford, South & West Devon, South Lancashire, Southampton & South West Hampshire, Stockport, West Pennine, Wigan & Bolton.

In association with:

HPA Laboratory of Enteric Pathogens, Campylobacter Reference Unit; HPA Centre for Infections, Environmental and Enteric Diseases Department; HPA Local and Regional Services; HPA Statistics Unit.

DECLARATION OF INTEREST

None.

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Appendix 1.
The history of the discovery of campylobacters as major gastrointestinal pathogens.

Table A1.1: Notable events in the history of campylobacters.

Year	Human medicine	Veterinary medicine
1886	Theodore Escherich describes spiral bacteria in intestinal mucus in 16 of 17 children who had died of 'cholera infantum'. Spiral bacteria also observed in 35 of 72 children suffering from enteric disease. Presence thought prognostic rather than causative. (Kist, 1985)	Escherich observes spiral, curved non-culturable bacteria in the faeces of kittens which died of diarrhoeal disease. Terms these bacteria *Vibrio felinus*. (Kist, 1985)
1887	Pfeiffer observes spiral bacteria in the large intestine of a nun who had died of a disease resembling campylobacter colitis. He wrongly concludes that gut inflammation had produced conditions favourable for *Vibrio cholera* to develop spiral forms. (Kist, 1985)	
1892	Fuerbringer observes spiral, curved, non-culturable bacteria in the small intestine of a patient who died of severe cholera-like disease. *V. cholera* not detected. (Kist, 1985)	
1893	Kowalski reports highly motile non-culturable spirilla in 11 patients with "cholera" and two patients with "cholera-like" disease. Similar observations published in 1894. (Kist, 1985)	
1906		McFadyean and Stockman isolate vibrios from the uterine mucus of a pregnant sheep from a flock experiencing an abortion rate of 33%. (Skirrow, 2006)
1911		Vibrios isolated from cases of abortion in cattle in Ireland & Wales. (Smith, 1918)
1913	Curtis notes curved, motile, anaerobic bacilli from a post-instrumental abortion and from a complicated labour. (Curtis, 1913)	
1918		Theodore Smith isolates vibrios from the aborted foetal tissue of 14 cattle negative for *Bacillus abortus* (now *Brucella abortus*). Describes growth requirements, investigates pathogenicity and demonstrates antigenic similarity. Names the organism *Vibrio fetus*. (Smith, 1918;Smith, 1919;Smith, 1923;Smith, Little, & Taylor, 1920;Smith & Taylor, 1919)
1931		Jones and Little isolate 'tiny motile vibrios' from the intestines of cattle and calves suffering from epidemic winter scouring, establish infectivity and exclude a dietary cause. Demonstrate antigenic differences from *V. fetus* and propose the name *Vibrio jejuni* after isolation from ulcers in the jejunum. (Jones & Little, 1931)
1944		Doyle isolates vibrios from the colon of pigs suffering from Swine dysentery and demonstrates pathogenicity. (Doyle, 1944)

Year	Human medicine	Veterinary medicine
1947	Vinzent grows *V. fetus* from the blood of three pregnant women. Suspects milkborne transmission. (Vinzent, Dumas, & Picard, 1947)	
1948	Levy describes the isolation of vibrios from the blood of 47 cases in a milkborne outbreak of gastroenteritis affecting 357 inmates in two prisons in the USA. The organism 'bore a close resemblance' to *V. jejuni*. (Levy, 1928)	
	Ward describes a mild *V. fetus* human laboratory infection (cheek pustule). (Ward, 1948)	
		Further observations on swine dysentery by Doyle. Organism named *V. coli* due to the site of infection. (Doyle, 1948)
1949		Stegenga and Terpstra demonstrate the pathogenic role of *V. fetus venerealis* in enzootic sterility in cows. (Butzler, 2004)
1957	Examining in detail 32 human and 13 veterinary vibrio isolates, King differentiates *V. fetus* strains from four 'related vibrio' strains on cultural, biochemical, and serological characteristics and relates this to the symptomology and epidemiology of the infected patients. Infections with *V. fetus* occurred systemically in predisposed individuals whilst related vibrios occurred in infants and children with diarrhoea. With regard to the latter, she noted that chickens are known to have a disease caused by a similar, if not identical, organism. (King, 1957)	
1958		Peckham, Hofstad and co-workers isolate vibrios from the livers and gallbladders of chickens with 'Vibrionic Avian Hepatitis'. Strains biochemically indistinguishable from related vibrios. (Peckham, 1958)
1959		Florent distinguishes *Vibrio venerealis* from *Vibrio intestinalis*. (Butzler, 2004)
1961	Wheeler and Borchers describe four cases of 'vibrionic enteritis' in infants. As an aside, a link between chicken and a 'related vibrio' is described and an hypothesis of asymptomatic infections in adulthood due to childhood exposure is generated. (Wheeler & Borchers, 1961)	
1963	Sebald and Veron demonstrate that the DNA base composition of the microaerophilic vibrios differs from the cholera group, and suggest a new genus called Campylobacter. (Sebald & Veron, 1963)	

Year	Human medicine	Veterinary medicine
1972	Dekeyser applies successfully veterinary techniques to isolate related vibrios from the faeces of two patients with vibrionic enteritis. The organisms are biochemically and antigenically similar to each other and to an isolate from one patient's blood. Thirty five strains of related vibrios subsequently isolated from 1000 enterobacteriaceae-negative stool samples. (Dekeyser et al., 1972)	
1973	Butzler isolates related vibrios from 41/800 (5%) and 4/100 (4%) of stools from children and adults with diarrhoea respectively, compared with 13 (1.3%) of 1000 children without diarrhoea. (Butzler et al., 1973)	
1977	Skirrow repeats and extends Butzler's work. Demonstrates 57/803 (7.1%) patients with diarrhoea are infected with campylobacters compared with 0/194 control patients. (Skirrow, 1977)	

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Appendix 2.

An assessment of the role of campylobacters in reported mortality statistics in England and Wales.

Methods.

The Health Protection Agency Centre for Infections maintains a database of all certified deaths, reported to the Office for National Statistics, where an infection was recorded as the certified underlying or contributory cause of death. These represent approximately 10-15% of all deaths reported annually. Descriptions of the underlying or contributory causes are provided, in addition to their relevant International Classification of Diseases (ICD) coding (ICD-9 from 1993-2000 and ICD-10 from 2001 to 2006).

Deaths with any link to campylobacters were identified by searching the accompanying text fields for instances of 'camp*'. For deaths reported from 2001 to 2006 those attributed directly to campylobacters were identified where the underlying cause field was coded as A045 ('Campylobacter enteritis'). For deaths from 1993-2000 only the first four digits of the death codes were available, and therefore campylobacter deaths (ICD-9 code 008.43) were coded as 008.4 ('Intestinal infections due to other specified bacteria'). Accordingly, campylobacters were assigned as the underlying cause for those deaths where the underlying cause was coded as 008.4 and campylobacters were the only infectious agent recorded.

Data on all cases of campylobacteriosis reported to the Health Protection Agency between 1993 and 2007 were extracted from the national laboratory database to act as a denominator data for the calculation of case fatality rates. Relative risks and 95% confidence intervals were calculated using Stata version 10 (Stata Corporation, 1999) and chi squared tests calculated using Epi Info (Dean et al., 1996).

To assess which factors might lead to the underestimation of campylobacter-associated mortality, a binary outcome variable was created to compare those deaths where campylobacter was <u>not</u> recorded as the underlying cause versus those where it was. Explanatory variables were created to represent ICD-9 or ICD-10 coding, gender, patients who were elderly or who had a recorded underlying condition. An additional variable was created to

compare the period after 2000 with previous years, as a rule change on the recording of pneumonia as an underlying cause was introduced at this time. A categorical variable was created to represent approximations of the seasons in which death occurred (Winter=December to February; Spring=March to May; Summer=June to August; Autumn=September to November). The effect of each explanatory variable on the outcome of interest was assessed using single variable logistic regression. Variables significantly associated with the outcome of interest at a level of 90% or higher were included in a multivariate logistic regression model, which was simplified subsequently using the likelihood ratio test with a P value cut-off of 0.05.

Results.

Between 1993 and 2006 campylobacters were recorded as the underlying cause of 45 deaths in England and Wales, giving an incidence of 6.6 deaths per 100,000 cases of infection (95% confidence interval (95%CI) 4.8-8.9) or a case fatality rate of 0.007% (95%CI 0.005%-0.009%). However, when all-cause mortality was examined 153 deaths were identified, giving an incidence rate of 22.5 deaths per 100,000 infections (95%CI 19.1-26.3), or a case fatality rate of 0.022% (95%CI 0.018%-0.026%). Hence, underlying cause mortality underascertains the role of campylobacters by a factor greater than three (incidence ratio (IR) 0.29; 95%CI 0.21-0.41). Subsequent analysis relates to all-cause mortality unless stated otherwise.

Campylobacter patients who died were often elderly (83/153; 54%) or had an underlying condition (most commonly cardiovascular conditions (37%) or malignancies (22%)). Over a quarter of patients fulfilled both criteria (43; 28%). The case-fatality rate in those aged 70-79 years (0.12%; 95%CI 0.08-0.16%) was higher than in those aged <70 years (0.005%; 95%CI 0.003-0.007%), with the rate in those over 80 years (0.49%; 95%CI 0.38-0.60%) higher still. Gender alone had no effect on mortality (RR 1.07; 95%CI 0.78-1.46), although mortality was higher in males than females between 30 and 69 years (RR 4.3; 95%CI 0.9-20.1), but not in older age groups (RR 1.0; 95%CI 0.7-1.4; figure A2.1).

Campylobacteriosis-associated all-cause mortality was higher in winter months (December to February) compared with the rest of the year (RR 2.31; 95%CI 1.65-3.23; figure A2.2). Cases who died in the winter months were no more likely to be elderly (86% vs. 81%; χ^2 P=0.5), male (45% vs. 55%; χ^2 P=0.3) or have a reported underlying condition (55% vs. 54%) than cases who died at other times of the year.

Factors leading to the underestimation of the role of campylobacter in reported mortality are shown in table A2.1. Of the parameters under investigation by single variable analysis, only the presence of an underlying

condition was significantly associated with underestimation of the role of campylobacters in all-cause mortality. This association remained when logistic regression analysis, controlling for ICD coding, season and gender, was applied (Odds Ratio (OR) 2.3; 95%CI 1.1-4.6; P=0.03). In addition, campylobacter-associated all cause mortality was independently more likely to be underestimated in patients aged 80 years and over compared to those under 60 years (OR 3.2; 95%CI 1.1-9.2; P=0.03).

Conclusions.

- Underlying cause mortality statistics underestimate the role of campylobacters by a factor of more than three, and this underestimation is greatest where the patient is either very old or has another known underlying condition. Hence the overall disease burden of *Campylobacter* infection is greater than current estimates suggest.

- Nevertheless, campylobacter-associated all-cause mortality is rare in England and Wales in comparison to other common gastrointestinal pathogens, with a case-fatality rate of only 0.02%.

- Campylobacter-associated all-cause mortality appears to be dependent on age, gender and season.

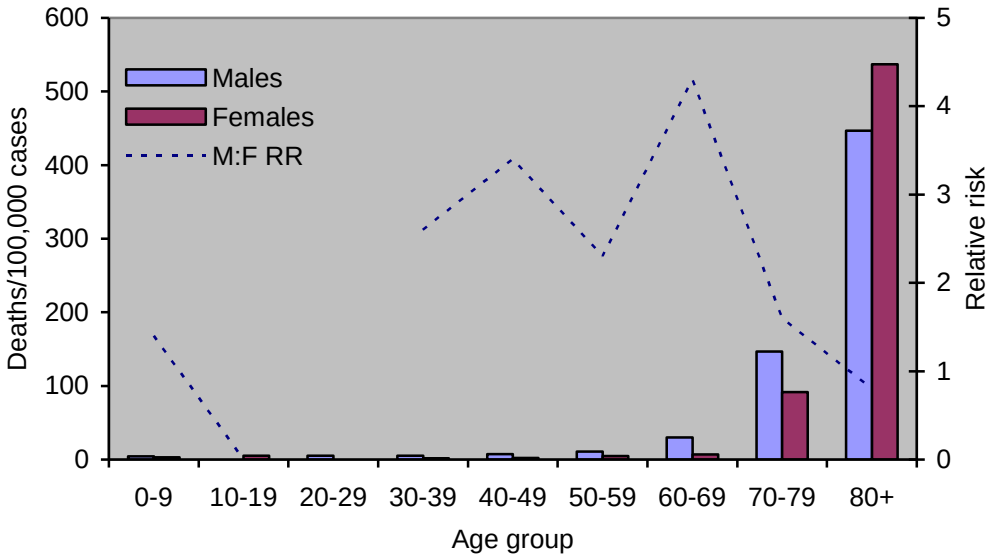

Figure A2.1: All-cause campylobacter-associated mortality by age group and gender. England and Wales, 1993-2006.

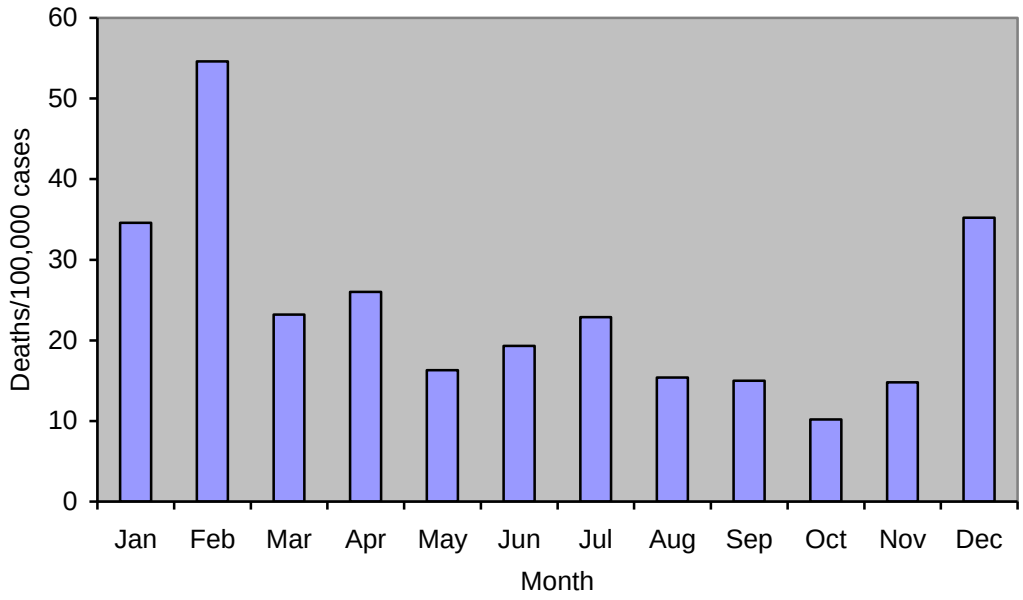

Figure A2.2: All-cause campylobacter-associated mortality by month. England and Wales, 1993-2006.

Table A2.1: Factors affecting the underestimation of the role of campylobacters in campylobacter-linked all-cause mortality. England and Wales, 1993-2006.

Parameter	Deaths		Odds Ratio	95% CI‡		P value
	Non-Campy*	Campy†		Lower	Upper	
<59 years	8	15	1.0	-	-	-
60-69 years	6	5	2.3	0.5	10.2	0.28
70-79 years	22	20	2.1	0.7	6.0	0.18
80+ years	43	34	2.4	0.9	6.4	0.08
Non-elderly (<65 years)	11	15	1.0	-	-	-
Elderly (≥65 years)	68	59	1.6	0.7	3.7	0.30
Female gender	36	38	1.0	-	-	-
Male gender	43	36	0.8	0.4	1.5	0.48
ICD-10	38	27	1.0	-	-	-
ICD-9	41	47	1.6	0.8	3.1	0.15
No underlying condition	50	33	1.0	-	-	-
Underlying condition	29	41	2.1	1.1	4.2	0.02
Winter	25	26	1.0	-	-	-
Spring	19	13	1.5	0.6	3.8	0.36
Summer	23	23	1.0	0.5	2.3	0.92
Autumn	12	12	1.0	0.4	2.8	0.94

*, All-cause mortality linked to campylobacters where campylobacteriosis was not recorded as the underlying cause; †, All-cause mortality linked to campylobacters where campylobacteriosis was recorded as the underlying cause; ‡, Confidence Interval

References.

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Appendix 3.
An analytical review of published case-control studies of sporadic *Campylobacter* infection

Methods.

The PubMed database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) was interrogated to identify citations which contained the Medical Subject Heading (MeSH) term “Campylobacter” or the text word “Campylobacter” and which also contained the MeSH term, MeSH subheading or text word "Epidemiology", but where no fields in the database contained “periodontal” or “pylori”. The latter statements were included to exclude manuscripts relating to campylobacters as a cause of periodontal disease (e.g. *Campylobacter rectus*) and articles relating to *Helicobacter pylori*, which was originally termed *Campylobacter pylori*. The search results were then limited to English language articles relating to human subjects.

The titles and abstracts for the resulting citations were then scrutinized and potential case-control studies on sporadic human *Campylobacter* infection, undertaken in developed countries, were identified. Manuscripts were obtained, read, assessed and categorised. Reference lists were inspected in order to identify additional studies not found through the PubMed search. Salient epidemiological characteristics of the investigation and findings were stored in a bespoke Microsoft Access database.

Simple statistical analyses of the resulting data were undertaken using Microsoft Excel. Frequencies, percentages and means were calculated where required. Stata version 10 (Stata Corporation, 1999) was used to assess factors affecting the number of reported risk factors for infection identified in case-control studies. Three categorical variables were created. One compared studies conducted in the eighties with those conducted in the nineties and those conducted from 2000. A second compared studies conducted in North America with those conducted in the United Kingdom, those conducted in the rest of Europe and those conducted in Australasia. The third compared studies of less than one year duration with those lasting 12 months and with those lasting longer than 12 months. Binary variables were created to compare those studies where multivariate techniques were applied with those where they were not and to compare those studies limited

to indigenously acquired infection with those which included all cases. For each continuous variable (the number of risk factors identified; number of cases included; number of controls included; number of variables investigated; the exposure period in days, the overall study sample size; the ratio of cases to controls) Stata's 'ladder' command was used to determine the transformation which best converted that variable into a normally or near-normally distributed variable, then that transformation was performed on that variable.

The effect of each of these variables on the outcome of interest (the transformed number of reported risk factors) was investigated initially using single variable Poisson regression. Variables significantly associated with the outcome of interest at or above the 90% level were then included in a multiple variable Poisson regression model which was simplified using the likelihood ratio test.

Results.

Initially, 1734 articles were identified through a search of PubMed undertaken on the 23rd September 2007, which gave rise to 36 potential articles on case-control studies on sporadic human *Campylobacter* infection in developed countries (Murray, 1986; Deming et al., 1987; Southern, Smith, & Palmer, 1990; Hudson et al., 1990; Lighton, Kaczmarski, & Jones, 1991; Hudson et al., 1991; Kapperud et al., 1992; McElroy & Smyth, 1993; Ikram et al., 1994; Schorr et al., 1994; Neal & Slack, 1995; Adak et al., 1995; Neal et al., 1996; Eberhart-Phillips et al., 1997; Neal & Slack, 1997; Svenungsson et al., 2000; Studahl & Andersson, 2000; Effler et al., 2001; Rodrigues et al., 2001; Tenkate & Stafford, 2001; Smith et al., 2002; Neimann et al., 2003; Kapperud et al., 2003; Potter, Kaneene, & Hall, 2003; Evans, Ribeiro, & Salmon, 2003; Cameron et al., 2004; Friedman et al., 2004; Engberg et al., 2004; Schonberg-Norio et al., 2004; Michaud, Menard, & Arbeit, 2004; Carrique-Mas et al., 2005; Olesen et al., 2005; Baker et al., 2005; Ethelberg et al., 2005; Wingstrand et al., 2006; Fullerton et al., 2007). A further 27 articles were identified through the reference lists of these papers (Pearson et al., 1977; Bruce, Zochowski, & Ferguson, 1977; Blaser & Reller, 1981; Norkrans & Svedhem, 1982; Kist, 1982; Severin, 1982; Taylor et al., 1983; Hopkins & Scott, 1983; Blaser, Taylor, & Feldman, 1983; Santosham et al., 1983; Potter et al., 1983; Kist, 1983; Oosterom et al., 1983; Hopkins, Olmsted, & Istre, 1984; Oosterom et al., 1984; Engleberg et al., 1984; Nolan, Harris, & Canova, 1984; Hopkins & Olmsted, 1985; Kist & Rossner, 1985a; Harris, Weiss, & Nolan, 1986; Harris et al., 1986; Harris, Weiss, & Thompson, 1986; Salfield & Pugh, 1987; Schmid et al., 1987; Harris et al., 1987; Saeed, Harris, & DiGiacomo, 1993; Kassenborg et al., 2004), giving 63 articles in total. Scrutiny of the manuscripts revealed that eight were not case-control studies (Pearson A et al., 1977; Bruce, Zochowski, & Ferguson, 1977; Norkrans & Svedhem, 1982; Hopkins & Olmsted, 1985; Hudson et al., 1990; Svenungsson et al., 2000; Engberg et al., 2004; Olesen et al., 2005), four were case-case comparisons (Murray, 1986; Neal & Slack, 1995; Evans, Ribeiro, & Salmon, 2003; Kassenborg et al., 2004), three were non-exposure case-control studies (one examined the role of various drugs on patient

susceptibility to *Campylobacter* infection (Neal, Scott, Slack, & Logan, 1996), one examined the impact of *Campylobacter* infection on health and health-related behaviour (Smith et al., 2002), and one examined demographic and geographic parameters in relation to *Campylobacter* infection (Ethelberg et al.. 2005), three described case-control studies in detail too scant to contribute meaningfully to understanding (Santosham et al., 1983; Kist 1983; Baker et al., 2005), two were review articles (Blaser & Reller, 1981; Blaser, Taylor, & Feldman, 1983), two described outbreaks of *Campylobacter* infection (Potter et al., 1983; Harris et al., 1987), two were reports which went on to peer-reviewed publications already included (Oosterom et al., 1983; Nolan, Harris, & Canova, 1984) and one focussed on factors which reduce the risk of *Campylobacter* infection (Cameron, et al., 2004). One manuscript (Harris, Weiss, & Thompson, 1986) cited in another (Saeed, Harris, & DiGiacomo, 1993) did not exist. These papers were excluded, and three papers (Harris, Weiss, & Nolan, 1986; Harris et al., 1986; Saeed, Harris, & DiGiacomo, 1993) reporting different aspects of the same study were combined into a single record, leaving 35 studies for analysis.

Twelve studies were published in the 1980s, ten in the 1990s and thirteen to date this decade, with most studies conducted in North America, the United Kingdom (UK) and the rest of Europe in each of these decades respectively (table A3.1). Studies were most frequently conducted over twelve months on subjects from all age groups, but some were restricted to adults or infants/children. The average number of study participants increased over the surveillance period, with the number of parameters under investigation increasing commensurately. Studies increasingly focused on indigenously-acquired infections, employed matching in control selection and utilised multivariate statistical techniques in analysis. Surprisingly, the period of exposure for which information was sought did not vary greatly, averaging nine days.

Based on the information reported, most studies asked participants about recent exposure to poultry (especially chicken) or dairy produce, as well as foreign travel and contact with animals and the wider environment. A

disproportionately high number of questions on poultry and/or chicken consumption were included compared with other meat types, and the number of poultry-related questions posed increased over the surveillance period. The number of reported questions on selected epidemiological parameters, reported in each study, is provided in table A3.2.

General poultry consumption was the most commonly identified risk factor, with three quarters (75%) of studies reporting this exposure where it was investigated, followed by animal contact (48%), water consumption (48%), dairy consumption (46%) and foreign travel (non-indigenous studies; 44%). Where investigated, chicken consumption was the most commonly identified specific exposure (58%), and the number of specific chicken risk factors reported (26) was exactly double the second most commonly reported specific risk factor (contact with animals other than dogs; 13; table A3.3). Other specific risk factors identified included the consumption of unpasteurised milk (47%), barbecued food (44%) or raw water (44%), and contact with dogs (42%). No case-control studies identified beef or pork as a risk factor for *Campylobacter* infection.

Population Attributable Fractions are estimates of the proportion of disease in the general population that is attributable to a particular risk factor. Where reported (seven studies; table A3.4), chicken accounted for between 0 and 24% of campylobacter cases, and an average of 12% of cases.

On average, four risk factors were identified in each study, with the number of factors ranging from one to twenty. Single variable Poisson regression analysis revealed that the number of risk factors identified in studies was unaffected by the decade in which it was undertaken, the area covered, or the duration of the study. Limiting studies to indigenous cases, altering the exposure period, or applying multivariate statistical techniques in analysis similarly had no effect. However, the number of reported risk factors identified in studies was positively influenced by the number of cases or controls included in the study (and hence the overall study size), and the number of variables considered. Multivariable analysis controlling for study

year demonstrated that only the number of controls included (RR 1.42; 95%CI 1.03-1.94; P=0.031) and the number of variables investigated (RR 1.33; 95%CI 1.00-1.77; P=0.048) were independently associated with the number of risk factors identified.

Conclusions.

- Case-control studies of *Campylobacter* infection are increasing in size and complexity without the corresponding improvement in our understanding of disease transmission.

- The move towards larger studies are perhaps magnifying the biases inherent in the methodology.

- They appear to be influenced heavily by investigator and reporter bias, as evidenced by the disproportionate pursuit of the poultry hypothesis, which continues to explain only a fraction of cases, emphasising the need for more creative approaches to hypothesis generation.

Table A3.1 Reported epidemiological features in published case-control studies of sporadic *Campylobacter* infection.

Factor	Decade (N)			Total
	80s (12)	90s (10)	00s (13)	
Publication area (%)				
N America	58	0	38	34
Rest of Europe	33	20	46	34
UK	8	60	8	23
Australasia	0	20	8	9
Study population				
All	75	80	77	77
Adults	17	20	0	11
Infants & children	8	0	23	11
Percentage indigenous	9	40	62	38
Mean study length (months)	14	7	12	11
Mean sample size	326	456	565	452
Mean number of variables	19	32	106	55
Mean exposure period	7	10	10	9
Mean interview lag	10	10	14	11
Percentage matching	83	100	100	94
Percentage multivariate analysis	17	50	92	54
Foreign travel[†]				
% enquiry	60	83	100	76
% risk factor	33	33	50	39
Poultry variables				
% enquiry – any	75	80	85	80
% enquiry – ch*	58	70	77	69
Mean no. variables – any	4	9	10	8
Mean no. variables – ch*	4	6	8	6
% risk factor – any	89	63	73	75
% risk factor – ch*	86	43	50	58
Other (non-poultry) meats				
% enquiry	42	70	92	69
Mean no. variables	8	5	6	6
% risk factor	40	29	42	38
Dairy				
% enquiry	40	100	100	80
% risk factor	80	51	31	46
Water				
% enquiry	42	60	77	60
% risk factor	80	33	40	48
Animal contact				
% enquiry	42	60	77	60
% risk factor	80	33	40	48
Total risk factors identified	44	41	55	140
Mean risk factors identified	4	4	4	4

[†], Excludes indigenous-only studies; *, chicken

Table A3.2. Selected investigated exposures reported in published case-control studies of sporadic *Campylobacter* infection.

Parameter	Kist 1982	Severin 1982	Taylor et al. 1983	Hopkins & Scott 1983	Hopkins, Olmsted, & Istre 1984	Oosterom et al. 1984	Engleberg et al. 1984	Kist & Rossner 1985b	Harris, Weiss, & Nolan 1986; Harris et al. 1986; Skirrow et al. 1993	Saffield & Pugh 1987	Schmid et al. 1987	Deming et al. 1987	Southern, Smith, & Palmer 1990	Lighton, Kaczmarski, & Jones 1991	Hudson et al. 1991	Kapperud et al. 1992	Ellroy & Smyth 1993	Ikram, et al. 1994	Schorr et al. 1994	Adak et al. 1995	Eberhart-Phillips et al. 1997	Neal & Slack 1997	Studahl & Andersson 2000	Effler et al 2001	Rodrigues et al. 2001	Tenkate & Stafford 2001	Neimann et al. 2003	Kapperud et al. 2003	Potter et al. 2003	Friedman et al. 2004	Schonberg-Morio et al. 2004	Michaud, Menard, & Arbeit 2004	Carrique-Mas et al. 2006	Wingstrand et al. 2006	Fullerton et al. 2007
Foreign travel		1			1	1		1	1			1		1				1	1	1	1	1			1	1			1		1			1	1
Restaurants		1			1									2		4	1	1				2		1			1	1		7		2			
Poultry - all	1	2		2	6	1		1	18		2	7	3	3		16		24	5	4	15	3	4	11	8		24	11	1	40		7	1	3	1
Poultry - chicken		2		2	5	1			10		2	6	3	3		2		13		4	14	1	4	10	8		16	3		36		1	1	1	1
Beef		2				1			10				1			3	1		3			1		2			2	1	1	10					1
Pork		2			1	1			10				1			2						1	4	3		3	3	1	1	8				1	
Lamb		2							1							2						1				1		1		1					
Other meat					1	1						1				7	3				1	3	5		1	1		7		3	1		1		
Barbecued food					1	1								1		1	1	7		5	1	1	1		1		2	2		2		1	1	1	
Fish and shellfish									10			1				2		1	1			1			2			1		2	1				
Salad, vegetables and fruit					1				7		1					3			2		6				4	2	4	2		2				4	1
Food hygiene practices							1		1		1					9		4				2	3		6	4	3			1		1			1
Pasteurised milk									7				7	6	4	1	1			1		2			1	2								
Unpasteurised milk					1			1	4		1	1		1		1	1		1		1	1	1	1			1	1	1	1		1	1		
Other dairy					1			1	29							2	3	1	2		1	3	1			2				1	1			1	1
Raw water			1		1		2		1		1			1		1		1	1	1	1			1	1			2		1			1		
Municipal water														1				2		1					1		1	2			1		1	1	1
Private water																					3					1	1				1				
Contact with dogs	1	1				1			4	1	2	1	2			2		1			2	2	1	2	1	2		2		5			1		
Contact with other animals		8			1	4	10		12		3	3	2	2		10		2	1	2	10	6	4	1	2	8	5	8	29	16		1	9		1
Environmental exposure					1		1		2		1		1	11	1	3		1	1	1	4	7	2			2		7	3	3	1		1	2	1
Contact with other ill people	1	1			2		1	1	3		1	4		1	1					1		3				1		1		1					

Table A3.3 Selected reported risk factors in published case-control studies of sporadic *Campylobacter* infection.

Parameter	Kist 1982	Severin 1982	Taylor et al. 1983	Hopkins & Scott 1983	Hopkins, Olmsted, & Istre 1984	Oosterom et al. 1984	Engleberg et al. 1984	Kist & Rossner 1985b	Harris, Wicks, & Nolan 1986; Harris et al. 1986; Saeed et al. 1993	Saffield & Pugh 1987	Schmid et al. 1987	Deming et al. 1987	Southern, Smith, & Palmer 1990	Lighton, Kaczmarski, & Jones 1991	Hudson et al. 1991	Kapperud et al. 1992	Kapperud et al. 1992	Elroy & Smyth 1993	Ikram, et al. 1994	Schorr et al. 1994	Adak et al. 1995	Eberhart-Phillips et al. 1997	Neal & Slack 1997	Studahl & Andersson 2000	Effler et al 2001	Rodrigues et al. 2001	Tenkate & Stafford 2001	Neimann et al. 2003	Kapperud et al. 2003	Potter et al. 2003	Friedman et al. 2004	Schonberg-Norio et al. 2004	Michaud, Menard, & Arbeit 2004	Carrique-Mas et al. 2006	Wingstrand et al. 2006	Fullerton et al. 2007
Foreign travel								1	1											1			1			1									1	1
Restaurants																																	1			
Poultry - all	1	1		1	1	1		1	6			2				1			1	1		6	1	1	1	1		1	1		3		1		1	
Poultry - chicken		1		1	1	1			5			2							2			6	1	1	1	1					2				1	
Beef																																				
Pork						1																		2					1							
Lamb																																				
Other meat																						1				1					1	1				
Barbecued food						1										1		2		1	1		1					1	1							
Fish and shellfish									2																						1					
Salad, vegetables and fruit									1													1						1							1	1
Food hygiene practices									1																			1								1
Pasteurised milk													6	1	2								1													
Unpasteurised milk					1			1	1		1											1		1				1			1		1			
Other dairy									1																											
Raw water			1		1		1		1												1								1					1		
Municipal water																																		1		1
Private water																						1										1				
Contact with dogs									3	1						1						1	1				1				1			1		
Contact with other animals		1			1		1		1			1									1	1		1			1		1	1	1					1
Environmental exposure																								2							2	1				1
Contact with other ill people		1						1	2		1																									

Table A3.4. Population Attributable Fractions for all risk factors and for chicken risk factors in published case-control studies of sporadic *Campylobacter* infection.

Year	All risk factors	Chicken risk factors	Reference
1997	75	11	Eberhart-Phillips et al., 1997
2001	20	11	Rodrigues et al., 2001
2003	74	0	Neimann et al., 2003
2004	77	24	Friedman et al., 2004
2005	102	0	Carrique-Mas et al., 2005
2006	-*	24	Wingstrand et al., 2006
2007	114	12	Fullerton et al., 2007

*, Not reported

Table A3.5. The effect of various reported study features on the log-transformed number of reported risk factors identified in published case-control studies of sporadic *Campylobacter* infection. Single variable Poisson regression analysis.

Parameter	Relative risk	95% CI[†]		P value
		Lower	Upper	
Study decade:				
- 80s	1	-	-	-
- 90s	1.33	0.57	3.12	0.51
- 00s	1.50	0.68	3.28	0.32
Area:				
- North America	1	-	-	-
- Rest of Europe	1.15	0.53	2.49	0.73
- United Kingdom	0.75	0.28	2.00	0.57
- Australasia	1.81	0.66	4.97	0.25
Study period:				
- 1-11 months	1	-	-	-
- 12 months	1.49	0.68	3.27	0.33
- >12 months	1.47	0.68	3.16	0.33
Indigenous cases vs. all cases	0.91	0.47	1.76	0.78
Exposure period (days)*	0.68	0.00	195.02	0.89
Multivariate vs. univariate analysis	1.32	0.68	2.54	0.41
Cases[‡]	1.40	1.04	1.88	0.03
Controls[‡]	1.47	1.10	1.96	0.01
Cases : controls*	0.25	0.04	1.60	0.14
Sample size[‡]	3.25	2.60	4.07	0.00
Variables[‡]	1.37	1.07	1.76	0.01

[†], Confidence Interval;*, reciprocal root transformed; [‡], log transformed

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Appendix 4.
The Campylobacter Sentinel Surveillance Scheme questionnaire.

CAMPYLOBACTER INVESTIGATION FORM.

Date completed ...../...../..... **NHS no.** ..... **Lab. code** .....

Personal details

Family name _____ First name_____

Date of Birth ___/___/___ (day/month/year) Age ____ years _____ months (if <1yr)

Sex ☐ Male ☐ Female Telephone number _____ Postcode _____

Occupation (please include retired, student, pre-school child etc.) _____

Are you a commercial food handler? Yes ☐ No ☐

Describe your ethnic origin: _____

2. Symptoms.

On what date did your illness start ___/___/___ (day/month/year)

How long did your illness last ____ (days)

Have you experienced any of the following symptoms due to your illness:

Diarrhoea (four or more loose/runny stools in 24 hours)	☐ Yes☐ No ☐ Unsure
Bloody stools	☐ Yes☐ No ☐ Unsure
Vomiting	☐ Yes☐ No ☐ Unsure
Abdominal pain (cramps)	☐ Yes☐ No ☐ Unsure
Fever (feeling hot and cold)	☐ Yes☐ No ☐ Unsure

Are you still ill? ☐ Yes ☐ No

Did you seek advice from a doctor ☐ Yes ☐ No

Were you admitted into hospital ☐ Yes ☐ No

If yes, for how many days were you admitted _____ (days)

For how many days were you prevented from going to work or from undertaking normal daily activities because of your illness _____ (days)

3. **Travel**

Did you travel OUTSIDE THE UK in the two weeks before your illness started

□ Yes □ No

If yes, where did you go

Country _____ Town/Resort _____

Hotel _____ Date of arrival ___/___/___ (day/month/year)

Date of departure ___/___/___ (day/month/year)

Did you travel IN THE UK in the two weeks before your illness started □ Yes□ No

If yes, where did you go

Town/Resort _____ Hotel _____

Date of arrival ___/___/___ Date of departure ___/___/___ (day/month/year)

4. Food consumption in the two weeks before your illness

Food type	How often eaten		
Baby food	□ Never	□ Once	□ More often
Barbecued food	□ Never	□ Once	□ More often
Beef (inc roast, mince, steak)	□ Never	□ Once	□ More often
Cheese	□ Never	□ Once	□ More often
Chicken	□ Never	□ Once	□ More often
Cold meats (pre-cooked)	□ Never	□ Once	□ More often
Fish/shellfish	□ Never	□ Once	□ More often
Halal meat	□ Never	□ Once	□ More often
Lamb	□ Never	□ Once	□ More often
Meat pies	□ Never	□ Once	□ More often
Offal or tripe	□ Never	□ Once	□ More often
Other poultry	□ Never	□ Once	□ More often
Organic meat	□ Never	□ Once	□ More often
Organic vegetables	□ Never	□ Once	□ More often
Pate	□ Never	□ Once	□ More often
Pork, ham or bacon	□ Never	□ Once	□ More often
Pre-prepared sandwiches	□ Never	□ Once	□ More often
Salads	□ Never	□ Once	□ More often
Sausages	□ Never	□ Once	□ More often
Vegetarian food	□ Never	□ Once	□ More often

Were any of the above foods cooked 'rare' (i.e. was pink inside) □ Yes □ No □ Unsure

Have you eaten in a restaurant in the last two weeks □ Yes □ No □ Unsure

If yes please give details _____

Please estimate how often you handled raw meat in the two weeks before your illness

□ 0 □ 1 □ 2 - 5 □ 6 - 10 □ 11plus

Did you drink (or have in your cereal) unpasteurised (e.g. farm fresh; green top) milk in the two weeks before illness

□ Yes□ No □ Unsure

Did you drink (or take in cereal) bird-pecked milk in the two weeks before illness

□ Yes□ No □ Unsure

Is most of your milk: □ Doorstep-delivered □ Supermarket-bought

5. Water consumption

Did you drink cold, unboiled water in the two weeks before illness from:

Mains water supply □ Yes □ No

Private water supply □ Yes □ No *If yes, was it treated* □ Yes □ No □ Unsure

Bottled water □ Yes □ No

River, stream, spring □ Yes □ No

A filter jug □ Yes □ No

Had you noticed any engineering work or supply problem (e.g. discoloured or tainted water)

□ Yes □ No

*If yes, please specify*_____

How many glasses of unboiled water do you drink a day (i.e. straight from the tap or in squash) _____

Recreational water activity

Did you take part in any of the following water (fresh or sea) sports or activities in the two weeks before illness:

Swimming/paddling	☐ Yes ☐ No
Sailing	☐ Yes ☐ No
Windsurfing	☐ Yes ☐ No
Fishing	☐ Yes ☐ No

If yes, please give details

_____

7. Contact with animals

Have you had any contact with animals in the two weeks prior to illness? ☐ Yes ☐ No

If yes

Do you have any pets ☐ Yes ☐ No

*If yes, please specify type*_____

Have any of your pets had diarrhoea in the two weeks before illness ☐ Yes ☐ No

If yes, please list _____

Did you clean up the faeces (mess) ☐ Yes ☐ No

Have you visited a farm in the two weeks before illness ☐ Yes ☐ No

If yes, please give details

_____

8. Household members

How many people live in your household _____ Adults _____ Children

Has anyone else in your household been ill with similar symptoms recently (whether they ate the same food or not) □ Yes □ No

If yes, please give details

_____
_____
_____

Has anyone else outside the household had a similar illness recently □ Yes □ No

If yes, please give their name and address

_____
_____
_____