

## Human campylobacteriosis in Scotland: seasonality, regional trends and bursts of infection

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(Accepted 31 March 2004)

### SUMMARY

Fourier time-series models were constructed to study regional and national seasonality of human campylobacteriosis in Scotland between 1997 and 2001. Strong seasonality was demonstrated with an annual peak of reported cases in late June to early July. The prominence of this peak varied between regions, which was exemplified for the two major population centres: Lothian, with mixed urban/rural population, had a more prominent peak than Greater Glasgow, which has a predominantly urban population. No significant trend of annual cases of campylobacteriosis was found nationally and Fourier models successfully predicted the seasonal pattern of national and regional cases in 2002. During the period studied, the Fourier model identified >20 bursts of infection (potential outbreaks). Multi-regional bursts were also identified in the summers of 1998 and 2000 – the latter comprising the vast majority of the regions in Scotland, which could suggest a national outbreak.

### INTRODUCTION

Human campylobacteriosis is recognized as being the most common cause of bacterial gastrointestinal infection in the developed world [1]. In Scotland, the annual incidence of human cases during 2002 was 101 cases/100 000 [2]. This compares to reported incidences ranging from 13 in the United States [3], 37 in Canada [4], and 232 in New Zealand [5]. However, it has been claimed that there is a poor reporting rate of campylobacteriosis throughout the world, so the actual number of cases could be much greater [6]. In the United States, for example, it has

been claimed to be responsible for up to 2·4 million cases every year (i.e. approximately 800/100 000) [7].

Symptoms of campylobacteriosis usually persist for 3–4 days but can last more than 1 week and include diarrhoea, fever and abdominal cramp [1]. Approximately 0·1% of cases have been reported to lead to Guillain–Barré disease, which is a neural disorder causing acute neuromuscular paralysis [8]. The vast majority of infections in the human population are sporadic [9] but a number of small outbreaks have been recorded. For example, six outbreaks detected between 1992 and 1995 in England and Wales were associated with contaminated private water supplies [10]. The most common forms of campylobacter found in humans are *C. jejuni*, which accounts for approximately 93% of cases, and *C. coli* (7%) [11].

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*Campylobacter* sp. can be found in wild animals, birds and untreated water supplies [12]. In particular, it is found to be endemic in farm animals such as sheep, cattle, turkeys, broiler chicken and swine [13–16]. A survey performed for the Food Standards Agency in the United Kingdom found that approximately 75% of retail chickens in Scotland, between 2000 and 2001, were contaminated with campylobacters [17].

There are many possible foodborne and environmental pathways that can lead to campylobacter infection in humans. Case studies have shown the main risk factors to include travelling abroad, handling or consumption of undercooked poultry, living or working on a farm, contact with animals, and drinking unpasteurized milk [18–21].

Campylobacteriosis shows striking seasonality in the United Kingdom with a peak in the late spring/early summer [22, 23]. Seasonal trends can be effectively studied by using time-series analysis [24]. Fourier/harmonic analysis techniques have been used in various epidemiological investigations [25–27], in particular, to model human campylobacteriosis infections in Belgium during the dioxin crisis [28].

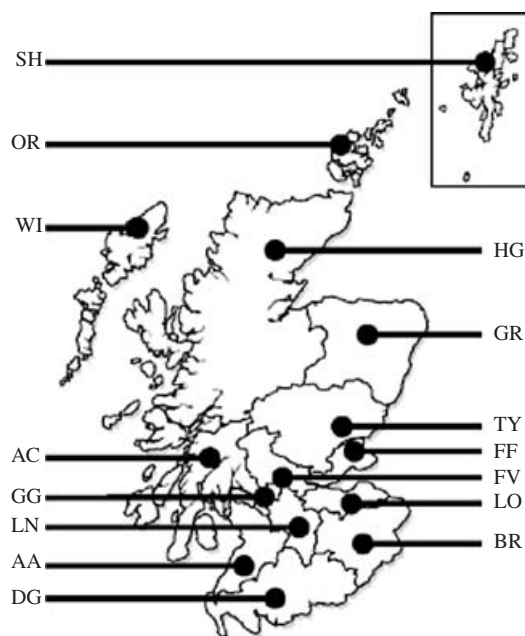
In addition to seasonal variation, it has been proposed that regional differences of campylobacter infection within countries exist [29]. In Northwest England, for example, it has been demonstrated that the incidence of human campylobacteriosis is greater in rural areas than urban communities [30] and in Norway it has been shown that there is a more prominent seasonal peak with increasing latitude [31]. Furthermore, investigations of human infection data on a regional basis may also help to detect outbreaks that have previously been overlooked.

We present an investigation of the annual and regional trends of human campylobacteriosis in Scotland during the years 1997–2001. Fourier models are constructed using data of reported human infections for each region, which enables characterization of seasonal trends, as well as identification of regional variations. In addition, the potential of the Fourier model to predict future infection rates and to identify bursts of infection is demonstrated.

## MATERIALS AND METHODS

### Data

The weekly reported cases of human campylobacteriosis in Scotland between the years 1997 and 2002



**Fig. 1.** Map of Scottish health boards. (Reproduced courtesy of SCIEH.) AA, Ayrshire & Arran; AC, Argyll & Clyde; BR, Borders; DG, Dumfries & Galloway; FF, Fife; FV, Forth Valley; GG, Greater Glasgow; GR, Grampian; HG, Highlands; LN, Lanarkshire; LO, Lothian; OR, Orkney; SH, Shetland; TY, Tayside; WI, Western Isles.

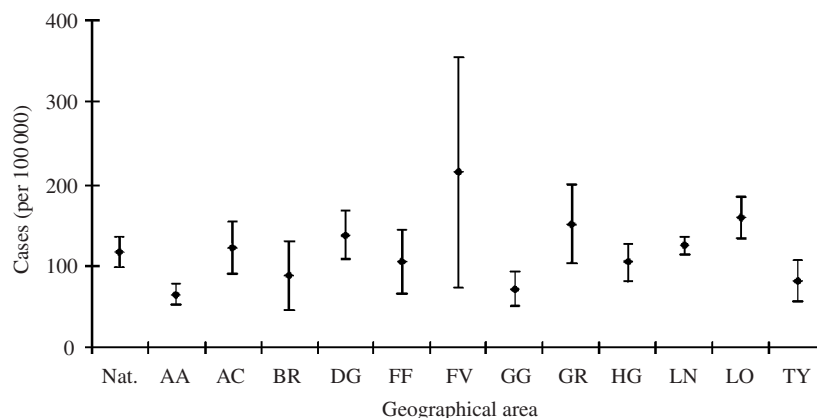
were obtained from the Scottish Centre for Infection and Environmental Health (SCIEH). The collection of data is part of a national surveillance system, where diagnostic laboratories throughout Scotland voluntarily provide SCIEH with weekly reports of detected infections. These data are split into 15 regional health boards (Fig. 1). Shetland, Orkney, and the Western Isles were omitted from regional analyses due to their small populations and low number of reported cases (<26 cases per year). Data were smoothed in Microsoft Excel using a double three-point moving average [25], given by the equation:

$$S_t = (y_{t-2} + 2y_{t-1} + 3y_t + 2y_{t+1} + y_{t+2})/9,$$

where  $S_t$  is the smoothed data-point and  $y_t$  is the raw data-point at week  $t$ .

### Incidence

The annual numbers of cases nationally and regionally, were divided by the appropriate population to produce the incidence for the years 1997–2001 [32]. Regression analysis was performed to identify national and regional trends. The mean annual incidence was calculated to identify regional variations.



**Fig. 2.** Mean national and regional Scottish campylobacteriosis incidence in humans with 95% confidence intervals, 1997–2001. (For abbreviations see Fig. 1 legend.)

### Fourier models

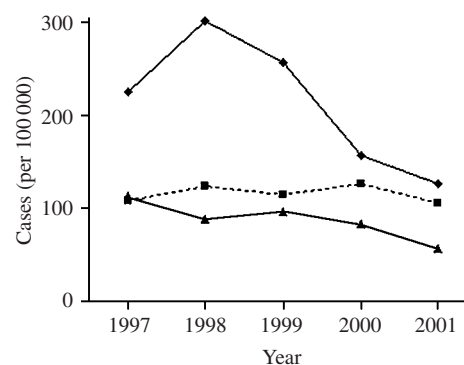
Fourier modelling was used to describe the seasonality of campylobacteriosis between 1997 and 2001. The Fourier method allows a model to be formed from the addition of a series of basic sinusoidal waves, or 'harmonics'. Each successive wave reduces in period by a factor of 2. Harmonic periods of 1 year, 6 months, 3 months, etc., were individually fitted to the data. The number of reported cases in week  $t$  are given by

$$y_t = a_0 + \sum_{n=1}^r \left[ a_n \cos \left( \frac{2n\pi(t - b_n)}{k} \right) \right],$$

where  $a_n$  and  $b_n$  are constants representing the amplitude and lag of phase for each harmonic,  $k$  is the number of measurements in a year (i.e. 52 weeks), and  $r$  is the number of harmonics used. The values of  $a_n$  and  $b_n$ , were found by using the Solver function in Microsoft Excel to apply a least squares fit method on the smoothed human case data. The final Fourier model is constructed from the sum of the harmonics and the mean number of cases per week ( $a_0$ ). A regression test was performed for each harmonic, using the Microsoft Excel regression function, to determine which were significant in the model. The model was then plotted against the reported human infection data and 95% confidence intervals (CIs) were determined [33].

### Model prediction

The Fourier models generated from the 1997–2001 data were used to predict frequencies of reported cases throughout 2002 on a regional and national basis.



**Fig. 3.** Trends in annual campylobacteriosis incidence in humans 1997–2001. National (---■---), Borders (—▲—), and Forth Valley (—◆—).

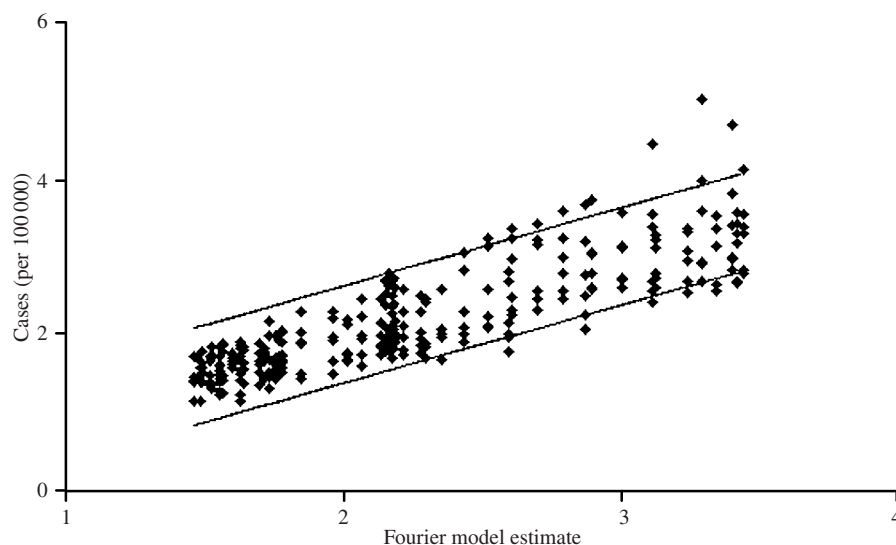
### Detection of potential outbreaks or bursts of infection

A simple detection algorithm was applied to indicate a warning of a potential outbreak if the reported data were above the 95% prediction interval. A second visual inspection of the data was performed to identify potential outbreaks/infection bursts (short periods of unusually large incidence) which had characteristic outbreak curves [34] but which were not above the 95% prediction interval.

## RESULTS

### National and regional incidence

The national and regional mean incidence for each year were plotted with 95% CIs (Fig. 2). The national incidence shows a variation of approximately 17% ( $120 \pm 20$  cases/100 000). Most regions fall within 60–160 cases/100 000 some of which show significant differences, such as between Greater Glasgow



**Fig. 4.** Plot of National Fourier model against human reported infection case data with 95% prediction intervals.

( $70 \pm 20$ ) and Lothian ( $160 \pm 20$ ). Forth Valley has an unusually high incidence as well as an atypically large CI ( $200 \pm 100$ ).

#### Annual trends in incidence

The annual incidence (Fig. 3), shows no significant trend ( $P=0.97$ ). The only region to have a significant trend ( $P=0.04$ ) is Borders (Fig. 3), where there is a reduction in cases. Forth Valley showed erratic annual trends (Fig. 3), where in 1998 the incidence was very high (302 cases/100 000) followed by 3 years with a significant reduction ( $P=0.02$ ).

#### Fourier models

After examination of the  $P$  values, it was determined that only the first four harmonics of the Fourier models were significantly correlated ( $P < 0.05$ ) with the weekly reported data on human infections (data not presented), and hence, the Fourier models were constructed comprising these four harmonics only. Normal distribution plots (e.g. Fig. 4) showed that these data were sufficiently normalized to allow the inclusion of 95% prediction intervals. The occurrence of some high outliers was allowed, as they are indicative of the infection bursts found in the data (Fig. 4).

#### Seasonal trends

Seasonal trends are seen nationally (Fig. 5*a*) as well as in the models for every region (e.g. Fig. 5*b–d*).

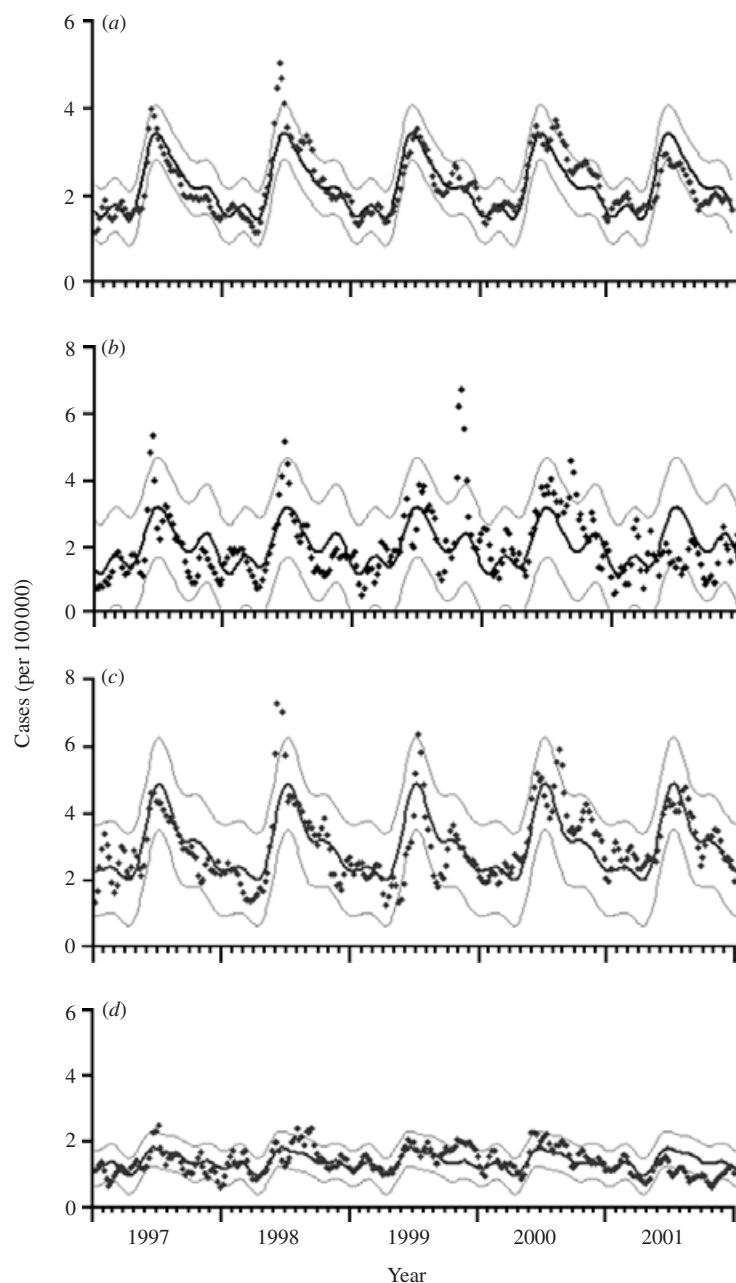
A large peak is seen towards the end of June and the beginning of July (weeks 26–28), with a small peak also apparent during the later part of April (week 16, e.g. Fig. 5*b*). Some of the regions also show a minor peak during late October (e.g. week 42 in Fig. 5*b*).

#### Regional variations

The times at which the main peak and the preceding minimum occur are consistent for all regions (see Table). However, noticeable differences can be seen in the shape of the regional models. Some variation is found in the prominence of the main peak (e.g. Lothian's annual peak is far more prominent than Greater Glasgow's; Fig. 5*c, d*). In some regions there is a sharp reduction after the summer peak, whereas in others there is a gradual reduction (e.g. Fig. 5*c, d*).

#### Predictability of model

The smoothed 2002 data were superimposed on the national model (Fig. 6). These data generally fit within the prediction intervals and it can be readily seen that the annual peak appears less prominent than in previous years with a burst of infection starting at week 32 and reaching a maximum during week 34. For the regions, more than 90% of the 2002 data-points fit within the prediction intervals of the models (results not presented). However, as with the national trend, many regions show a less prominent annual peak.



**Fig. 5.** Fourier models generated from the weekly number of reported campylobacteriosis cases in humans during 1997–2001, with case data superimposed on the graphs. (a) National ( $r=0.87$ ), (b) Fife ( $r=0.57$ ), (c) Lothian ( $r=0.77$ ), (d) Greater Glasgow ( $r=0.57$ ) including 95% prediction intervals. ◆, Human infection data; —, model; —, 95% prediction interval.

#### Detection of bursts of infection or potential outbreaks

There were 26 detected bursts of infections or potential outbreaks (occasions when the data peaked above the prediction interval with the peak having the typical shape of an outbreak curve [34]; e.g. see Fig. 7). In addition, by visual inspection there were further occasions where bursts of infection occurred

that were not above the 95% prediction intervals (e.g. Fig. 5a; autumn 1999).

#### DISCUSSION

The results have shown that there is a strong seasonality in human campylobacteriosis cases both on a

Table. Fourier model determination of the weeks in which the main summer peak and preceding minimum occur. Including the correlation coefficient (*r* value) between each regional model and reported cases

| Region                               | National | AA   | AC   | BR   | DG   | FF   | FV   | GG   | GR   | HG   | LN   | LO   | TY   |
|--------------------------------------|----------|------|------|------|------|------|------|------|------|------|------|------|------|
| Minimum (week)                       | 15       | 16   | 17   | 15   | 15   | 16   | 14   | 15   | 16   | 15   | 14   | 15   | 14   |
| Summer peak (week)                   | 26       | 27   | 27   | 25   | 25   | 26   | 25   | 25   | 26   | 30   | 25   | 27   | 26   |
| Correlation coefficient ( <i>r</i> ) | 0.87     | 0.70 | 0.70 | 0.59 | 0.72 | 0.57 | 0.66 | 0.57 | 0.73 | 0.72 | 0.70 | 0.77 | 0.72 |

AA, Ayrshire & Arran; AC, Argyll & Clyde; BR, Borders; DG, Dumfries & Galloway; FF, Fife; FV, Forth Valley; GG, Greater Glasgow; GR, Grampian; HG, Highlands; LN, Lanarkshire; LO, Lothian; TY, Tayside.

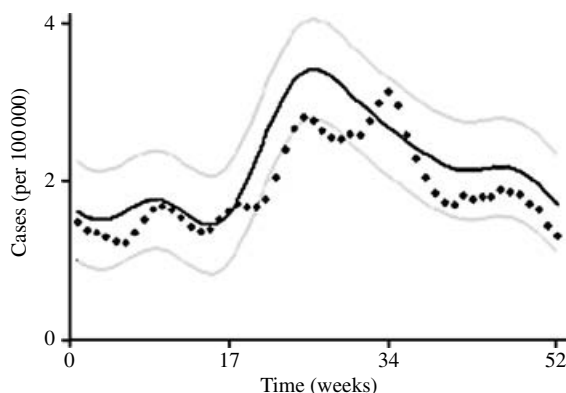
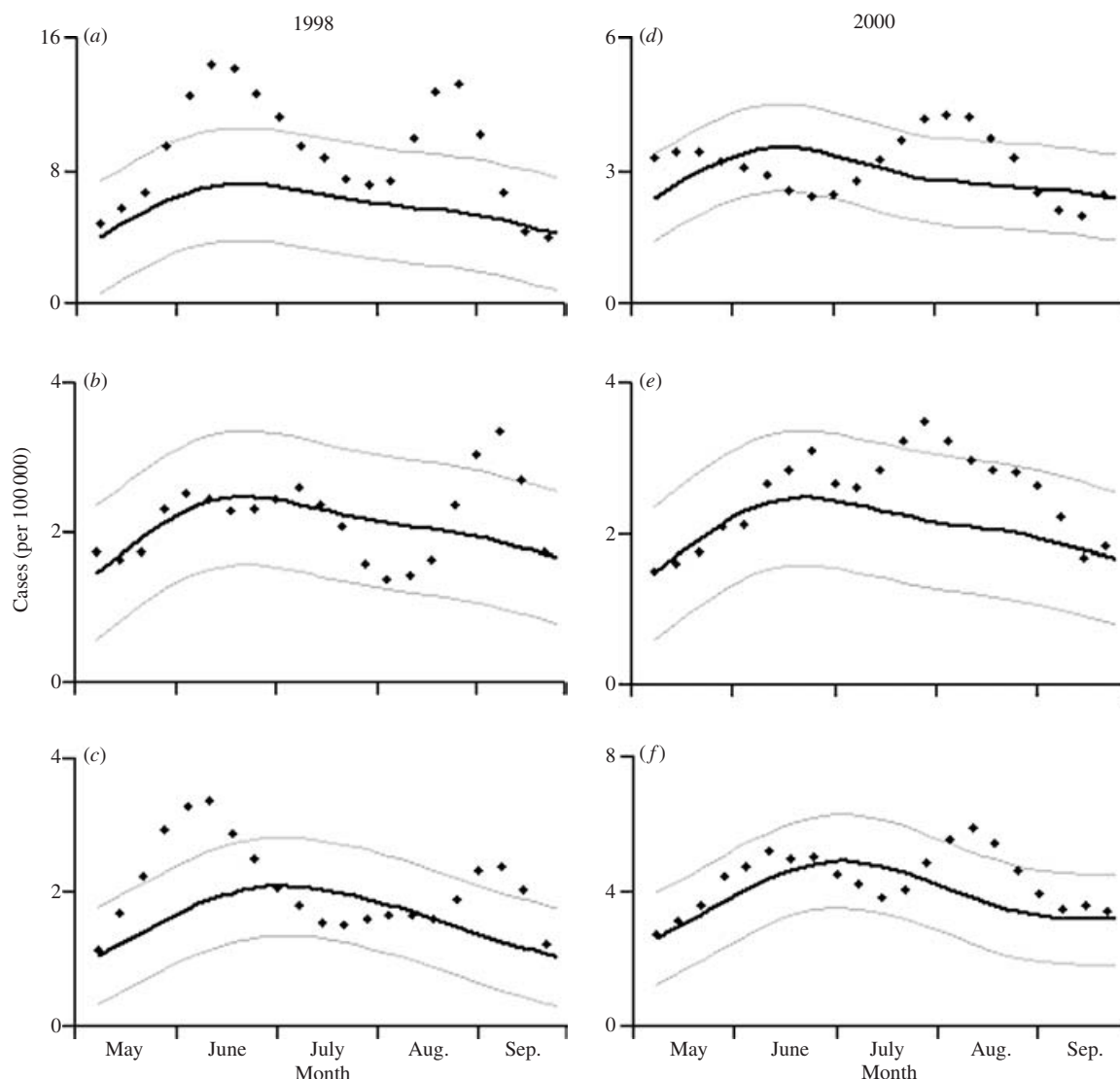


Fig. 6. A Scottish national Fourier model prediction of human campylobacteriosis in 2002 based on the 1997–2001 reported case data. Superimposed are the actual reported number of cases of human campylobacteriosis in 2002 (smoothed). ♦, Human infection data; —, model; —, 95% prediction interval.

national and regional basis with an early summer peak, between weeks 25 and 27, occurring in all Scottish regions (except Highlands). However, the prominence of this seasonal peak varies from region to region. This variation is most clearly demonstrated when comparing the two regions of highest population, Greater Glasgow with a population of 900 000, and Lothian, which includes the capital city Edinburgh (780 000). The summer peak, which is strikingly prominent in Lothian, is minimal for Greater Glasgow (Fig. 5*c, d*). Further, the general number of cases per 100 000 throughout the year is consistently higher in Lothian, as is seen in the incidence data (Fig. 2). Lothian like most regions in Scotland comprises large amounts of farmland/countryside as well as more densely populated urban areas, whereas Greater Glasgow is the exception being almost entirely urban. It would be very informative to know if the majority of the cases in Lothian lay within the city or close to the surrounding farmland. This could be achieved by spatial mapping of the postcode data for each of the cases.

Edinburgh has a very large number of international and national tourists during the summer months who visit the Edinburgh Festival (throughout August) and the historical and cultural attractions of the capital city. However, if it is tourists that are either becoming infected or importing immigrant strains it would be expected that the peak reported infection rates would continue from the end of July into September. There are short bursts around August in some years, which could, in part, be due to immigrant strains, however, in the majority of cases this is not evident. Hence, we hypothesize that the striking annual campylobacteriosis peak in Lothian is of indigenous cause.

Superimposed upon the seasonal pattern of campylobacteriosis is a considerable amount of intermittent fine structure including peaks and troughs (e.g. Fig. 6). This is demonstrated most vividly in the summers of 1998 (for Forth Valley, Tayside and Ayrshire & Arran; Fig. 7) and 2000 for all of the regions studied (excluding Ayrshire & Arran, Borders, and Dumfries & Galloway) where summer double peaks occur, usually superseding the 95% prediction intervals (e.g. Fig. 7). The second peaks appear within a period of 2 weeks throughout the different regions. The shapes of these peaks are typical to that of outbreaks [34]. These data show bursts of campylobacter infection (that may be multi-regional/national outbreaks), which have not previously been recognized in the United Kingdom. Further epidemiological and typing investigations are required to determine whether these cases have a common cause. Furthermore, the possible reasons for a multi-region outbreak needs to be investigated. Could these be caused by a large batch of contaminated food being distributed to the different regions by a supermarket chain? Or could this be caused by an unusual campylobacter strain spread by an environmental vector or immigrant strains distributed by people returning from holiday? As well as



**Fig. 7.** Examples of bursts of infection (or possible multi-regional outbreaks) detected by the Fourier models during the summer (weeks 19–40) of 1998 [(a) Forth Valley, (b) Tayside and (c) Ayrshire & Arran] and 2000 [(d) Lanarkshire, (e) Tayside and (f) Lothian].

possible multi-region outbreaks, these data suggest that within-region bursts of infection, which could be outbreaks, are common but further epidemiological studies are required to substantiate this. The minor peaks near the beginning and end of most years, although below the prediction interval, are regular in almost every region (e.g. Fig. 5a); however, the cause of these is unknown. This technique could be adapted to provide quick detection of infection bursts, which could be used to allow rapid epidemiological analysis.

Regression analysis showed that there was no noticeable increase or decrease in the number of cases of campylobacteriosis found in Scotland from

1997 to 2002 ( $P=0.97$ ). All the individual regions showed the same result, with the exception of Forth Valley and Borders. The reason for the uncommonly high level of reporting in Forth Valley is unknown, although it could, in part, be due to a generally higher level of reporting by the health board in this region. Borders shows a reduction in incidence due to the low number of cases in 2001, this may be the result of the foot-and-mouth crisis which affected this region at that time as found in other gastrointestinal infections [35].

This study has demonstrated that the Fourier technique can describe the seasonality of human campylobacteriosis throughout Scotland, retrospectively

detect possible outbreaks/bursts of infection on both a regional and national scale and predict the pattern of infection in future years. Currently we are working with the local health authorities to determine the nature of some of the bursts of infection, through analysis of the serotypes and spatial distribution of local campylobacteriosis cases. A greater understanding of the causes, trends and outbreaks of human campylobacteriosis could be gained by using quantitative microbial risk assessment techniques (QMRA) to quantify the key factors involved in each of the main routes of infection. However, the best results would be achieved through use of QMRA (validated by case-control studies), combined with temporal analysis (e.g. Fourier), spatial epidemiology, and molecular typing.

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