

# Campylobacter epidemiology: a descriptive study reviewing 1 million cases in England and Wales between 1989 and 2011

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## ABSTRACT

**Objectives:** To review *Campylobacter* cases in England and Wales over 2 decades and examine the main factors/mechanisms driving the changing epidemiology.

**Design:** A descriptive study of *Campylobacter* patients between 1989 and 2011. Cases over 3 years were linked anonymously to postcode, population density, deprivation indices and census data. Cases over 5 years were anonymously linked to local weather exposure estimates.

**Setting:** Patients were from general practice, hospital and environmental health investigations through primary diagnostic laboratories across England and Wales.

**Participants:** There were 1 109 406 cases.

**Outcome measures:** Description of changes in *Campylobacter* epidemiology over 23 years and how the main drivers may influence these.

**Results:** There was an increase in *Campylobacter* cases over the past 23 years, with the largest increase in people over 50 years. Changes in the underlying population have contributed to this, including the impacts of population increases after World War I, World War II and the 'baby boom' of the 1960s. A recent increase in risk or ascertainment within this population has caused an increase in cases in all age groups from 2004 to 2011. The seasonal increase in cases between weeks 18 (Early May) and 22 (Early June) was consistent across ages, years and regions and was most marked in children and in more rural regions. *Campylobacter* prevalence by week in each region correlated with temperature 2 weeks before. There were higher prevalences in areas with a low population density, low deprivation and lower percentage of people of ethnic origin. Data from sero-phage and multilocus sequence typing show a few common types and many uncommon types.

**Conclusions:** The drivers/mechanisms influencing seasonality, age distribution, population density, socioeconomic and long-term differences are diverse and their relative contributions remain to be established. Surveillance and typing provide insights into *Campylobacter* epidemiology and sources of infection, providing a sound basis for targeted interventions.

## ARTICLE SUMMARY

### Article focus

- *Campylobacter* is the most common bacterial cause of diarrhoea, affecting about half a million people annually.
- Chicken is thought to be the most common source of infection and the most common vehicle for transmission while environmental sources are suspected to play an important role the seasonality.
- A few types are common and many types are rare.

### Key messages

- *Campylobacter* is increasing in older people, particularly men, and population structure is partly driving this increase.
- Antibiotic resistance has increased over recent years.
- There are lower rates of reporting in more densely populated areas and more deprived areas.
- The distribution of types suggests that immunity may be important.

### Strengths and limitations of this study

- The study is large and captures patients from across the country, pulling together a good picture of the epidemiology of *Campylobacter*.
- The disease burden may be underestimated due to low reporting in deprived areas that may reflect poor access to healthcare or prior infection.

## INTRODUCTION

*Campylobacter* is the most common bacterial cause of gastroenteritis in many developed countries and has been the subject of extensive research, with over 7500 peer-reviewed articles with *Campylobacter* in the title. It has been estimated that in the UK there were

over half a million cases in the community in 2008–2009 and around 80 000 general practice (GP) consultations.<sup>1</sup> Chicken has been implicated as the source of infection in up to 80% of infections<sup>2</sup> and as the risk factor associated with transmission in 41%.<sup>3</sup> Actions to reduce the contamination of chickens in New Zealand have shown dramatic reductions in human cases.<sup>4–5</sup> Despite this, the epidemiology of *Campylobacter* remains complicated and some of the features seem difficult to explain. These include the strong seasonal increase in cases,<sup>6</sup> the higher rates of infection in men,<sup>6</sup> the changing age distribution,<sup>7</sup> the higher rates of infection and different risk factors in rural than in urban environments and the greater seasonality in rural than in urban environments.<sup>4–8–14</sup> The study was set up to review the data reported to national surveillance on human *Campylobacter* infections in England and Wales over the past 22 years to provide an overview of trends and possible drivers, mechanisms and transmission routes.

## METHODS

*Campylobacter* surveillance data reported from diagnostic laboratories in England and Wales from 1989 to 2011 were extracted from the Oracle (LabBase) database and analysed. Most of the analyses were for the period 1989 to 2009, but annual cases were extended to 2011 (2011 data provisional). All were laboratory-confirmed cases, most were symptomatic and included patients with extraintestinal infections. Standard antimicrobial testing methods, used in primary diagnostic laboratories, were predominantly disc diffusion methods. Where speciation was reported, it was conducted in diagnostic laboratories using conventional phenotypic methods. Cases were linked by postcode to lower-level super output area and medium-level super output area (MSOA), deprivation index, ethnic origin, population density and census data using data held on the Office for National Statistics website (<http://www.statistics.gov.uk/cci/nugget.asp?id=6>). Postcodes of the diagnostic laboratories involved in primary isolation were used to link cases to local weather parameters held by the Met Office for 2005 to 2009. Temporal data were adjusted from day of year using a 7-day rolling mean, systematic adjustments for the reduced reporting over bank holidays and for long-term trend.

Phenotypic typing results were on human isolates, predominantly from samples taken in defined studies rather than during routine sampling. Data for the period of 1989 to 2009 included patients in a *Campylobacter* sentinel surveillance project,<sup>15</sup> a case–control study<sup>3</sup> and miscellaneous other sources. The majority of isolates were collected in a systematic way from all age groups, although the case–control study was confined to adults older than 18 years. Serotyping and phage typing were conducted at HPA Colindale using standard protocols,<sup>16–17</sup> and multilocus sequence typing (MLST) used recognised methods.<sup>18</sup> Data from clinical samples are archived on the PubMLST database along with

isolates from other sources, and figures are those entered in the database to September 2011.

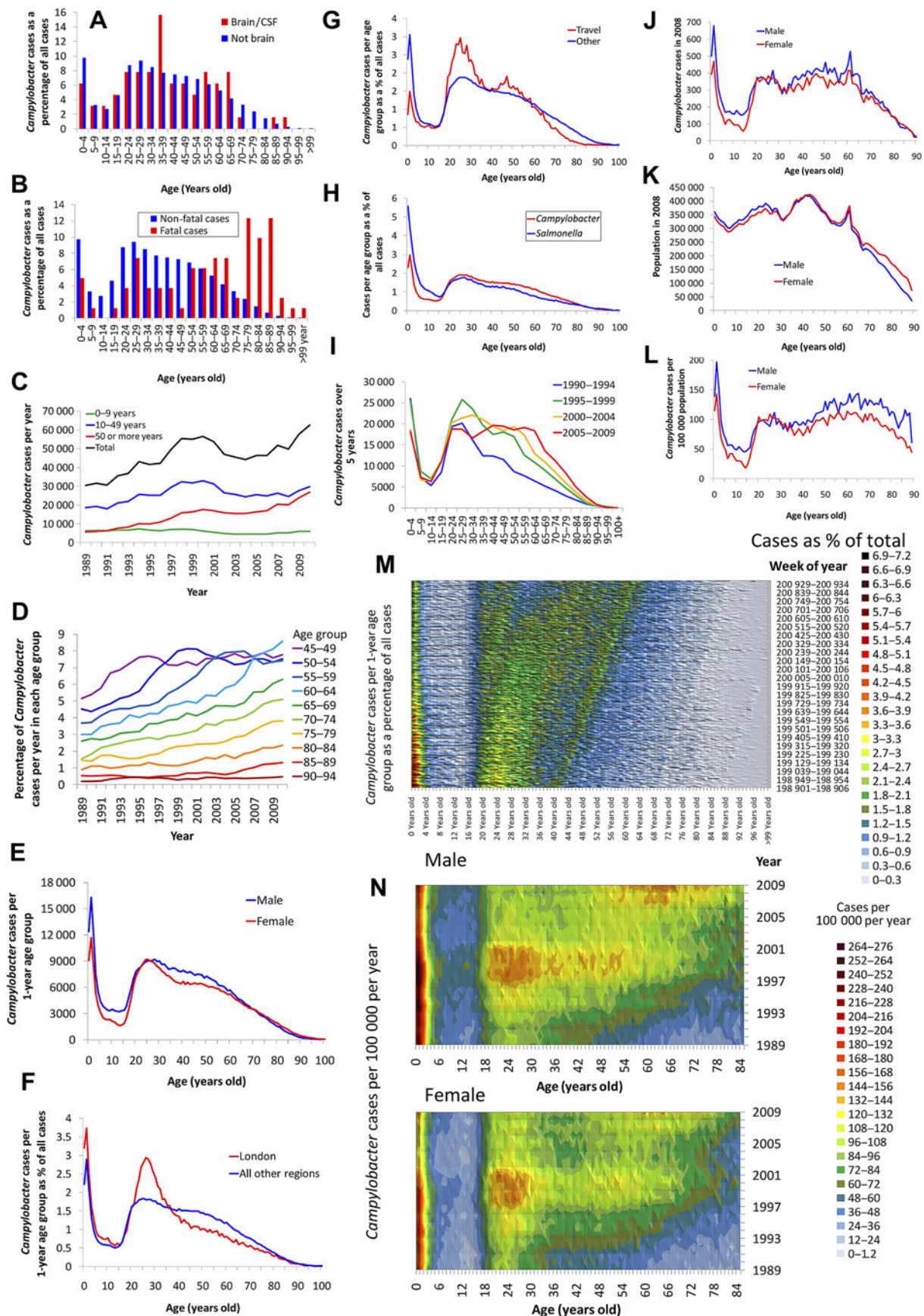
## RESULTS

### Clinical presentation

Routine surveillance of 994 791 *Campylobacter* patients between 1989 and 2009 showed that they were predominantly from gastrointestinal sites (99.65%) and were associated with diarrhoea. There were 82 *Campylobacter*-related deaths (0.008%). Overall, 242 (0.25%) of isolates were from infections involving a sterile body site, including blood (1665), brain or cerebrospinal fluid (67), wounds (45), cardiac prostheses (15), peritoneum (6) and joints (3). A majority of *Campylobacter fetus* cases (61 of 72; 85%) were invasive and 75% of *C. fetus* patients were older than 50 years compared with 44% of all *Campylobacter* isolates. Invasive infections were below 0.13% of all infections in people younger than 60 years (1013/793 874), but represented 0.37% of those between 60 and 79 years (539/145 533) and 0.78% of infections in people older than 80 years (190/24 252). Central nervous system cases were spread across the age groups in a broadly similar distribution to non-CNS cases when examined as a percentage of all cases (figure 1A), whereas fatal cases were more common in people older than 60 years than in other ages (figure 1B). There were 48 *Campylobacter* patients with Guillain–Barré or Miller–Fisher syndromes. Published studies indicate that the rate of Guillain–Barré syndrome in *Campylobacter* infections, when examined using a general practice research database,<sup>19–20</sup> was higher by a factor of 10–40 times in England, with an estimated 1.17 cases per 1000 per year.<sup>21</sup> Three patients with *Campylobacter* had haemolytic uraemic syndrome, but without evidence that *Campylobacter* was the cause. Because reporting is passive and reliant on clinical details being recorded, there is likely to be under-reporting in both Guillain–Barré or Miller–Fisher syndromes and mortality data and differences in ascertainment of these between regions.

### Long-term changes

There were 1 109 406 laboratory-confirmed cases reported to national surveillance between 1989 and 2011. Cases in 2011 were 45% above 2004 figures and 3% above 2010 figures (figure 1C). The cases rose from 33 280 in 1989 to a peak of 58 235 in 2000 before dropping to 44 544 in 2004 and rising to a maximum 64 582 in 2011 (2011 data provisional). There was a marked long-term increase in the percentage of cases in people older than 50 years (figure 1D), with a decline in the incidence in babies and children younger than 10 years from 2000 and a subsequent increase from 2006 to 2010. Figure 1C shows an increase in cases within all three age groups between 2004 and 2011 (<10, 36%; 10–49, 25%; 50+, 81%), but for the period 1994 to 2000, a 17% decrease in babies and children younger than 10 years, an increase in ages 10–49 years of 28% and an increase in people older than 50 years by 75%.



**Figure 1** Age distribution. Data from 1 109 406 laboratory-confirmed cases reported in England and Wales to national surveillance between 1989 and 2011. (A) *Campylobacter* isolates from patients with and without meningitis in different age groups as a percentage of all cases, 1989–2009. (B) *Campylobacter* isolates from fatal and non-fatal cases in different age groups as

## Age distribution

There were 14% more reported *Campylobacter* cases in men than in women and a 1.14 M/F ratio across most ages (figure 1E). This was mirrored by the age-specific prevalence, which showed a 30% higher prevalence in men compared with women across most age groups (figure 1L). The age distribution varied geographically, with London having more infections in young adults and less in people older than 40 years (figure 1F). The age distribution of travel-related cases showed lower rates in children and people over 60 years and more cases in people between 20 and 35 years (figure 1G). The age distribution of cases between 1989 and 2010 differed significantly between *Salmonella* and *Campylobacter*, with a higher proportion of *Salmonella* cases in children and a higher proportion of *Campylobacter* cases in adults (figure 1H). The age structure of cases has shifted over 20 years with more infection in older people in recent years (figure 1I). For example, comparison of *Campylobacter* data from 2008 (figure 1J) with 2008 population estimates (figure 1K) shows the impact of the age structure of the population on the prevalence in 2008 (figure 1L). The steady increase in the percentage of people older than 50 years (figure 1M) partly reflects ageing of the underlying population. When examined as an age-specific prevalence, there has been a recent increase in infections in older people, particularly in men (figure 1N). There was also an increase in 20–32-year-olds of both sexes around 2000 that was linked to the general increase in cases at this time. There was also a decline in the prevalence in children younger than 4 years from 2000 onwards. The seasonality of *Campylobacter* was much more marked in young children than in other ages (figure 2).

## Typing

*Campylobacter* isolates from human cases between 1989 and 2009 (29 081/994 791; 2.9%) could be differentiated into 64 serotypes (HS), 86 phage types (PT) and 949 combined HS/PT types. Isolates of *Campylobacter jejuni* contained 57 serotypes, 80 phage types and 866 HS/PT types and two thirds of serotypes of *C. jejuni* were represented in seven serotypes (table 1). *Campylobacter coli* contained 25 serotypes, 30 phage types and 102 HS/PT types, with five serotypes making up 84% of isolates (table 1). When the combined ST/PT of typable isolates were examined, then no type exceeded 9% of the total typed *C. jejuni* and 18% of typed *C. coli* strains. Among the combined HS/PT types, most isolates had few repre-

sentatives (figure 3A), although the distribution differed when HS and PT were examined separately (figure 3B). Only 18 013 of 26 688 (67%) *C. jejuni* isolates and 1936 of 2393 (81%) *C. coli* isolates were typable. When combined as HS/PT type, this decreased to 16 362 of 26 688 (61%) for *C. jejuni*, making phenotyping a poor tool for use in epidemiological investigation. Most of the HS/PT typing was undertaken between 2000 and 2004.

For the MLST data, all human cases reported on the PubMLST database were grouped by the seven sequenced genes (figure 3C–J), the ST and CC (figure 3K; table 1). Up to September 2011, there were 33 CCs and 757 STs among isolates from people with *Campylobacter* submitted to the PubMLST website (<http://pubmlst.org/campylobacter/>). 94.8% of *C. coli* were of one type (ST-828 complex) and 34.2% of *C. jejuni* of two types (ST-21 complex and ST-257 complex). While most isolates clustered into one of the predominant CCs, the STs showed a distribution with a few common types and many types with low numbers of isolates (figure 3C–J). This may partly reflect the submission patterns for the PubMLST database, with 'rare' STs over-represented as a proportion of all isolates, although a similar distribution was found for the combined HS and PT types (figure 3A) where this was not an issue. The distribution of individual serotypes and phage types (figure 3B) mirrored that of the CCs (figure 3I).

## Antimicrobial resistance

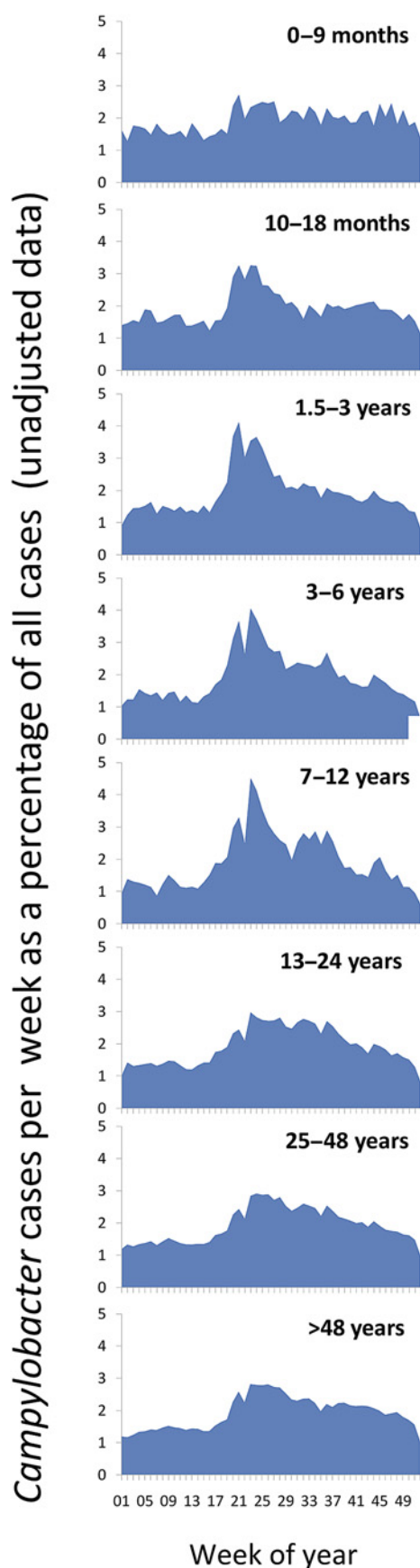
Over the period from 1989 to 2009, there was an increase in the percentage of *Campylobacter* isolates that were fully or intermediately resistant to ampicillin, ciprofloxacin, nalidixic acid, tetracycline and erythromycin (figure 4A). The percentage of strains that were resistant to ciprofloxacin was higher in people who had recently travelled abroad (1042/1601; 65%) compared with those who had not (2005/6530; 31%) and where travel status was not recorded (28 646/90 095; 32%). Isolates with high rates of resistance to ciprofloxacin were found in people who had travelled to India (79%), Egypt (79%), Spain (78%) and Thailand (80%).

## Weekends, bank holidays and other holidays

The onset date was not reported for most *Campylobacter* infections; the specimen date was recorded in surveillance. Specimens with any single weekday ranged from 16.8% to 22.3% (average 19.0) of all cases, whereas cases were less common on Saturday (2.5%–4.1%; average

[Continued]

a percentage of all cases, 1989–2009. (C) *Campylobacter* cases per year from 1989 to 2011 by age (2011 data provisional). (D) *Campylobacter* cases per year 1989–2010 as a percentage of cases in different age groups over 45 years. (E) *Campylobacter* cases by age and sex, 1989–2009. (F) *Campylobacter* cases by age as a percentage of all cases for London and all other areas, 1898–2009. (G) *Campylobacter* cases in people who had recently returned from abroad and all other cases, 1989–2009. (H) Age distribution of *Salmonella* and *Campylobacter*. (I) Change in age distribution over four 5-year time periods. (J) *Campylobacter* age and sex distribution in 2008. (K) Population age and sex distribution in 2008. (L) *Campylobacter* cases per 100 000 in 2008 by age and sex. (M) *Campylobacter* cases per 1-year age group as a percentage of all cases per year, 1989–2009. (N) *Campylobacter* prevalence per 100 000 per year between 1989 and 2009 by age and sex. CSF, cerebrospinal fluid.



**Figure 2** The weekly distribution of *Campylobacter* cases as a percentage of all cases over different age groups (unadjusted data).

3.2) and Sunday (1.4–2.1; average 1.7%), presumably reflecting problems accessing medical services on weekends. This would include access to GP, hospital or diagnostic laboratory. The reporting of infections was on average 28% lower in the 7 days of bank holiday weeks, presumably reflecting difficulties in accessing medical services. There was extra reporting in the week following some bank holiday weeks, suggesting that some cases are merely delayed by the holiday (figure 4B). Other school holidays (eg, half term) may have some effect on case reporting but are more difficult to determine as they are arranged locally rather than nationally. There was no long-term trend in the bank holiday effect. August bank holidays are during a period when there is no school attendance, and school holidays are therefore less likely to contribute.

### Seasonality

Cases were normalised to take account of day of week, bank holidays and long-term trend. This was applied to daily infection rates to create a well-defined time series that shows a regular seasonal increase in the late spring with some of the features of an annual epidemic (figure 4C), as previously observed,<sup>22</sup> and is followed by a gradual decline over the rest of the year. The timing of the increase varies slightly between regions and between years. The increased rate of infection between weeks 18 (Early May) and 22 (Early June) is consistently seen every year in all regions but is more pronounced in young children (figure 4D,E), in some regions than others, and was less marked in London (figure 4F). Cases in this period represent 8%–12% of all annual cases and show a dramatic change over a few weeks in the exposure of people to infection, as short-term changes in ascertainment or susceptibility are unlikely. There was a relationship between *Campylobacter* prevalence and temperature that was partly a reflection of the higher seasonality in summer months when it is warmer (figure 4K) but could also represent a temperature-sensitive driver.

### Postcode prevalence

The patient postcode is required to determine the local prevalence of *Campylobacter* and to produce maps of the MSOAs (figure 4G). However, in 2009, only 76% of patient surveillance records had an associated postcode, so the actual prevalence for some MSOAs was higher than this. The prevalence was higher in young children than in other ages (figure 1L). Overall prevalence in England and Wales for 2009 was 105 per 100 000 per year. *Campylobacter* prevalence in some MSOAs was artificially lowered due to low postcode reporting. These maps show some areas with much higher rates of infection locally (320–1290 cases per 100 000) that were not all in areas of low population density. When MSOAs were examined, 76.5% of the areas had between 10 and 150 *Campylobacter* cases per 100 000 per year, with 10.9% showing <10 per 100 000 per year and 12.6% having between 150 and 560 per 100 000 per year.

**Table 1** Serotypes (HS)\*, phage types (PT)†, MLST sequence types (ST) and MLST clonal complexes (CC) of *Campylobacter jejuni* and *Campylobacter coli* in England and Wales, 2000–2009‡

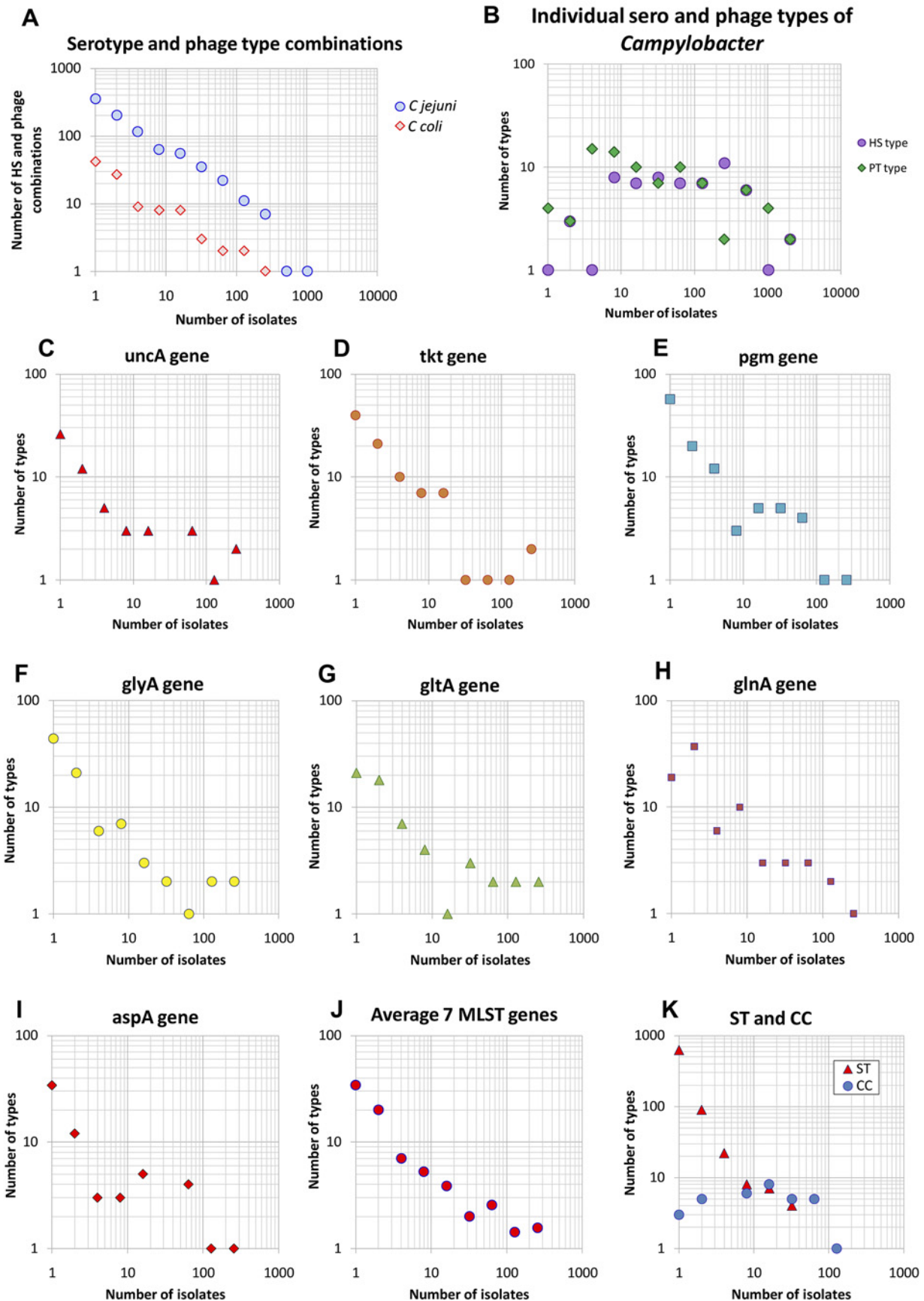
Serotype	C. jejuni	C. coli	Total	Phage type	C. jejuni	C. coli	Total	Clonal complex	From PubMLST dataset	Sequence type	From PubMLST dataset
HS				PT				CC	C. jejuni	ST	C. coli
HS1	397		397	PT1	8647	201	8848	CC 21	268	ST 5	17
HS2	778	2	780	PT2	2681	758	3439	CC 22	22	ST 17	4
HS3	155		155	PT3	4		4	CC 42	19	ST 19	25
HS4	691		691	PT4	7		7	CC 45	92	ST 21	44
HS5	592		592	PT5	1636	5	1641	CC 48	79	ST 22	9
HS6	466		466	PT6	538	7	545	CC 49	16	ST 42	6
HS7	22		22	PT7	8	139	147	CC 52	24	ST 44	3
HS8	398		398	PT8	545	11	556	CC 61	51	ST 45	31
HS9	357	33	390	PT9	15		15	CC 206	51	ST 47	7
HS10	22		22	PT10	63	2	65	CC 257	117	ST 48	32
HS11	203		203	PT11	13		13	CC 283	16	ST 49	7
HS12	347	1	348	PT13	12		12	CC 353	80	ST 50	27
HS13	4008		4008	PT14	557	3	560	CC 354	40	ST 51	35
HS14	13	263	276	PT15	34	1	35	CC 362	2	ST 52	6
HS15	19	1	20	PT16	1		1	CC 403	19	ST 53	22
HS16	161		161	PT17	63	5	68	CC 433	3	ST 61	26
HS17	2		2	PT18	63		63	CC 443	58	ST 93	7
HS18	889	1	890	PT19	473	1	474	CC 446	11	ST 104	15
HS19	386		386	PT20	336		336	CC 460	14	ST 137	7
HS21	295		295	PT21	138		138	CC 464	9	ST 205	4
HS22	31		31	PT22	4		4	CC 508	3	ST 206	11
HS23	280		280	PT23	23		23	CC 573	12	ST 227	6
HS24		32	32	PT24	14		14	CC 574	40	ST 233	3
HS25		4	4	PT25	100	2	102	CC 607	22	ST 257	59
HS26		9	9	PT27	1		1	CC 658	30	ST 262	7
HS27	239		239	PT28	14		14	CC 661	12	ST 267	7
HS28	3	259	262	PT29	9	3	12	CC 677	1	ST 311	3
HS29	1		1	PT30	3		3	CC 692	2	ST 353	6
HS30	33	17	50	PT31	7		7	CC 702	2	ST 354	14
HS31	1315	2	1317	PT32	9	9	18	CC 828	1	ST 356	5
HS32	11		11	PT33	1726	4	1730	CC 1034	9	ST 367	5
HS33	28		28	PT34	1499		1499	CC 1287	1	ST 397	3
HS34	3	10	13	PT35	630	1	631	CC 1332	1	ST 400	9
HS35	69		69	PT36	573	2	575	No CC	166	ST 436	3
HS36	9		9	PT37	4		4	Total	1293	ST 447	3
HS37	892		892	PT38	150	1	151			ST 464	3
HS39		9	9	PT39	968	27	995			ST 475	7
HS40	20		20	PT40	117	1	118			ST 572	8
HS41	9		9	PT41	20		20			ST 573	4
HS42	57		57	PT42	6		6			ST 574	29
HS43	33		33	PT43	32		32			ST 583	7
HS44	127		127	PT44	922	927	1849			ST 607	5
HS45	10		10	PT45	34		34			ST 658	9
HS48	1	23	24	PT46	4		4			ST 814	3
HS49	1	200	201	PT47	2		2			ST 824	3
HS50	3528		3528	PT48	64		64			ST 825	0
HS51	2	41	43	PT49	5		5			ST 827	0
HS52	50		50	PT50	15		15			ST 828	0
HS53	2		2	PT51	3		3			ST 829	0
HS55	70		70	PT52	10		10			ST 843	3
HS56	7	699	706	PT53	75		75			ST 872	0
HS57	42		42	PT54	127		127			ST 877	3
HS58	2		2	PT55	4		4			ST 883	5
HS59	4	32	36	PT56	18		18			ST 904	3
HS60	413		413	PT57	7		7			ST 977	3
HS61	1	82	83	PT58	19		19			ST 1009	0
HS62	10		10	PT59	18		18			ST 1079	3
HS63	217	1	218	PT60	13		13			ST 1371	3
HS66		215	215	PT61	11		11			ST 1374	3
HS67	117		117	PT62	170		170			ST 2496	3
HS68	101		101	PT63	139	2	141			ST 3466	3
HS69	74		74	PT64	87	2	89			ST 2 cases	126
UT	8675	457	9132	PT65	102	1	103			ST 1 case	572
Total	26688	2393	29081	PT66	16	3	19			ST unknown	7
				PT67	201	1	202			Total	1293
				PT68	6		6				101
				PT69	11	1	12				1394
				PT70	8		8				
				PT71	20		20				
				PT72	7		7				
				PT73	66		66				
				PT74	18		18				
				PT75	61		61				
				PT76	12		12				
				PT77	43		43				
				PT78	20	1	21				
				PT79	9	3	12				
				PT80	147		147				
				PT81	1		1				
				PT82	47	2	49				
				PT83	5		5				
				PT84	7		7				
				PT85	4		4				
				PT86	1		1				
				PT87	1052	53	1105				
				PT88	1334	214	1548				
				PT89	26688	2393	29081				

While isolates from some HS/PT types were confined to *C. jejuni* or *C. coli*, 17 types occurred in both, although in most there was a predominance of one species. The exception was HS9 PT44, which was roughly equal in numbers. Other types included HS12 PT44, HS14 PT1, HS14 PT44, HS18 PT2, HS2 PT44, HS30 PT1, HS31 PT39, HS34 PT1, HS49 PT2, HS51 PT2, HS56 PT2, HS56 PT44, HS61 PT1, HS9 PT1, HS9 PT2. It is notable that in isolates showing the same phage and serotype pattern between *C. jejuni* and *C. coli*, the HS56, HS9, PT1, PT2 and PT44 phenotypes were prominent.

\*Two thirds of serotypes of *C. jejuni* were represented in seven serotypes (HS13, 22%; HS50, 20%; HS31, 7%; HS37, 5%; HS18, 5%; HS2 and HS4, 4%).

†84% of *C. coli* were in five serotypes (HS56, 36%; HS14, 14%; HS28, 13%; HS66, 11%, HS49, 10%).

‡Campylobacter typing results are from *C. jejuni* and *C. coli*, but other species identified at HPA Colindale were: *Arcobacter butzleri* (50), *A. cryaerophilus* (4), *A. species* (1), *Campylobacter fetus* (123), *C. hyointestinalis* (2), *C. lari* (8), *C. upsaliensis* (50), *Helicobacter canadensis* (2), *H. cinerea* (1), *H. pullorum* (2).



**Figure 3** Typing. Typing data on cases of *Campylobacter* from England and Wales, 1989–2009. Data in the HPA data set (29 081 isolates) includes the number of *Campylobacter jejuni* and *Campylobacter coli* combined serotype (HS) and phage type (PT) combinations (HS/PT) against the number of isolates in each type (A) the separate HS and PT types for *C jejuni* and *C coli* (B).

### Population density, urban/rural distribution, ethnicity and deprivation

For years 2007 to 2009 data, population density and deprivation were derived from the postcode data. Cases of *Campylobacter* per 100 000 population were higher in areas of low population density (rural) compared with areas of high population density (urban settings) (figure 4I). Less postcode reporting in areas of high population density or deprivation could introduce some bias; however, subset analysis of areas with over 90% postcode reporting still showed higher prevalence in areas of lower population density. The reason for the urban/rural difference remains unclear but could reflect proximity to ruminants and other farmed animals or differences in access to healthcare. There was an inverse relationship between *Campylobacter* prevalence and the Oxford Index of Multiple Deprivation. People with *Campylobacter* from deprived areas were less frequently reported to surveillance than in less deprived areas (figure 4J). The reason could reflect different diets, prior exposure conferring some resistance or reduced access to healthcare. The prevalence of *Campylobacter* in communities where more than 95% of the population was 'white British' was greater than those where the percentage was <50%, possibly due to poorer access to healthcare, greater susceptibility or increased exposure.

### Overseas travel

Overseas travel to both EU and non-EU countries was associated with almost a fifth of all *Campylobacter* infections in data from enhanced surveillance. Spain, the country most visited, remains the country with the largest source of travel-related cases. Routine surveillance of travel-related cases shows poor and inconsistent ascertainment. Less is known about the risk factors responsible for travel-related *Campylobacter* than from indigenous infections and the risks may vary between countries visited.

### Chicken production

The long-term change in *Campylobacter* cases in England and Wales was compared with poultry produced in the UK after removing exports and including imports (figure 4H). Data were from the Defra website (<http://www.defra.gov.uk/statistics/foodfarm/food/slaughter/>). Chicken production was used as a surrogate for chicken consumption and showed that over the 23-year period the relationship was not linear, implying that *Campylobacter* prevalence is not directly related to the amount of chicken consumed.

## DISCUSSION

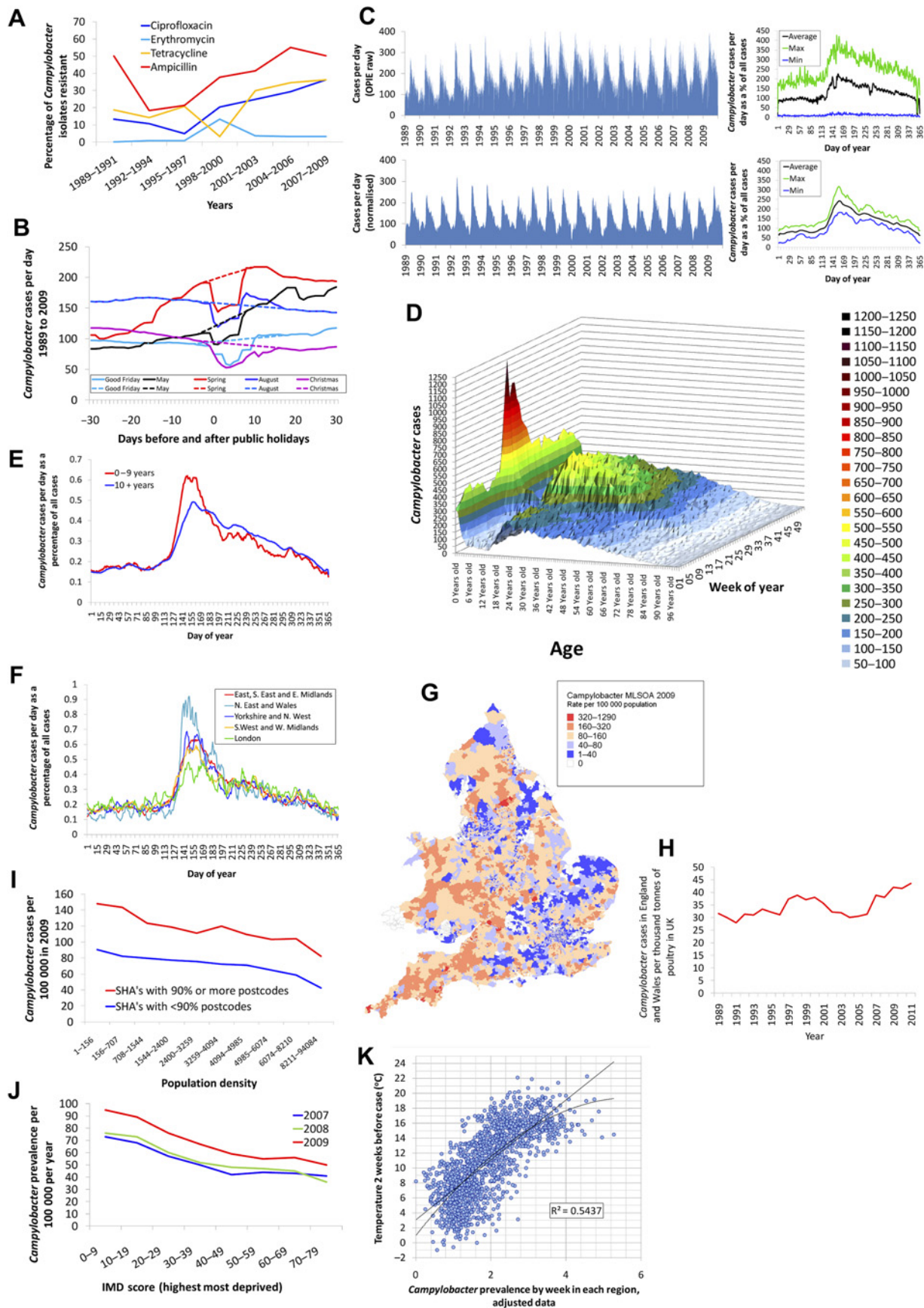
The reasons for large long-term changes in *Campylobacter* cases, the spring increase, the increase in older people,

the higher cases in rural communities and more cases in less deprived people could be related to features of diagnosis and reporting (commonly referred to as ascertainment) or of disease within the population as a result of increased exposure or susceptibility (here referred to as risk). The increase in cases in all three age groups between 2004 and 2009 can be compared with the period 1994 to 2000 where there was a decrease in cases in babies and children younger than 10 years, the increase in cases in people aged 10–49 years and the large increase in people older than 50 (figure 1C). This suggests that the drivers are complex and may include changes in attribution and risk. It has been suggested that some of the cases in children may be less likely to attend a physician and have a specimen taken as a result of the triaging associated with NHS Direct,<sup>7</sup> although the people responding to NHS Direct are a small proportion of those with diarrhoea.<sup>1</sup>

In order to examine the impacts of various factors on the long-term change, seasonal increase, increase in people more than 50 years old, the urban/rural split and the socioeconomic factors, a table was drawn up (table 2). The increase in *Campylobacter* in patients older than 50 years between 2004 and 2010 is dramatic and may be linked to proton pump inhibitor use. These drugs may increase people's susceptibility to *Campylobacter*,<sup>3 8 23–25</sup> and the older population group are more likely to be taking these drugs than the younger ones. The underlying demographic drive in figure 1M, where the increased birth rate after World War I and World War II and the 1960s baby boom is represented by diagonal lines, shows the impact of population size on *Campylobacter* cases over the years. This demographic drive is likely to contribute to the age distribution of cases, as the number of older people in the population is increasing but may also influence year-on-year changes. The economic downturn, which began in 2008, may have changed people's eating habits and exposed people to foods that are more commonly contaminated with *Campylobacter*. Alternatively, the chicken products within retail shops may have become more contaminated or there could be increased consumption of more contaminated products like chicken liver. There may also be effects resulting from a reduction in GP consultations for infectious intestinal disease.<sup>26</sup> The increase in cases since 2004 seems to be across all ages. People may be eating outside the home more than they were 20 years ago and travel abroad is more common. Some of the discontinuities in laboratory reporting may have an impact on long-term trends as the data show particular periods where reporting was incomplete. However, there is also evidence from laboratories that have consistently reported over the 20-year surveillance period that the

[Continued]

The PubMLST database (1394 isolates) shows the number of types from human cases against the number of patient isolates. The figures represent individual sequenced genes for *uncA* (C), *tkf* (D), *pgm* (E), *glyA* (F), *gltA* (G), *glnA* (H) and *aspA* (I), with an average of the seven genes (J) and the individual ST and CC (K).



**Figure 4** Resistance, spatial, social and temporal distribution. (A) Resistance of *Campylobacter* isolates to antibiotics between 1989 and 2009. (B) *Campylobacter* cases per day before and after bank holidays in England and Wales, 1989–2009. The dotted line represents an estimate of the cases that would have occurred if there had not been a bank holiday. (C) Time series of

rates of long-term change were similar to those for all laboratories. There could have been systematic change in recent years in the efficiency of isolation, either through reduced specimen delay or improved culture media or culture conditions (eg, atmosphere). In a longitudinal study of infectious intestinal disease, detection of *Campylobacter* was better with culture and/or PCR than with culture alone.<sup>1</sup> In addition, there was better isolation by culture alone in community cases than in those presenting to GPs when compared with culture and PCR, possibly reflecting greater delay in GP samples being sent for culture compared with community cases (Tam, personal communication).

### Seasonality

The late spring increase in cases, particularly in children where the increase over a few weeks can be fourfold in some regions, has remained an enigma for many years<sup>6 27 28</sup> and implies a seasonal driver that is probably indirect and related to environmental and climatic conditions.<sup>6</sup> The seasonality differs by region, by year and by latitude and longitude, suggesting that weather combined with the farming environment is important. Possible drivers include increased contamination of chicken<sup>29–32</sup> and transmission by flies<sup>22 33</sup> (table 2). Published evidence indicates that children in rural areas are more likely to be infected with ruminant strains,<sup>10</sup> presumably from direct or indirect contamination from the environment. Data on seasonal distribution (figure 4C), and from typing data (table 1), make it unlikely that a single common source is the driver and imply contamination from multiple sources. There remains a need to tease out the contributions from possible drivers. There is a similar seasonality in *Campylobacter* contamination of chicken flocks<sup>34</sup> and human disease<sup>35</sup> where environmental drivers may be important.<sup>6 28 36</sup> While the seasonality of human infections correlates with climatic variables<sup>28 36</sup> and chicken contamination,<sup>37 38</sup> the rise in human cases can precede that in chickens,<sup>39</sup> consistent with a common factor causing the increase in both. It has been suggested that flies might be the route by which *Campylobacter* enter chicken flocks,<sup>40–42</sup> and some modelling of chicken data supports this hypothesis.<sup>43</sup> In addition, transmission of *Campylobacter* to humans by flies has been hypothesised as a way of explaining the characteristic seasonality of human *Campylobacter* infections,<sup>22 33 44</sup> although testing this may prove difficult.<sup>45</sup> The seasonal distribution of

*Campylobacter* in different countries may be related to their differing weather patterns.<sup>28</sup> While water-based hypotheses are attractive because *Campylobacter* is common in natural waters, the general absence of geographically located point-source outbreaks would be inconsistent with this transmission route contributing to seasonality. Travel-related infections are seasonal but do not coincide with the spring increase.

### Typing

The typing of *Campylobacter* isolates has proved useful in outbreak investigation using HS/PT typing and MLST typing and also in attributing strains to particular host sources using MLST typing.<sup>46 47</sup> The distribution of different HS/PT types, with a few common types and a long tail of rare ones, is similar to that previously reported for *Campylobacter* using MLST typing, but the ability to group into clonal complexes makes MLST a more practical scheme for attribution. These data provide some indication of the potential diversity of phenotypes that reflect the labile genetic structure of this organism.

Data on the individual seven MLST alleles and on the HS/PT typing provide a way of looking at the genetic diversity of *Campylobacter* isolates from human infections. The frequency of different types from PubMLST may be influenced by inconsistencies in data submission and by bias towards rarer types so more unusual types appear than they would in a natural population. For the Sentinel Surveillance data, the isolates were collected in a more systematic way and are therefore more representative. The observed distribution for individual MLST alleles, for ST types and for combined HS/PT types might suggest that the most common types are perhaps those most easily able to propagate themselves within human or animal hosts. However, there is little evidence supporting this conjecture. The CCs have a clear utility in gathering up the organisms that are genetically similar, with the result that there is a different distribution with many CCs having more isolates within them, making source attribution more straightforward. The CCs shows a rough similarity, in comparing the number of isolates of different type, to the individual HS types and to the individual PT types.

### Antibiotics

The increasing resistance of isolates to antibiotics is partly due to an increase in quinolone resistance in

[Continued]

*Campylobacter* by day of year 1989–2009 showing unmodified data (OPIE raw), data adjusted for day of week (OPIE), for bank holidays (adjusted) and also adjusted for long-term trend (normalised). (D) *Campylobacter* cases by age and week of year. (E) Seasonal distribution of cases over and under 10 years of age (normalised data). (F) Regional differences in seasonal distribution (normalised data). (G and H) *Campylobacter* prevalence per 100 000 for 2009 based on the medium-level lower super output areas (MLSOA) (H) *Campylobacter* cases in England and Wales per thousand tonnes of poultry in the UK. (I) *Campylobacter* cases per 100 000 in 2009 by population density and completeness of postcode reporting. (J) *Campylobacter* prevalence per 100 000 per year and the Index of Multiple Deprivation (IMD) score. Differences between 2007 and 2009 reflect improving postcode reporting as cases cannot be included in the figures without a postcode. (K) *Campylobacter* prevalence by week in each region against the local temperature 2 weeks before the case specimen date (2005–2009).

**Table 2** The main hypothesised drivers/mechanisms/transmission routes for changes in *Campylobacter*

Hypothesised contributing factor	Estimated likelihood of causing				
	Long-term change	Seasonal spring increase	Increase in adults older than 50 years	More rural than urban cases	More cases in the more affluent
Surveillance ascertainment					
Impacts of NHS Direct	Medium	Low	Low	Low	Low
National reporting	Medium	Low	Low	Low	Low
Changes in the surveillance system	Low	Low	Low	Low	Medium
Changes in <i>Campylobacter</i> culture media	Medium	Low	Low	Low	Low
Laboratory testing policy	Medium	Low	Low	Low	Low
New laws requiring laboratory notification of <i>Campylobacter</i> *	Low	Low	Low	Low	Low
Susceptibility					
Increased proton pump inhibitor use	High	Low	High	Low	Low
Immunity through prior exposure or infection	Low	Low	Low	Low	Medium
Physiological differences between gender	Low	Low	Low	Low	Low
Exposure					
Increased contamination of chicken	High	Medium	Low	Low	Low
Increased consumption of chicken	Medium	Low	Low	Low	Medium
Increased systemic <i>Campylobacter</i> infection in chicken	High	Medium	Low	Low	Low
Sourcing chicken from different areas	Medium	Low	Low	Low	Medium
Increase in non-chicken-related sources	Low	Low	Low	Medium	Low
Transmission from cattle to chickens by flies	Low	High	Low	Low	Low
Transmission from faeces or raw meat to ready-to-eat food by flies	Low	High	Low	High	Low
Biosecurity interventions for <i>Salmonella</i> control	Medium	Low	Low	Low	Low
Country walks	Medium	Medium	Medium	High	Medium
Contamination from agricultural animals	Medium	Medium	Low	High	Medium
Contamination from pets	Low	Medium	Low	Medium	Low
Contamination from wild birds	Low	Medium	Low	Low	Low
Food preparation involving raw meats	Medium	Low	Low	Medium	Low
Educational farm visits	Medium	Medium	Low	Medium	Medium
Barbecued or grilled meat	Medium	High	Medium	Low	Low
Private or untreated water supplies	Low	Medium	Low	Medium	Medium
Mains drinking water	Low	Low	Low	Low	Low
Surface water/sewage exposure	Medium	Medium	Low	Medium	Low
Social factors					
Population ageing/demographic change	High	Low	High	Medium	Low
The economic situation	Medium	Low	Low	Low	Medium
Socioeconomic status	Medium	Low	Low	Medium	High
Changes in <i>Campylobacter</i> in other countries	Medium	Medium	Low	Low	Low
Kitchen behaviour	Low	Low	Low	Low	Low
GP access	High	Low	Low	High	High
Two weekly waste bin collections	Low	Low	Low	Low	Low
Travel abroad	Medium	Low	High	Low	High
Eating out	Medium	Low	Medium	Low	Medium
Environmental factors					
Temperature	Low	Medium	Low	Low	Low
Rainfall	Low	Low	Low	Low	Low
Latitude/longitude	Low	Medium	Low	Medium	Low

The evidence for the above scoring is included as a supplementary file with this paper.

\*Human disease notification.

people returning from travel abroad and partly increased resistance to other antibiotics in isolates from all areas. The rise in resistance to erythromycin has been less dramatic and does not show an association with foreign travel. It is therefore probably related to domestic human use of this drug.

### Poultry

This study suggests that long-term changes in *Campylobacter* infection in humans do not correlate well with poultry production. This suggests that the degree of contamination may be more important than the total poultry weight produced. Most human infections are

caused by *C jejuni* and *C coli*. Large studies have indicated that the *Campylobacter* isolates causing human infection contain a large diversity of types. Attribution studies indicate that strains that are commonly found in chickens are found in a majority of human infections.<sup>2 48</sup> This implies that the source of the *Campylobacter* is chicken. Epidemiological studies of *Campylobacter* patient's risk factors suggest that contact with or consumption of chicken is important as the transmission route of infection. In published studies, the chicken attribution to source of *Campylobacter*<sup>2</sup> is higher than the risk factor data representing the transmission route.<sup>3</sup> This may result from transmission from chicken being indirect and not through the usual eating or handling routes. Chickens can carry multiple strains<sup>49</sup> and co-infection with more than one isolate occurs in about 8% of patients.<sup>50</sup>

### Disease burden

The disease burden from *Campylobacter* has been estimated to be 500 000 cases per year with 80 000 GP consultations, based on cohort and GP studies conducted over 16 months.<sup>1</sup> However, there could be substantial underascertainment in areas with greater deprivation and/or a larger ethnic population. It remains unclear why there are more cases in men than in women, and why infection is more common in rural than in urban environments.

### Implications

Research needs to be focused on intervention, which in turn requires a better understanding of the epidemiology. Typing data has been useful for attribution to sources and may also be useful in measuring the impact of interventions targeted at reducing the contamination of chickens. This work suggests that there could be advantages in using the archive of strains that have been typed by serotype and phage type as a resource for examining longer term changes by linking the phenotypic and MLST typing and applying source attribution. There is a need for whole genome MLST typing on a percentage of strains obtained through surveillance over a longer time period. However, there is also a need to better understand the drivers for change other than source (eg, transmission route, climate, impacts of immunity). The work suggests that the underlying population contributes significantly to the disease epidemiology and this is an area where further examination may be productive. The five elements of difference and the factors that are driving these are examined in table 2. It would be attractive to better understand whether the numerous rare types are a reflection of recent emergence as a result of immunological pressure or are just rare, with a longer pedigree. There is also scope for additional work on transmission vectors, such as flies, which seem to play a role in biosecurity problems and may also directly contribute to human disease.

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**Contributors** GLN compiled the surveillance data and did the descriptive analysis. JFR compiled the phenotyping data. SKS compiled the genetic typing data. CL linked surveillance data to geographic markers, population density and socioeconomic variables. CS linked the location and date with recent local rainfall and temperature. All contributed to the final manuscript.

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**Competing interests** None.

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**Data sharing statement** The descriptive data presented in the paper are available for use by others. Numbers for the figures are available as a supplementary file with this paper and on the Dryad website. The evidence base for table 2 is also available.

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Justification for the drivers in: **Table 2. The main hypothesised drivers for changes in *Campylobacter*.**

Below are the hypothesised contributing factor and their estimated likelihood of causing: 1. Long term change; 2. Seasonal spring increase; 3. Increase in adults over 50 years old; 4. More rural than urban cases; 5. More cases in the more affluent, in *Campylobacter* cases. The scoring as Low, Medium or High is on the basis of published literature and rational examination of the evidence base.

Table 2. The main hypothesised drivers for changes in *Campylobacter*.

Hypothesised contributing factor	Estimated likelihood of causing:				
	Long term change	Seasonal spring increase	Increase in adults over 50 years old	More rural than urban cases	More cases in the more affluent
<b>Surveillance ascertainment</b>					
Impacts of NHS Direct	Medium	Low	Low	Low	Low
National reporting	Medium	Low	Low	Low	Low
Changes in the surveillance system	Low	Low	Low	Low	Medium
Changes in <i>Campylobacter</i> culture media	Medium	Low	Low	Low	Low
Laboratory testing policy	Medium	Low	Low	Low	Low
New laws requiring laboratory notification of <i>Campylobacter</i> *	Low	Low	Low	Low	Low
<b>Susceptibility</b>					
Increased proton pump inhibitor use	<b>High</b>	Low	<b>High</b>	Low	Low
Immunity through prior exposure or infection	Low	Low	Low	Low	Medium
<b>Exposure</b>					
Increased contamination of chicken	<b>High</b>	Medium	Low	Low	Low
Increased consumption of chicken	Medium	Low	Low	Low	Medium
Increased systemic <i>Campylobacter</i> infection in chicken	<b>High</b>	Medium	Low	Low	Low
Sourcing chicken from different areas	Medium	Low	Low	Low	Medium
Increase in non-chicken related sources	Low	Low	Low	Medium	Low
Transmission from cattle to chickens by flies	Low	<b>High</b>	Low	Low	Low
Transmission from faeces or raw meat to RTE food by flies	Low	<b>High</b>	Low	<b>High</b>	Low
Biosecurity interventions for <i>Salmonella</i> control	Medium	Low	Low	Low	Low
Country walks	Medium	Medium	Medium	<b>High</b>	Medium
Contamination from agricultural animals	Medium	Medium	Low	<b>High</b>	Medium
Contamination from pets	Low	Medium	Low	Medium	Low
Contamination from wild birds	Low	Medium	Low	Low	Low
Food preparation involving raw meats	Medium	Low	Low	Medium	Low
Educational farm visits	Medium	Medium	Low	Medium	Medium
Barbecued or grilled meat	Medium	<b>High</b>	Medium	Low	Low
Private or untreated water supplies	Low	Medium	Low	Medium	Medium
Mains drinking water	Low	Low	Low	Low	Low
Surface water/ sewage exposure	Medium	Medium	Low	Medium	Low
<b>Social factors</b>					
Population aging/demographic change	<b>High</b>	Low	<b>High</b>	Medium	Low
The economic situation	Medium	Low	Low	Low	Medium
Socioeconomic status	Medium	Low	Low	Medium	<b>High</b>
Changes in <i>Campylobacter</i> in other countries	Medium	Medium	Low	Low	Low
Kitchen behaviour	Low	Low	Low	Low	Low
GP access	<b>High</b>	Low	Low	<b>High</b>	<b>High</b>
Two weekly waste bin collections	Low	Low	Low	Low	Low
Travel abroad	Medium	Low	<b>High</b>	Low	<b>High</b>
Eating out	Medium	low	Medium	Low	Medium
<b>Environmental factors</b>					
Temperature	Low	Medium	Low	Low	Low
Rainfall	Low	Low	Low	Low	Low
Latitude/longitude	Low	Medium	Low	Medium	Low

\*Human disease notification

**The Impact of NHS Direct** has been hypothesized to be to prevent a proportion of cases reaching surveillance as a result of a cohort being dealt with through NHS Direct and never having a laboratory examination. It is argued that this could have an impact on long-term reporting in children, but less so in adults (1). Others have argued that the impact of this is likely to be small (2). Because it is a systematic change in surveillance it would be unlikely to show as a seasonal effect. The steady increase in cases in the elderly suggests this effect has not had a substantial impact on reporting in the elderly. There is no evidence that any differential reduction of reporting should more greatly affect urban than rural or affluent than poor.

1. Long term change	Medium
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**National reporting** can be influenced by social factors with the bank holidays representing a particular example of a seasonal change that seems to be related to reduced access to primary healthcare services. Changes in national reporting could also have an impact on the number of annual cases reported as a result of local or national changes in the reporting process (anything from physician policy on faecal sample testing, laboratory policy on tests undertaken and completeness of reporting). These changes would be most obvious in influencing long-term changes in local or national reporting than they would in seasonal, adult, rural, or poor populations.

1. Long term change	Medium
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Changes in the surveillance system** that have occurred over the period of this study have included better data capture through computer reporting, the impacts of the change from PHLS to HPA, the more standardized data collection that began in 2002, changes in GP access including NHS Direct, the conducting of Sentinel Surveillance, CLASSP and case-control studies, which could have increased case numbers temporarily. There seem to be relatively few impacts of changes in surveillance on these five variables, and although the difference between more affluent and less affluent might be influenced by changes in the surveillance system these do not appear to be large if they occur at all.

1. Long term change	Low
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Medium

**Changes in *Campylobacter* culture** could influence the long term reporting of *Campylobacter*. The period of time between defecation and culture can influence isolation rate as can the antibiotic additives, the gas mixture and any enrichment used. There is little published information on the impact of these methodological factors on isolation, although the use of membrane methods in South Africa suggests that it is possible to routinely isolate a wider range of species using these methods, presumably because some strains such as *C. consisus* are more sensitive to the selective antibiotics used in *Campylobacter* isolation media. There is no evidence that this has had a significant impact on the five criteria, but if it had it would be most likely with the long term figures as culture methods have improved over time.

1. Long term change	Medium
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Laboratory testing policy** can greatly influence both national reporting and the age distribution of reported cases. The main impact would probably be on the completeness of reporting as measured by cases per year, rather than the other factors. Any changes would be likely to be over a long time period.

1. Long term change	Medium
2. Seasonal spring increase	Low

3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**New laws requiring laboratory notification of *Campylobacter*** might be found to have influenced national reporting as a result of voluntary laboratory reporting systems being made mandatory. At present this does not seem to be the case.

1. Long term change	Low
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Increased proton pump inhibitor use** has been postulated as an important factor in *Campylobacter* infection (3-6). Because the use of such drugs has increased over recent years there is a reasonable indication that the impact of there could have had a big effect on the overall numbers of cases of *Campylobacter* reported through surveillance, and because these are drugs frequently taken by older people then the higher incidence of infection in this group may be linked.

1. Long term change	High
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	High
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Immunity through prior exposure or infection** is found in a variety of enteric pathogens. With *Campylobacter* the argument is that some groups are more exposed to *Campylobacter* through chicken (7-9) with repeated infection comes a degree of resistance to symptomatic disease if not infection following exposure. The lower incidence of *Campylobacter* infection in people living in areas of low socioeconomic status could reflect lower exposure, poorer access to healthcare or more infection in childhood conferring resistance to infection as an adult. If community exposure to *Campylobacter* over the years has declined then one could expect more cases in the younger population rather than the observed increase in people over 50 years. In some case-control studies the recent consumption of chicken is protective, suggesting exposure is leading to immunity (10).

1. Long term change	Low
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Medium

**Increased contamination of chicken** might be an explanation for the increased cases over time. Chicken is commonly contaminated with *Campylobacter* and a significant fraction of human infection is thought to derive from chicken (11-19). There is some evidence that chicken flocks are more contaminated with *Campylobacter* in the summer, although this rise in contamination seems to follow the rise in human disease rather than precede it (20-25). The increase could be in percentage contamination of chicken or the heaviness of contamination. It is not impossible that a mechanism explaining a link between increased contamination of chicken and increases in the elderly or the more affluent might be possible, but is currently thought unlikely. If the seasonal contamination of flocks is caused by flies as has been suggested then this may play a role in both the seasonality of human disease and the increased seasonal contamination of chickens with cattle strains (check references). Cross contamination from chicken to salads and soft fruits (18;26-28) might be seasonal whereas to other ready to eat meals may not be. The types of *Campylobacter* on chicken may also be important in both seasonality and long term changes (29).

1. Long term change	High
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Increased consumption of chicken** could potentially be an explanation for a long term increase in human *Campylobacter* infection. However, there does not seem to be clear evidence that chicken consumption in England and Wales has had an

impact on the occurrence of human disease. The seasonality of *Campylobacter* is unlikely to be greatly affected by the seasonality of chicken consumption, although cross contamination of salad items might be expected to be more seasonal. As chicken is the commonest risk factor for *Campylobacter* infection, and it is a cheap food, then differences in socioeconomic status could affect chicken consumption and have an impact on infection, although there is no published evidence for this.

1. Long term change	Medium
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Medium

**Increased systemic *Campylobacter* infection in chicken** might expose people to infection more commonly if there are foci of infection in muscle and liver for example. The recent rise in outbreaks of *Campylobacter* infection are as a result of undercooking chicken livers. The contamination could be internal or external, but an explanation involving an increase in systemic or hepatic infection causing more livers to be internally contaminated might explain the long term increase in cases in general and the outbreaks in particular.

1. Long term change	High
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Sourcing chicken from different areas** might be a possible reason for an increase in *Campylobacter* in the longer term. This could be differences between *Campylobacter* contamination of chickens from different UK producers, but could also be those in other EU states and countries outside of the EU. There is little supporting evidence in this area.

1. Long term change	Medium
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Medium

**Increase in non-chicken related sources** remains a possibility for the long term increase in human *Campylobacter* infections. This is an area that may be resolved by source attribution. As non-chicken sources are more common in rural areas it will be interesting to see if the chicken related strains increase or decrease over time with interventions in chicken production. This has been observed in New Zealand following interventions to reduce chicken contamination (30-32).

1. Long term change	Low
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Medium
5. More cases in the more affluent	Low

**Transmission from cattle to chickens by flies** remains an important component of the biosecurity aspects of the control of *Campylobacter* in chicken flocks (33;34). As flies are seasonal and their numbers and activity have been hypothesized to coincide with the rise in flock contamination with *Campylobacter* and with human disease (35;36). Transmission from cattle to chicken flocks is more likely to occur in a rural setting, but chicken production is also likely to be rural so this may not have an impact on human disease.

1. Long term change	Low
2. Seasonal spring increase	High
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Transmission from faeces or raw meat to RTE food by flies** has been hypothesized as a transmission route that bypasses most of the HACCP food chain protection by the direct transmission of faecal contamination to ready to eat foods (35;36). This could

be expected to have a seasonal impact, and to be more marked in rural than urban areas. One could postulate that the poor might have greater exposure to flies than the rich but there is little evidence that this is the case in the UK. It is assumed that fly populations can change from year to year but are not the main driver for long term changes, or for the increase in adults.

1. Long term change	Low
2. Seasonal spring increase	High
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	High
5. More cases in the more affluent	Low

**Biosecurity interventions for *Salmonella* control** are an important part of the reductions in infection that have contributed to fewer *S. Enteritidis* infections over recent years (37). If these interventions work for *Salmonella* then it is reasoned that they could also have some impact on *Campylobacter* contamination of chicken flocks. It is possible that the reductions in *Campylobacter* during the early 2000's were associated with increased biosecurity and that the subsequent rise in cases has been as a result of less vigilant subsequent biosecurity because the vaccination is maintaining low *Salmonella* contamination rates in flocks.

1. Long term change	Medium
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Country walks** have been hypothesized as a source of exposure to *Campylobacter* becausee contamination of the environment is high. Although the sources of contamination are complicated, the country walk may be only one of a number of transmission routes (38). An increase in country walks could contribute to long term change, particularly in the elderly and more affluent. Walking could also contribute to seasonal changes in infection and is by it's nature more common in rural areas. However, evidence supporting this is not robust and the attributable fraction of people deriving their infections from country walks is probably low.

1. Long term change	Medium
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Medium
4. More rural than urban cases	High
5. More cases in the more affluent	Medium

**Contamination from agricultural animals** is a likely source for some *Campylobacter* infections because they are such a source of contamination within the agricultural environment (39). Large changes, such as the impacts of the 2001 foot and mouth outbreak, could have contributed to long term changes, and putting agricultural animals out to pasture in the spring may also contribute to direct or indirect exposure of people to *Campylobacter*.

1. Long term change	Medium
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	High
5. More cases in the more affluent	Low

**Contamination from pets** has long been argued as a source of *Campylobacter* infection (40-45), although the attributable fraction might be small. It is unlikely to have changed substantially over recent years, but supporting evidence for this is not available. It would be reasonable to assume that pets in the country might be more exposed to animal sources of *Campylobacter* contamination than those in urban areas, although the evidence for this is limited.

1. Long term change	Low
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Medium
5. More cases in the more affluent	Low

**Contamination from wild birds** is a recognized potential source of human infection (46-49). Because many birds are migratory it is possible that human exposure to their faeces will change through the year and be a driver for disease (50;51). The burden of disease attributed to bird sources seems however to be low. The commonest likely exposure route would be direct contact with contaminated bird faeces in the garden, contamination of field grown fruit and vegetables and contamination of source waters for irrigation. Bird-pecked milk in bottles can cause *Campylobacter* infection (52;52;53) and the source is probably cow faeces. Bird pecked milk related infections appear to be seasonal in distribution with a marked increase in May (54).

1. Long term change	Low
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Food preparation involving raw meats** can change over time and could have an impact on human *Campylobacter* infections. Preparing raw meats is an important risk factor for human disease and social and economic changes that influence meat preparation could affect disease. For example in a period of economic decline, such as we have experienced over the last four years, people may eat out less and prepare meals at home more. People in the countryside may have a different exposure to raw meats than those in urban areas.

1. Long term change	Medium
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Medium
5. More cases in the more affluent	Low

**Educational farm visits** can be a source of outbreaks with a variety of gastrointestinal infections. *Campylobacter* strains from cattle have been linked to strains from human infections (55;56). Cattle and sheep represent a significant reservoir of *Campylobacter* (57;58), and the occurrence of milk-borne outbreaks (13;59-65) suggests that other routes may occur. There is evidence that faecal shedding by sheep is more frequent around lambing (66). The perceived increase in attendances at farms over recent years could contribute to long term changes, is likely to be seasonal, may be more frequent in the more affluent and more likely in rural areas. However, outbreaks of *Campylobacter* linked to farm visits are infrequent compared to *Cryptosporidium* and VTEC so the attributable fraction of cases related to farm visits may be small. An outbreak of *Campylobacter* in workers on a Pheasant farm shows that farm workers can acquire infections directly (67).

1. Long term change	Medium
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Medium
5. More cases in the more affluent	Medium

**Barbecued or grilled meat** represent a source of exposure to *Campylobacter* that is known to be seasonal (3;68-75). If barbecuing is increasing then this could influence a long term increase in cases as well as the increase in older people, although there is no evidence for this. There is no evidence that barbecues are more of a risk to urban than rural or affluent than poor people.

1. Long term change	Medium
2. Seasonal spring increase	High
3. Increase in adults over 50 years old	Medium
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Private or untreated water supplies** can result in outbreaks of *Campylobacter* which is the commonest pathogen causing such outbreaks (76;77). Outbreaks linked to private water supplies may show some seasonality, and will be more common in rural than urban areas. There could be differences in wealth between people on private water supplies but it seems unlikely that this could explain the excess of cases in the affluent, the increase in adults over 50 years old or the long term trend.

1. Long term change	Low
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Low

4. More rural than urban cases	Medium
5. More cases in the more affluent	Medium

**Mains drinking water** has been involved in outbreaks of *Campylobacter* (78-88), and these are more common in countries where chlorination is not universal (89) or where chlorination has failed (90). There is no evidence that *Campylobacter* transmission through drinking water is common in England and Wales or is likely to have had a significant impact on the five parameters.

1. Long term change	Low
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Surface water/sewage exposure** through contamination of recreational water (91-94), including inland and coastal bathing and water-sports may be seasonal. Exposure can be influenced by changes in water quality or behavior, and may change over years. Exposure is more likely in rural areas but is unlikely to be greatly influenced by affluence.

1. Long term change	Medium
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Medium
5. More cases in the more affluent	Low

**Population aging/demographic change** is a good candidate for explaining the long term change in *Campylobacter* cases, and may similarly partly explain the increase in cases in the elderly. It is possible that movement of older people out of urban areas could be an explanation for some of the excess of cases in rural areas. However, the population effects are unlikely to have an impact on seasonality, although the age structure might (95).

1. Long term change	High
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	High
4. More rural than urban cases	Medium
5. More cases in the more affluent	Low

**The economic situation** has changed people's behavior and this may contribute to long term changes in *Campylobacter* infection. Measurements of these behavioral changes (e.g. change in eating arrangements) might contribute to long term changes in infection rates and could alter the rates between affluent and poor.

1. Long term change	Medium
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Medium

**Socioeconomic status** itself may explain the excess of cases in people living in more affluent areas, although ethnic origin, exposure to different foods (96) and other factors may contribute to this.

1. Long term change	Medium
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Medium
5. More cases in the more affluent	High

**Changes in *Campylobacter* in other countries** that resemble those seen in England and Wales are assumed to show some more fundamental relationship that affects all countries. For example the seasonality (more cases in summer months) can be seen in most European countries but the rise and fall in cases has a different timing in different countries, suggesting an indirect relationship to weather (97). Similarly changes in the long term rates of infection that move in a similar way across different countries might be assumed to reflect common drivers or mechanisms across these countries.

1. Long term change	Medium
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Kitchen behaviour** might be assumed to be common across most adults, over longer term periods, over different seasonal, in rural and urban areas and across the social spectrum. Whether this is the case is unclear, but there is little evidence that these factors influence the changes in disease over the five criteria.

1. Long term change	Low
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**GP access** is likely to be poorer in some social groups than others, and is probably variable geographically. This is unlikely to be an explanation for seasonality or the increase in people over 50 years, but could contribute to differences in urban/rural and socioeconomic status but may also have contributed to some of the changes over the longer term.

1. Long term change	High
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	High
5. More cases in the more affluent	High

**Two weekly waste bin collections** have been considered as potentially increasing the risks of food-borne diseases to people locally because food waste may decompose and flies may arise. Because there has been a recent trend to collecting household waste on a two weekly rather than weekly basis along with recycling parts of the rubbish it is plausible that there could have been a change in *Campylobacter* associated with this. However, there is no evidence for this having any effect on *Campylobacter* infections.

1. Long term change	Low
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Travel abroad** is an important risk factor for many enteric infections (98;99) and for *Campylobacter* (100-102), including military service (100;103) and probably represents a significant percentage of all cases of travellers diarrhoea (104-107). In some countries more than 50% of *Campylobacter* cases may be linked to foreign travel (108). In England and Wales about a fifth of *Campylobacter* cases are thought to follow travel abroad. The seasonality of infections can be specific for individual countries (109). Travel is more common in the more affluent and is increasingly common in the elderly, possibly contributing to the rise in cases in this group. Although travel is seasonal and contributes to the overall seasonality of *Campylobacter* it does not explain the late spring increase. Travel is probably not a significant cause of the differences seen between urban and rural populations.

1. Long term change	Medium
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	High
4. More rural than urban cases	Low
5. More cases in the more affluent	High

**Eating out** is an activity that can change our exposure to *Campylobacter*, either for the better or worse. Changes in the extent to which people eat out could contribute to longer term changes in exposure to *Campylobacter* and might be influenced by socioeconomic status and age.

1. Long term change	Medium
2. Seasonal spring increase	Low

3. Increase in adults over 50 years old	Medium
4. More rural than urban cases	Low
5. More cases in the more affluent	Medium

**Temperature** is known to have some association with *Campylobacter* and this is thought to be indirect (95;97). While it might explain some of the seasonality it is unlikely to be the only factor causing it. Temperature appears to have little explanatory value on relation to the other key factors.

1. Long term change	Low
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Rainfall** does not correlate well with *Campylobacter*, but could be involved in outbreaks linked to private water supplies. It does not appear to have a significant impact on any of the factors.

1. Long term change	Low
2. Seasonal spring increase	Low
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Low
5. More cases in the more affluent	Low

**Latitude/longitude** show some effect in relation to the spring rise in *Campylobacter* cases which increase earlier in more Western and Northern areas, and part of this may be down to more rural populations living in these areas.

1. Long term change	Low
2. Seasonal spring increase	Medium
3. Increase in adults over 50 years old	Low
4. More rural than urban cases	Medium
5. More cases in the more affluent	Low

#### Interpretation of what the paper shows

Based on the inferences drawn up in Table 2 the biggest influences on long term change appear to be chicken contamination, proton pump inhibitor use, demographics and access to a GP. For seasonal changes the flies and barbecued food seem to be the most likely drivers. For the long term increase in the percentage of *Campylobacter* cases in people 50 years, proton pump inhibitor use, demographics and travel seem to be the most important factors driving the change. In explaining the differences between urban and rural cases possible important factors are flies, walking in the countryside, contact with animals and GP access, although the generally older population in less urban areas may also contribute. The difference in rates of infection between deprived and non-deprived groups seems to relate to socioeconomic status and income, to access to health services and probably also to greater exposure to *Campylobacter* through travel.

Chicken remains an important source of infection, although the change in case numbers in this report does not seem to correlate to chicken consumption.

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