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The study of infectious intestinal disease in England: risk factors for cases of infectious intestinal disease with *Campylobacter jejuni* infection

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SUMMARY

This is a case-control study aimed at identifying risk factors for intestinal infection with *Campylobacter jejuni*. Cases were defined as subjects with diarrhoea occurring in community cohorts or presenting to General Practitioners (GPs) with *Campylobacter jejuni* in stools. Controls were selected from GP lists or cohorts, matched by age, sex, and GP practice. Travel abroad and consumption of chicken in a restaurant were statistically significantly associated with being a case. There was no statistically significant risk associated with consumption of chicken other than in restaurants nor with reported domestic kitchen hygiene practices. Consumption of some foods was associated with a lower risk of being a case. Most cases remained unexplained. We suggest that infection with low numbers of micro-organisms, and individual susceptibility may play a greater role in the causation of campylobacter infection than previously thought. It is possible that in mild, sporadic cases infection may result from cross contamination from kitchen hygiene practices usually regarded as acceptable. Chicken may be a less important vehicle of infection for sporadic cases than for outbreaks, although its role as a source of infection in both settings requires further clarification in particular in relation to the effect of domestic hygiene practices. The potential effect of diet in reducing the risk of campylobacteriosis requires exploration.

INTRODUCTION

Campylobacter has long been recognized as the most common pathogen reported in human cases of gastroenteritis in England and Wales [1] and the United States of America [2] and is the most common bacterial cause of diarrhoea in the industrialized world [3]. Although apparently sporadic cases are common, outbreaks are rarely identified [4]. Only 0·04% of cases in England and Wales reported to the Communicable Disease Surveillance Centre (CDSC) in 1995 and 1996 were part of identified outbreaks [5]. The cause of most outbreaks was not found, and vehicles of infection reported have included poultry, milk and dairy products, salads, vegetables and fruits.

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Studies of apparently sporadic cases have failed to explain the majority of cases [6, 7], although some risks have been identified: consumption of contaminated milk [1, 8, 9], water [6, 8], and poultry products [6, 8, 10]. Person-to-person spread seems to be unusual, although infection can result from direct spread from domestic pets [8, 11–13]. In addition to the epidemiological evidence, the frequent finding of campylobacter in poultry [14, 15] and in poultry products destined for human consumption [16, 17] suggests that these are potentially important sources and vehicles of infection. A number of studies, however, have shown consumption of some types of poultry to have a protective effect [6, 7, 18].

METHODS

We report the investigation of potential risk factors for *C. jejuni* infection in cases identified during a large study of infectious intestinal disease (IID) in England. The objectives, methods and initial results of the large IID study are described elsewhere [19–21] but, in brief, the study ascertained cases of IID presenting to 34 GP practices and also those occurring in 70 community based cohorts over a period of a year. One control per case was selected from the GP list or cohort, respectively, matched for age, sex and GP practice. Cases and controls were asked to collect a stool specimen and post it to Leeds Public Health Laboratory (PHL) for laboratory investigation. Leeds PHL employed four methods in parallel to identify *C. jejuni*: three direct methods (two different selective media and a filtration technique) and an enrichment method. Isolates were sent to the Public Health Laboratory Service (PHLS) Laboratory of Enteric Pathogens (LEP) for confirmation and typing. It is relevant that in this study all cases of IID had stool specimens examined, including those who did not present to their GP, and those who presented to the GP but whose stool would not routinely have been examined.

Informed consent was obtained from all patients and ethical committee approval obtained from the LSHTM and from the local ethical committees of all participating districts.

This paper reports the matched case-control analyses of 229 cases of IID with *C. jejuni* infection and their matched controls. Of these, 209 cases presented during the GP case-control component, and 20 occurred in the community based cohorts. Only 10 cases were identified by the enrichment culture method but not by the direct methods. All cases over 1 year of age were included. Eleven cases of IID with *C. jejuni* infection did not have a control. To avoid excluding these cases, 11 controls meeting the original matching criteria (age, sex and GP practice) were selected for these cases at random from those controls matched to cases of IID with other infections. The median time between interviewing cases and their matched controls was 22 days; for 75% of case-control pairs it was less than 41 days and for 25% less than 4 days.

Cases and controls completed a self-administered standard questionnaire on personal characteristics and a wide range of potential risk factors for food borne and non-food borne IID. The questionnaire was completed before the results of the stool investigations were known, and so the same questionnaire was used for cases of IID with *C. jejuni* infection as for all cases of IID. Information was obtained on a large number of variables but only those suspected on the basis of biological plausibility and previous knowledge to be associated with *C. jejuni* infection were analysed. The variables were: consumption of water and various foods in the 10 days before the onset of symptoms (before the completion of questionnaire in controls), the manner in which some foods – mainly chicken – were purchased, prepared or consumed; exposure to pets and other animals; habitual domestic hygiene practices; recreational water exposure, travel, education, ethnicity, and other socio-economic indicators. Our hypotheses were that risk was increased by: the consumption of certain foods including chicken, which are often contaminated with *C. jejuni*, and uncooked food, like salads and fruit, as vehicles; the consumption of, and recreational exposure to, water; and that travel increased the risk via consumption of untreated water. We also tested the hypotheses that some poor kitchen hygiene practices increased the risk of cross-contamination in food preparation at home; and that low socio-economic status, unemployment, and low educational status all increased the risk. We investigated selected seasonal factors described as risk factors in previous work, such as consumption of bird-pecked milk, but we were aware that the study was unlikely to have sufficient cases to find a significant association.

Analysis was initially univariate. We present an analysis adjusting for social class, education and employment status, to demonstrate that these were not confounding factors (in other words, that the ORs

Table 1. *Risk factors associated* ($P < 0{\cdot}01$) *for IID with* Campylobacter jejuni *in stools, with ORs and P values; univariate, adjusted for travel* (*No. = 229 cases and 229 controls*)

Intermediate factors	Case No. expt	Control No. expt	Unadjusted OR	Unadjusted *P*-value	Adjusted for travel OR	Adjusted for travel *P*-value	Adjusted for S.E.* OR	Adjusted for S.E.* *P*-value
Travel abroad	30	9	3·62	0·001				
Eating chicken at restaurant	43	21	2·38	0·004	1·86	0·049	1·80	0·086
Boiled rice eaten immediately	84	125	0·45	< 0·001	0·42	< 0·001	0·45	< 0·001
Pulses	42	86	0·39	< 0·001	0·36	< 0·001	0·34	< 0·001
Fruit with skins	152	183	0·48	0·001	0·44	< 0·001	0·41	< 0·000
Skinless fruit	136	184	0·34	< 0·001	0·34	< 0·001	0·33	< 0·000
Dried fruit	38	94	0·25	< 0·001	0·27	< 0·001	0·23	< 0·000
Salad at home	112	165	0·34	< 0·001	0·36	< 0·001	0·33	< 0·000
Pasteurized product	92	132	0·48	< 0·001	0·48	< 0·001	0·45	< 0·000
Home made desserts with raw eggs	16	35	0·41	0·006	0·37	0·004	0·28	< 0·000

* S.E., social class, education and employment status.

for the risk factors of interest are similar whether social class, education and employment status are controlled for or not). Travel was the only statistically significant risk factor for *C. jejuni* infection and the final model controls for this.

The decision to restrict the analysis to variables suspected to be associated with *C. jejuni* infection (rather than use all the data collected) aimed to reduce the likelihood of multiple testing erroneously identifying risk factors by chance. Because of the number of variables studied, an association was considered statistically significant when $P = < 0{\cdot}01$, but associations with *P*-value between 0·01 and 0·05 were regarded as borderline and are also reported.

The population-attributable fraction (the proportion of all cases attributable to a particular risk factor) was estimated for the two factors found to be statistically significantly associated with risk, using the formula: $p(OR-1)/p(OR-1)+1$, where 'p' is the proportion of exposed among controls, and 'OR' is the Odds Ratio. The sample size was a result of the number of cases identified. The power of a study depends on the frequency of the exposures of interest and the strength of the associations. The power to find an association with consumption of chicken, was 80% (for a precision of 95%), for associations with ORs ranging from 1·75 or over (for example for chicken bought fresh and cooked and consumed at home, to which 38% were exposed) to an OR of 4·4 or over (for barbecued chicken, to which 2% were exposed). The study would have 80% power to detect (with 95% precision) an OR of 2·8 associated with consumption of chicken in any form, as 87% were exposed.

RESULTS

Table 1 presents all factors found to be associated with being a case at a 1% significance level. Travel abroad was statistically significantly associated with increased risk on the univariate analysis (OR = 3·6, 95% CI = 1·7–7·9), and the final model controlled for this. The only other factor associated with an increased risk remaining statistically significant was the consumption of chicken at a restaurant or canteen. Factors significantly associated with a lower risk were consumption of pulses, fruit, boiled rice when freshly cooked and eaten at home, salad consumed at home, pasteurized dairy products and dessert made at home using raw eggs. These were not changed after control of socio-economic status (employment, social class, and level of education). The following factors had borderline statistical significance and are not shown in Table 1: the consumption of sliced meat bought in shops other than a delicatessen or a supermarket (OR = 2·1; $P = 0{\cdot}04$), the consumption of non-oily fish (OR = 0·7; $P = 0{\cdot}05$), or oily fish (OR = 0·7; $P = 0{\cdot}03$), and participating in recreational water sports when water is not swallowed (OR = 0·5; $P = 0{\cdot}02$). There were no statistically significant interactions between these factors and age, sex and season (in other words, the significant effects found were similar in all seasons, ages and both sexes).

Table 2 presents the OR and 95% confidence intervals for all the consumption of chicken in any form, and in 12 separate forms. Except for consumption of chicken in a restaurant or canteen (presented in Table 1), no other form of consumption

Table 2. *Forms of consumption of chicken not significantly* (P = > *0·01*) *associated with* Campylobacter jejuni *in stools in univariate analysis* (*No. = 229 cases and 229 controls*) *with ORs and 95% CI*

Factor	Cases number expt	Control number expt	OR	95% CI
Barbecued	5	12	2·4	0·85–6·81
Any chicken	201	204	1·2	0·70–2·15
Take-away	43	38	1·2	0·71–1·92
Fast food chicken	44	43	1·0	0·65–1·63
Ready gutted without giblets, fresh, cooked at home	94	106	0·9	0·61–1·38
Bought raw, fresh, cooked and eaten at home	58	70	0·8	0·55–1·19
Bought raw frozen, eaten at home	20	30	0·8	0·53–1·17
Pre-cooked, eaten at home cold	16	21	0·8	0·40–1·46
Subject prepared a chicken to be eaten	14	13	1·1	0·67–1·68

Table 3. *Other variables investigated, not significantly associated with* C. jejuni *in stools in matched univariate analysis* (*No. = 229 cases and 229 controls*) *with ORs and 95% CI*

Factor	Cases number expt	Control number expt	OR	95% CI
Part time employment (baseline: full time)	27	18	0·5	0·2–1·1
Other, including the unemployed (baseline: full time)	103	104	0·9	0·5–1·6
Ethnic minority	13	7*	5·8	0·8–6·5
Contact with pets	128	126	1	0·7–1·6
Contact with puppies	5	2	2·5	0·5–12·9
Contact with other animals	56	73	0·7	0·5–1·1
Consumption of mains water	145	153	0·8	0·6–1·2
Drinking milk from a bird pecked bottle	4	1	4	0·45–35·7
Having a kitchen less than 2 m in length	29	34	0·9	0·5–1·5
Kitchen work surface less than 1 m long	16	10	1·7	0·7–3·8
1–2 h from shopping to fridge (baseline 1 h)	27	23	1·4	0·7–2·4
More than 3 h from shopping to fridge (baseline 1 h)	6	2	3·1	0·6–15·7
Storing meat in the top half of the fridge	62	73	1·1	0·7–1·7
Using a separate chopping board for meat	113	103	0·9	0·6–1·3

* 2 controls and 6 cases with missing information.

of chicken attained even borderline statistical significance. Of particular interest is the absence of an association with consumption of chicken in any form (OR = 1·2, 95% CI = 0·7–2·2) and of barbecued chicken (OR = 2·4, 95% CI = 0·9–6·8). Although these are not significant, it is of interest that the associations between forms of chicken consumption and being a case fall on either side of OR = 1.

Finally, the variables that were investigated as potential risk factors on univariate analysis, but were not found to be statistically significantly associated even at the borderline value of $P = 0{\cdot}05$ are listed in Table 3. They include type of employment, ethnicity, contact with pets, puppies or with other animals, and consumption of mains water. Drinking milk from a bottle where the top had been pecked by a bird was not statistically significant but there were very few subjects exposed. None of the domestic hygiene practices expected to facilitate cross-contamination was found to be associated with being a case: having a kitchen less than 2 m in length, having a work surface in kitchen less than 1 m long, too long a time from shopping to putting food in the fridge, storing meat in the top of the fridge and not using a separate chopping board for meat. There was no statistically significant interaction in the risk of being a case between consumption of chicken and these reported domestic hygiene practices.

The population attributable fraction for travel abroad was 9% and for eating chicken in a restaurant or canteen, 11%. So 80% of the cases are not explained by the factors as investigated in this study.

DISCUSSION

The study confirmed our hypothesis that travel abroad increased the risk of *C. jejuni* infection, but failed to confirm the hypothesis of an increase in risk associated with consumption of chicken, owning a pet or puppies and poor kitchen hygiene. It also produced some unexpected results, with a lower risk of disease associated with some foods which were investigated as potential risk factors. Before considering why some of our findings might be at variance with previous studies, the advantages and disadvantages of the approach taken should be addressed. This study is unique in that it includes cases (although only 10% of all our cases) which did not present to GP, and cases (estimated to be about two thirds) who would not under routine circumstances had had a stool sample investigated. Current knowledge of the causation of IID with *C. jejuni* infection is based principally on studies either of sporadic cases identified by routine surveillance [6, 7, 18] or of outbreaks [9, 22–24]. Both these categories of case are likely to be atypical of campylobacteriosis as a whole: most cases are sporadic [5] and only 1 in 7 cases of *C. jejuni* occurring in the community is notified to routine surveillance in England [19, 21].

The main limitation to the study, the counterpart of the advantage discussed above, is that as all cases were tested, and cases completed the questionnaire as soon as they had symptoms, the questionnaire included questions that were not tailored for *C. jejuni* infection. Another limitation, to all epidemiological studies, is that hygiene practices are notoriously difficult to study, and thus lack of associations must be interpreted as lack of association with practices as reported.

We acknowledge that the limitations of our study may have reduced our ability to identify true risk factors. Despite the size of our study it may not have been sufficiently large to show small differences between exposures in cases and controls. Consumption of chicken, in particular, is very common and asking about consumption in a 10-day period may have increased the sensitivity of the questionnaire at the expense of its specificity. In addition, because we analysed cases occurring over a whole year, markedly seasonal risks may have been missed, as they would cause only a small proportion of cases over the whole year. Although the study includes 229 cases, these are distributed over the year, and we would not have had power to identify risk factors that operate only in a season.

But it is also possible that our results are not caused by chance or artefact, but reflect real causation. If so, why might they differ from previous studies? We suggest that cases that present to health services, and those who, presenting to health services have a stool sample tested, are likely to be more severe than those that do not, and in common with cases occurring in outbreaks, may have been exposed to a higher dose of organisms than mild sporadic cases. Our study includes cases in the community as well as those presenting to GPs, and cases that would not have their stools investigated under routine practice, and are thus more representative of all campylobacteriosis. We expect the analysis of these cases to provide a better picture of risk factors for all cases.

Only two factors were significantly associated with increased risk of campylobacteriosis: travel abroad and eating chicken at a restaurant or canteen. Travel associated illness is a common and increasing problem [25], and in this study travel abroad was found to be a risk factor although this explained only 9% of the cases. Travel is obviously a marker for some other risk factor: perhaps exposure to more heavily contaminated foods or water, or to novel strains of campylobacter to which the traveller has no immunity. Consumption of chicken at restaurants or canteens was associated with an increased risk and explained 11% of the cases. The association between eating chicken at restaurants was not unexpected as poultry meat on retail sale in the UK is often contaminated with *C. jejuni* [15, 16, 26, 27].

Other factors expected to be associated with infection were not found to be in this study. Keeping dogs and cats was not found to be associated with an increase in the risk in this study. Contact with dogs and cats have been described in association with outbreaks [28] and sporadic cases of campylobacter infection [8, 10] while others studies failed to find an association with pets [29]. The effect of pet ownership could be further explored by investigating whether its effect changes with duration of ownership.

Our study showed no association with the previously identified risks of consuming bird pecked milk [30], and consumption of barbecued chicken [2, 31]. This may be because these risks are markedly seasonal, occurring in spring and summer respectively, whereas

our study addressed the whole year, and had insufficient power to identify factors with a limited duration of risk. The confidence intervals for those two risk factors are wide, as the number exposed are very small, and even if there was a risk we failed to detect because of small numbers, these would explain to a very small proportion of all cases.

We explored other suspected food risk factors. Consumption of chicken other than in restaurants or canteens was not associated with an increased risk. The relative importance of consumption of chicken and of other vehicles of infection, and the form of chicken found to be a risk have varied in studies of sporadic campylobacter infection. In England, a study of sporadic campylobacter infection has shown consumption of poultry in the previous 3 days to be associated with a statistically significant reduction in risk [6]. There are many possible reasons for our finding. The sample size may not have been large enough to detect a risk given the frequency of reported chicken consumption; perhaps most chicken is not contaminated when consumed – if this were the case, the risk associated with chicken would be too small to be detected; frequent consumption of chicken may lead to some degree of immunity so that after some time it is no longer a risk. Another possibility is that although the campylobacter introduced by the contaminated chicken in the household is a frequent cause of disease, this is mainly through cross-contamination, not direct consumption [32, 33].

If cross-contamination was the main route for infection, would we not have found an increased risk with 'usual' (i.e. habitual) poor domestic kitchen hygiene practices? We did not find associations between being a case and usual domestic kitchen hygiene practices, either by themselves or interacting with the consumption or preparation of chicken. How can we explain this? Outbreaks of food borne IID are frequently reported to be associated with inadequate refrigeration, cross-contamination and inadequate heat treatment [5]. Domestic kitchen hygiene practices and knowledge are, however, notoriously difficult to measure and it is possible that our subjects were not prepared to disclose unhygienic behaviour. The study collected information on 'usual' practice, not practice in the days before illness, and so it may have missed the lapse that caused the infection. So one possible reason for the study not to find an association being *C. jejuni* the usual domestic hygiene practice is that the quality of information was not good enough. The other possible reason is much more worrying: that what is usually regarded, as acceptable kitchen hygiene is not sufficient to prevent low-level contamination of a food vehicle. Our study included the whole spectrum of disease severity, and it is possible that while major lapses in hygiene cause outbreaks and more severe sporadic cases, minor lapses which constitute acceptable practice, and which we could not measure, in fact cause most cases. If so, this would be an important finding. If what is perceived as acceptable domestic kitchen hygiene cannot protect against cross-contamination, against light contamination of food or the environment, which is nevertheless sufficient to cause infection and mild disease, there may be implications for prevention.

It has been suggested that sporadic cases of campylobacter infection are more likely to occur because of cross-contamination from raw chicken than because of consumption of the chicken [32, 33]. In other words, chicken may frequently be the source but not the vehicle of the infection for sporadic cases. This would explain the difference between vehicles associated with outbreaks and those that cause sporadic cases. If, in an outbreak, the vehicle is heavily contaminated, the important determinant of illness is whether a subject ate the contaminated food. Whereas if in sporadic cases the vehicle is only lightly contaminated, due to its being cross-contaminated from another source within the kitchen, individual susceptibility would play a larger role. This is biologically plausible, because light contamination is more likely with campylobacter than with, for example salmonella. This is because campylobacter unlike salmonella does not multiply on food [34] and time-temperature abuse will not increase the number of organisms ingested.

Finally, consuming certain foods was significantly associated with a lower risk. The foods were: pulses; salad consumed at home, rice consumed at home; and fruit, pasteurized dairy products and home made desserts made with eggs. This was unexpected: we had investigated consumption of these foods as potential risk factors for a variety of enteric pathogens. These findings should thus be treated with caution, and viewed as generating hypotheses rather than confirming them. It is possible that the findings are artefacts. The associations found were highly statistically significant ($P < 0{\cdot}001$), but the possibility remains that the findings are due to chance. Although measurement of precise dietary intake is notoriously difficult, vagueness without bias would only weaken an existing association, and not create one had none existed.

Reporting bias and confounding are possible: people who report eating these foods, or people who do eat these food may have a healthier life-style, which might include some practice not measured in the study (perhaps eating freshly prepared food) which protects them from campylobacteriosis. This is possible, but again information was collected about a large range of social, educational, and hygienic practices and none was associated with campylobacteriosis.

We cannot therefore reject the possibility that the effect may be causal. Consumption of fruit and vegetables has been shown to be associated with a lower risk of cancer of the intestinal tract [35–38], and a recent study found consumption of unpeeled apples to be protective against campylobacter infection [39]. Possible causal mechanisms for protection against IID include the effect of diet on the intestinal flora – for example, it has been suggested that bifidobacteria protect against infections [40, 41], and a boost to general immunity to infection mediated by micronutrients including antioxidants. Selenium deficiency has been suspected as leading to increased susceptibility to infection [42, 43] and vitamin A has been found to decrease duration and severity of IID in children in developing countries [44] and protect children from persistent diarrhoea [45]. Fruit, salad and pulses, found to be associated with lower risk in this study are rich in antioxidants and it is thus conceivable that they could have an effect boosting general immunity.

The cases we studied are more representative than those identified in national surveillance of sporadic cases or outbreaks of campylobacteriosis and our findings are likely to be more valuable in the formulation of preventive strategies.

Our study only explained a fifth of the cases and further research is needed to clarify how most apparently sporadic cases of *C. jejuni* infection acquire the pathogen. We recommend that further research include investigating the possible role of foods, including poultry in the causation of sporadic cases of campylobacter infection by studying not just consumption but also the presence of raw chicken meat in the household, and the effect of hygiene practices. We suggest that future studies (and past studies where appropriate data were collected) investigate the apparent effect of consuming fruit, salads, pulses, rice and dairy products in reducing the risk of acquiring campylobacter, and, if confirmed, that further research is undertaken to clarify mechanisms behind an effect.

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