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Identifying the seasonal origins of human campylobacteriosis

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SUMMARY

Human campylobacteriosis exhibits a distinctive seasonality in temperate regions. This paper aims to identify the origins of this seasonality. Clinical isolates [typed by multi-locus sequence typing (MLST)] and epidemiological data were collected from Scotland. Young rural children were found to have an increased burden of disease in the late spring due to strains of non-chicken origin (e.g. ruminant and wild bird strains from environmental sources). In contrast the adult population had an extended summer peak associated with chicken strains. Travel abroad and UK mainland travel were associated with up to 17% and 18% of cases, respectively. International strains were associated with chicken, had a higher diversity than indigenous strains and a different spectrum of MLST types representative of these countries. Integrating empirical epidemiology and molecular subtyping can successfully elucidate the seasonal components of human campylobacteriosis. The findings will enable public health officials to focus strategies to reduce the disease burden.

Key words: Bacterial typing, *Campylobacter*, foodborne zoonoses, modelling, molecular epidemiology.

INTRODUCTION

The reasons for the seasonality of human *Campylobacter* infections have proven difficult to ascertain [1]. This is despite the fact that *Campylobacter* is the leading cause of bacterial gastroenteritis in the world [2] with 69281 cases reported in the UK during 2009 [3] (a fraction of the actual 572000 community cases [4]) and the annual estimated 845000 foodborne domestically acquired cases in the USA [5]. However, a number of aspects are known about the seasonality of human *Campylobacter* infections. Most temperate

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countries have a seasonal peak of infection in spring while those with milder winters have peaks earlier in the year [6]. Those in tropical regions have little variation throughout the year. This geographical variation in the timing of the seasonal peak suggests that climate may be a contributing factor. The timing of the peak is loosely associated with the highest temperature in the year (the peak in human cases occurs about 3 months earlier than the peak in temperature) and that other climatic variables including rainfall and sunshine are also correlated [7]. The most marked seasonal effect was observed for children aged <5 years in England/Wales which precedes the peak in adults and it has been demonstrated that young children in rural areas have an increased likelihood of *Campylobacter* infection [8–10] compared to their urban counterparts. Hence it has been suggested [7] that the seasonal peak may be best understood through studies in infants.

Campylobacter is excreted by farm animals including cattle, sheep and pigs, as well as a range of wild and domesticated avian species and pets [11]. Over 65% of broiler meat at retail is contaminated with *Campylobacter* in the UK [12, 13], and although outbreaks are rare, a number have been reported from foodborne (e.g. chicken liver paté [14]), waterborne [15] and environmental [16] sources. This diversity of pathways has made it difficult to identify the origin of human *Campylobacter* infections and how this changes with season. Case-control studies have frequently identified consumption of chicken as a risk factor [17]. The advent of sequence-based typing methods [in particular multi-locus sequence typing (MLST)] has helped researchers attribute the sources of human infection. MLST studies from North West England [18], Scotland [19] and New Zealand [20] have all identified chicken as the most important single source of human infection (50–80%) with the most common types found in humans also being the most common in chickens. However, none of these studies have used source attribution to investigate directly the origin of the seasonality of human *Campylobacter* infections.

Travel abroad has been associated with a substantial component of human *Campylobacter* cases (e.g. 20% in the UK [21] and 13% in both Denmark [8] and the USA [22]). This can contribute in two ways to the seasonality of reported human *Campylobacter* cases. First, trips abroad occur most frequently in the summer months and second, campylobacteriosis may exhibit a seasonal pattern in the country visited. For example, foreign travel-associated cases peaked in the summer for those returning from temperate regions while seasonality was less distinct for those returning from the tropics [23]. Hence, to understand seasonality there is a need to unravel both the foreign travel-associated and indigenous components.

This paper aims to identify the causes of the seasonality of human infections. We achieve this by stratifying the seasonal pattern of human cases in terms of indigenously acquired, foreign and mainland UK travel, age and demography (i.e. living in urban or rural areas). We then apply source attribution together with empirical epidemiological methods to establish the origin of the seasonality. Finally, we reflect on the impact of these findings in terms of public health interventions to reduce disease incidence.

MATERIALS AND METHODS

Data

Three clinical datasets were collated with each case having reporting date, age, postal sector of residence and whether urban or rural (a population density >200 km^2 which was predominantly within the city of Aberdeen was designated as urban and rural as <200 km^2):

(1) 34 735 cases (<5 years, $n=2494$ cases; 5–14 years, $n=1937$ cases; 15–64 years, $n=26083$ cases; $\geqslant 65$ years, $n=4221$ cases) of which 27·7% were rural from across Scotland (population of 5 116 900 of which 27·6% were rural) encompassing the years 2000–2006;
(2) 4699 cases (<5 years, $n=151$ cases, 5–14 years, $n=157$ cases; 15–64 years, $n=2255$ cases; $\geqslant 65$ years, $n=417$ cases) of which 2980 isolates were MLST typed from across Scotland for 1 year commencing 1 June 2005 (35·2% of the typed isolates were rural);
(3) travel information (with foreign travel taken as an overnight stay abroad and domestic travel as an overnight stay outside the study area but in the UK mainland 14 days prior to the onset of disease) from 700 MLST typed cases over 27 months commencing 1 August 2005 from Aberdeen city and Aberdeenshire (population 490 060 of which 36·3% were rural) with travel information. This comprised 53% of the reported cases from that period, including all of the cases for which travel information had been returned by postal questionnaire (789, i.e. 59·7%) minus 89 cases for

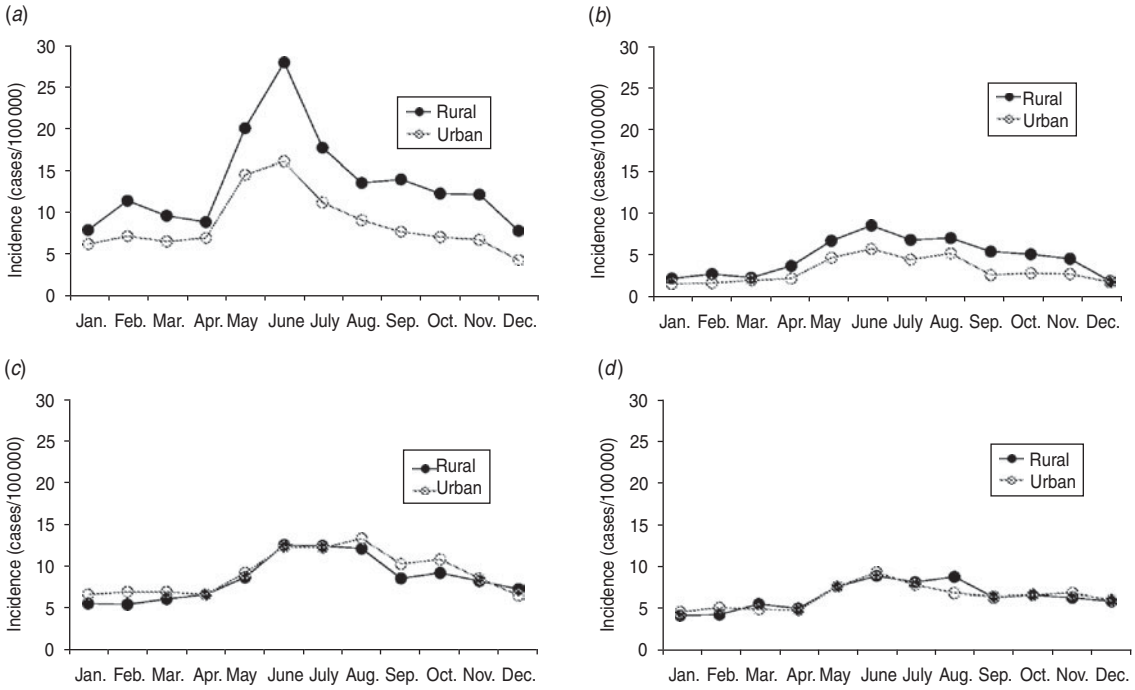

Fig. 1. Seasonality of human campylobacteriosis in Scotland (2000–2006) stratified by rural and urban populations for (*a*) 0–4, (*b*) 5–14, (*c*) 15–64 and (*d*) ⩾65 years age groups.

which either the isolate was unavailable or 7-loci MLST typing failed.

MLST typing

Genotyping by 7-loci MLST was performed as described previously [19]. Allele profiles and sequence types (STs) were assigned using the *Campylobacter* MLST profile database (www.pubmlst.org).

Source attribution

Data (MLST) at the level of ST were used to identify the reservoir origin based on source attribution scores generated from the software programme STRUCTURE [24]. The source dataset for *C. jejuni* comprised 96 cattle, 66 sheep, 165 wild bird and 242 retail chicken isolates from the Scottish CaMPS study [25]. For *C. coli* the source dataset comprised data from both the CaMPS study and PubMLST [19, 25] providing in total 85 (26) cattle, 57 (56) sheep, 322 (28) pigs and 459 (45) chicken isolates (figures in parentheses are the number of isolates from CaMPS). The PopTools (http://www.cse.csiro.au/poptools) add-in to Microsoft Excel was used to generate 95% confidence intervals (CI) and significant differences were determined using the @RISK software (Palisade, UK) (chicken/non-chicken or by particular reservoir: cattle, chicken, sheep, pigs, wild birds).

Analysis

The diversity of cases was determined by Simpson's index [26] using the online facility V-DICE (www.hpa-bioinformatics.org.uk/cgi-bin/DICI/DICI.pl). This has value 0 when there is no diversity and moves closer towards 1 as diversity increases. Odds ratios (OR) were calculated to compare whether particular types were more common in foreign travel-associated or indigenous cases. Statistical significance was determined using the Excel add in for Fisher's exact test (www.obertfamily.com/software/fisherexact.html). For multiple comparisons the false discovery rate Q-VALUE (www.genomics.princeton.edu/storeylab/qvalue/index.html) was used.

RESULTS

There was a seasonal pattern of human campylobacteriosis across all age groups in Scotland (Fig. 1). The seasonality was most pronounced in the youngest age group (<5 years) with the peak incidence occurring in June. In this age group the incidence was higher across the year in rural compared to urban

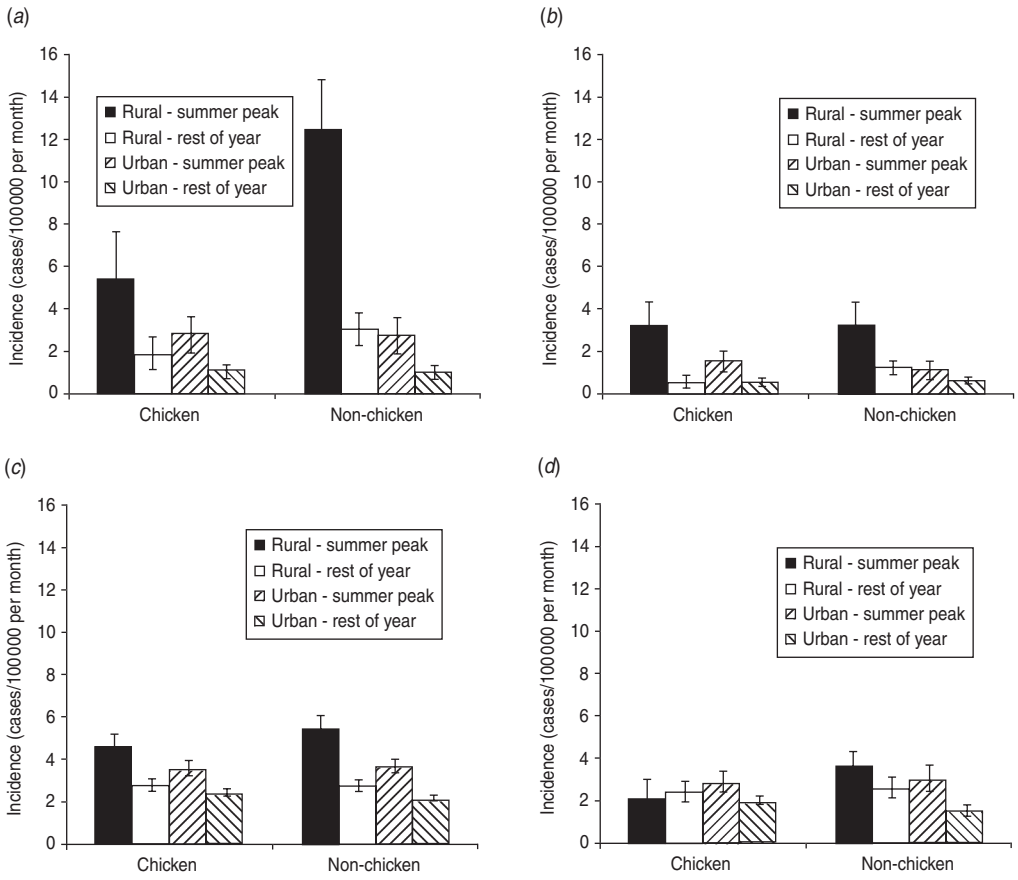

Fig. 2. Source attribution of human campylobacteriosis cases in Scotland comparing the summer peak (May–July) with the rest of the year for (*a*) 0–4, (*b*) 5–14, (*c*) 15–64 and (*d*) ⩾65 years age groups. Non-chicken types include cattle, sheep, pigs and wild birds.

children by a factor of 1·6. This elevated incidence in the rural population was also observed (factor of 1·5) in older children but was absent in the adult population. For the adult age groups the peak was extended throughout the summer months.

Source attribution applied to the 1 year of genotyped clinical isolates across Scotland was used to determine the origin of the strains in the seasonal peak (Fig. 2). For rural children (<5 years) the summer peak comprises isolates that are 2·3-fold more likely to be non-chicken (predominantly ruminant) compared to chicken types. For the remainder of the year non-chicken types dominate chicken types by a factor of 1·7. Young urban children present 5·1-fold less non-chicken-like isolates in the summer peak compared to their rural counterparts. Moreover, for urban children the pattern of chicken and non-chicken-type cases is similar throughout the whole year. Both the 5–14 and 15–64 years age groups have a higher incidence of chicken and non-chicken types in the rural population throughout the year. This is not the case for the elderly (⩾65 year old) where the incidence of chicken type is constant throughout the year in both urban and rural populations.

Seventeen percent and 18% of cases were associated with foreign travel and travel in the UK mainland outside the study area, respectively. Foreign travel-associated cases (Fig. 3*a*) were rare in young children and the elderly. Domestic travel was uniform across all age groups except the elderly where association was rare. Travel-associated cases (Fig. 3*b*) tended to occur in the holiday season with the highest proportion of travel cases occurring during July, August and September which explains part of the extension of the summer peak in adults.

Foreign travel-associated isolates had a Simpson's diversity index of 0·972 (95% CI 0·964–0·981) that was significantly ($P<0·0001$) higher than those acquired indigenously 0·954 (95% CI 0·946–0·961). There was no difference ($P>0·05$) in the diversity of the remaining isolates, those from within the study

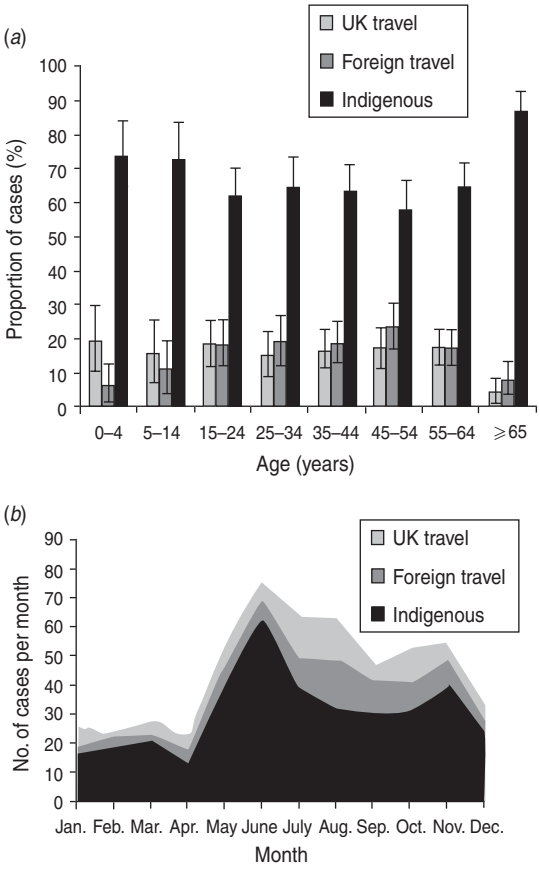

Fig. 3. Comparison of indigenous and travel-associated human campylobacteriosis from Aberdeen city and shire during 1 August 2005–31 October 2007 by (*a*) age group and (*b*) month (adjusted to give the numbers per month reported across Aberdeen city and shire).

area, and from those cases that had travelled within the UK mainland (see Supplementary Table 1).

Seven STs were more commonly associated with travel abroad than acquired indigenously (Table 1). In particular, ST50 was associated with cases returning from North America, Europe and the Middle East, whereas ST572 was identified in travellers visiting countries bordering the Mediterranean. The two STs which were more commonly identified in indigenous rather than in travel cases were ST21 and ST257, both of which were the most common in Scotland over the study period [25].

Aberdeen city and shire clinical isolates grouped by foreign travel, UK mainland travel-associated and indigenous all indicated that chicken was a major putative source of infection by attribution (Fig. 4). The only difference in attribution was that travel-associated isolates were relatively more likely to originate from wild birds.

DISCUSSION

The combination of findings on increased incidence of *Campylobacter* in young rural children, and that this group peaks prior to the summer holiday season, coupled with evidence that these isolates are dominated by non-chicken (predominantly ruminant, 91%; wild bird, 9%) genotypes indicates an environmental origin of the infection peak. Foodborne transmission is unlikely to explain this pattern because if this was the case it would be expected that adults would contract it also because they are likely to eat the same food. Further, most food in rural areas is purchased from supermarkets serving the population as a whole and consumption of unpasteurized milk, which is a known risk factor for human campylobacteriosis [22], is banned in Scotland. The question then arises as to how these children are contracting the disease from the environment. Private water supplies, contaminated with faecal matter originating from ruminants and wild birds, are a plausible route of infection. In a case-control study in north-east Scotland cases were 2–4 times more likely to be on a private water supply than controls [27]. However, this explanation is inadequate since there was only a poor correlation between the number of private water supplies in rural areas and the incidence of human campylobacteriosis across Scotland as a whole (data not presented). Direct contact with the environment or farm animals is possible, similar to the situation with the *E. coli* O157 pathogen [28]. The highest incidence of campylobacteriosis in young children occurs in those aged 1–2 years [21] who are most likely to be sampling their environment with a hand-to-mouth behaviour, are dependent on adults to ensure good hygiene (e.g. washing hands prior to eating), and are also immunologically naive. Transmission of *Campylobacter* to this cohort in rural areas may arise by a number of mechanisms: ingesting the pathogen following petting of animals, transfer from soles of shoes to carpet/floor within the house or indirectly sampling faeces in the garden or play area environment [29]. Further studies are required to determine which mechanisms are most important.

The only other age group that shows an increased incidence in rural areas is older children (5–14 years). Again, this may be due to environmental sources but the source attribution data do not provide convincing evidence that these strains originate from non-chicken sources. For this age group and adults and the elderly there is a prolonged summer peak. Part of the

Table 1. Campylobacter *strains that are found more commonly in cases associated with travel abroad or acquired indigenously*

Strain	No. of cases		Foreign countries	OR* (95% CI)	*P* value†
	Home	Abroad			
More common abroad					
ST50	13	10	France (1), Italy (1), Middle East (2), more than one (3), Spain (2), USA (1)	4·05 (1·73–9·48)	**0·0021**
ST227	0	3	Spain (2), Portugal (1)	Infinity	**0·0047**
ST460	0	3	North Africa (1), Turkey (1), India (1)	Infinity	**0·0047**
ST464	2	4	Eastern Europe (1), France (1), Portugal (1), Spain (1)	10·18 (1·84–56·2)	**0·0088**
ST572	7	9	Cyprus (1), more than one (2), North Africa (1), Spain (3), Turkey (2)	6·78 (2·47–18·60)	**0·0003**
ST824	0	2	North Africa (1), USA (1)	Infinity	0·0282
ST883	0	2	Turkey (2)	Infinity	0·0282
ST2065	0	3	Portugal (2), more than 1 (1)	Infinity	**0·0047**
ST2331	0	3	Spain (3)	Infinity	**0·0047**
More common at home					
ST21	79	6	France (3), Spain (2), Turkey (1)	0·34 (0·15–0·80)	**0·0082**
ST45	40	2	Spain (2)	0·23 (0·06–0·98)	0·0316
ST257	53	1	Europe (1)	0·09 (0·01–0·62)	**0·0009**

OR, Odds ratio; CI, confidence interval; ST, sequence type.

* The odds ratio expresses the relative frequency of a ST in the 'Yes' cases compared to its frequency in the 'No' cases, and is expressed as 'zero' or 'infinity' when one of the 'No. of cases' cells is empty.

† *P* values are from Fisher's exact tests of 2×2 contingency tables of each strain. All the *P* values $<0{\cdot}05$ are shown, and those in bold were judged significant after false discovery rate correction for the tests performed on the non-singleton STs.

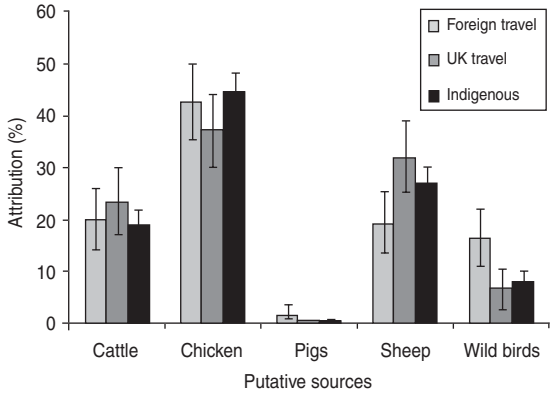

Fig. 4. Attribution of foreign, UK mainland travel-associated and indigenous isolates from Aberdeen city and shire during August 2005–31 October 2007.

duration of this peak can be explained by the excess of cases associated with both foreign and UK travel (Fig. 3). In the $\geqslant$65 years age group there is a higher incidence in the rural population in August (Fig. 2) but the potential origin of this difference is unknown. The classification (Figs 1 and 2) of adults as 15–64 years is broad and it is likely that behaviours will vary across this group and as such this is a potential area for further research.

Cases associated with foreign travel are most prominent in adults and are relatively rare in children and the elderly. The behaviour of travellers, and hence their exposure may be different from the indigenous population. For example, travellers are much more likely to eat at restaurants and this is known to be a risk factor for *Campylobacter* when chicken is consumed [22]. About half (48%) of the foreign travel-associated cases occur during July–September which coincides with the main holiday season in Scotland (July–August). It is interesting to note that the higher diversity of foreign travel-associated strains compared to those acquired indigenously supports the hypothesis that *Campylobacter* strains vary geographically. This is further supported by the evidence that shows particular types are more commonly associated with foreign travel than are acquired at home and vice versa (Table 1). It should be noted that for a number of STs where there are statistical differences there are only a small number of isolates in the numerator. Hence, a larger study in this area would be beneficial. The percentages of travel cases reported (17% travel abroad, 18% associated with UK domestic travel) are likely to be an overestimate because some of these cases may have

contracted the pathogen within the study area. This is possible because only a single overnight stay in the previous 14 days prior to onset of disease was required to trigger the case as being travel associated. Indeed, if further data were available it would be beneficial to correlate the length of time away with the likelihood of a travel associated genotype being present.

Various MLST studies from other countries are now being published that can shed light on the geographical variation of *Campylobacter* strains. In a Spanish study ST572 was the second most frequently isolated from a collection of cattle, sheep and poultry isolates while it was the most common ST found in human isolates [30]. This ST was absent in poultry isolates and found only once in human isolates from Finland [31] and was absent in studies of poultry isolates from Grenada and the USA [32, 33]. This is consistent with our findings that show that this ST is commonly found in travellers returning from Southern European/Mediterranean countries but is relatively rare in the indigenously acquired cases and in animal/food isolates from Scotland. Further, ST257, the most common ST in both humans and poultry in Scotland, is also isolated from cattle in Spain [30] as well as being the most prevalent ST isolated from poultry meat in Belgium [34]; however, is absent or rare from human, cattle and poultry isolates in Finland and Grenada [31, 32]. Evidence that types vary geographically can be seen in New Zealand [35] where ST474 is a dominant poultry-associated strain causing infection in humans but very rare in humans, poultry and other animals in Scotland [25].

The similar source attribution patterns for both foreign travel-associated and indigenous strains suggests that the sources are likely to be similar, with chicken the principal vehicle but ruminants also being important. The only difference in attribution occurred for wild birds which were more likely to be associated with travel cases; at present this is difficult to explain. Much foreign travel from the UK is to warmer countries where eating outside is more common and exposure to birds and their faeces may be more likely. Wild bird to chicken transmission may be greater in other countries compared to the UK which would help explain the results. However, there is no evidence to support these hypotheses and further research is required.

Strains associated with UK mainland travel had the same diversity as cases acquired within the study area and had the same source attributions. This is unsurprising for two reasons. First is that UK mainland travel cases are likely to spend shorter periods of time away from home and hence it is very possible that the infection was actually acquired within the study area. Second is that the majority (78%) of this local travel was within mainland Scotland where a previous study has shown no significant difference in the distribution of strain types [25].

A study in Norway showed the seasonality of human campylobacteriosis cases occurs at about the same time as in broilers suggesting that the peak of infection is due to a common environmental source or reservoir [36]. In a UK study [37] the prevalence in broiler flocks was higher in the summer months. Further, in a study from Wales [38], the highest incidence in human *Campylobacter* infections coincided or preceded that found in retail chicken isolates which further supports this hypothesis. However, foreign travel isolates were not excluded in the Welsh study and this may have had some influence on these data. In our study the epidemiological and typing evidence suggests that young rural children are exposed to non-chicken sources (ruminant and wild bird) during May–July, the consequence being an early peak in infection. It would not be surprising for these environmental sources to contaminate broiler farms through lapses in biosecurity, fly transmission, etc. at this time of year. There may then be selection of strains within the broiler houses to favour those best fit to survive and multiply within the chicken host. As a consequence these 'chicken type' strains will contaminate the food chain and subsequently infect human hosts thus generating the peak in human infection (the peak in adult human infection being later than that observed for young rural children). It is unlikely that the infection of the adult population by direct environmental contamination is as important in the peak months as from food (e.g. poultry) because we see no supporting evidence in the rural/urban ratio of disease incidence.

Correlations with climate have been used previously to investigate the seasonality of campylobacteriosis, e.g. [7] and for reference in Supplementary Figure S1 weather data are included for Scotland. However, our findings here indicate that climate is not the intimate cause of the seasonality. For example, foreign travel is important but the intimate cause is the behaviour of adults who travel in the warmer summer months. Moreover, the high disease burden for young children in the spring is likely to be caused by the increased environmental infection pressure at this time of year due to turning out of farm animals

after winter housing, and the increased activities of both wildlife (e.g. birds) and humans initiated by the improving weather.

Our study findings lead to the following three conclusions and we propose some appropriate actions. First, young rural children are at elevated risk of *Campylobacter* infection from the environment during late spring/early summer and are also at increased risk to a number of other gastrointestinal pathogens (e.g. *E. coli* O157:H7, *Cryptosporidium*, *Salmonella*) over the summer [39]. Targeted public health strategies to inform parents and the children in this group should be employed. This would emphasize the importance of hand washing after coming into contact with animals and before eating (especially after playing outside) as well as ensuring that water supplies are properly protected from potential sources of pathogens by being adequately treated. Second, travel abroad is associated with a significant burden of disease from *Campylobacter*. Public health should target messages to travellers and this can be combined in general information associated with travellers' diarrhoea [40]. Third, poultry consumption is likely to be the main cause of human disease throughout the year in both indigenously acquired and travel-associated cases. Increased biosecurity on poultry farms, combined with practices and processes that reduce contamination along the food chain including education to reduce cross-contamination and proper cooking of chicken in the home and restaurants will potentially lead to significant reductions in human infection.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268812002063.

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DECLARATION OF INTEREST

None.

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