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# Editorials

## A human case of swine influenza virus infection in Europe – implications for human health and research

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Swine are susceptible to the same influenza A virus subtypes as humans – H1N1, H3N2 and H1N2 - and the histories of influenza in pigs and people are closely linked [1]. Many swine influenza viruses are a result of reassortment and their genes are composed of human and avian and/or swine virus genes. Indeed, it is known that both human and avian influenza viruses occasionally transmit to pigs, and that pigs can serve as "mixing vessels" for these viruses, meaning that viruses can exchange genetic material and lead to the production of a new "hybrid" virus [2]. This has led to the thinking that perhaps pandemic viruses could emerge following reassortment in pigs. However, since nobody has observed the start of a pandemic, there remains no direct evidence to make this more than a theory.

Influenza is one of the major causes of acute respiratory disease in pigs, but subclinical infections are also common. Unlike the non-zoonotic swine fevers it is not a disease that comes under the European Union's harmonised Animal Disease Notification System and there are no routine European surveillance data. The symptoms and pathogenesis of influenza in pigs show remarkable similarities with those of seasonal influenza in humans, but the epidemiology is different. Part of this is due to the structure of the swine industry and the extremely rapid turnover of the swine population, with the constant introduction of immunologically naïve animals into swine herds. In swine-dense regions in particular, most pigs show serological evidence of having been infected with influenza by the end of the six-month-long fattening period, and many of them have undergone simultaneous or consecutive infections with two or even three swine influenza subtypes [3]. Unlike human viruses in temperate climates, swine influenza viruses circulate at comparable levels year round. Also, the viruses in Europe differ significantly in their antigenic and genetic make-up from those circulating in North America, even though they consist of the same H and N subtypes, and hence findings in the United States should not necessarily be extrapolated to Europe.

Humans in contact with pigs occasionally become infected by swine influenza viruses [4]. This issue of Eurosurveillance reports on a case of swine influenza in a middle-aged woman in Spain [5] which came to attention almost by chance. The woman worked with pigs and suffered a mild self-limiting influenza-like illness for which few physicians would have taken a swab. However the general practitioner (GP) she consulted happened to be part of an active influenza surveillance scheme and a specimen was taken. This was passed on to the laboratory as a regular surveillance specimen and then recognised as being influenza A (H1N1) phylogenetically close to European H1N1 swine influenza viruses. Retrospective epidemiological investigations found no evidence of any further cases apart from the GP who had experienced similar symptoms but was not laboratory-confirmed [5].

Infection with swine influenza virus has been detected sporadically in humans since the 1950s and the human disease is usually clinically similar to disease caused by infections with human influenza viruses [4]. However, complications that include pneumonia and death have occasionally been reported in the literature in otherwise healthy adults without underlying disease [4]. On the whole, human infections with swine influenza virus, to date, have been different and much milder than those seen with avian influenza A (H5N1) [6] and more similar to infections with low pathogenic avian influenza viruses [7]. Single generation person to person transmission has been reported but appears to be rare and chains of transmission have not been observed in general [4]. Though it is not entirely clear what measures public health authorities should pursue when they discover such human infections, it seems reasonable to regard them as comparable to low pathogenic avian influenza and so deserving a similar approach [7].

There is one well-known exception to these generalisations. In 1976 an outbreak of swine influenza virus infections in humans was detected in recruits in a military camp in Fort Dix, New Jersey in the United States. The presumed link to pigs was never discovered but there was extensive human to human transmission, with over 200 infections resulting in 12 hospitalisations and one death [8]. This was human to human transmission of a novel influenza virus causing some significant human pathology, which today might be described as WHO Pandemic Phase 4 [9]. The unilateral decision was made by the national authorities to develop, produce and deploy a specific pandemic vaccine based on the new strain. However, the infections petered out and the vaccine was seemingly associated with occurrence of Guillain-Barré syndrome in a few recipients. Mass immunisation was terminated but the incident remains part of public health lore and has been reviewed extensively for its learning points [10,11].

While the reported case in this issue and other sporadic cases pose little direct threat to humans, they expose important gaps in knowledge about these zoonotic influenzas. The true incidence of swine influenza in humans, for example, is unknown. Recent serologic studies in the United States, where there has been

more attention to zoonotic swine influenza than in Europe, have consistently found higher seroprevalence rates and higher antibody titres against all swine influenza viruses in those working with pigs than in non-swine-exposed controls [12-15]. This, and the fact that the current infection was detected by accident, suggests that the few reported cases of symptomatic swine influenza in humans represent a larger number of undetected infections among those in contact with pigs. However, there are no comparable data available for Europe and the prevalence of swine influenza in humans cannot be estimated from such studies because of the possibility of partial serologic cross-reactivity in the haemagglutination-inhibition test between human and swine influenza virus strains of the same subtype. Epidemiologists have tried to adjust for this by statistical methods, but they agree "it is possible that the elevated titers compared by proportional odds modeling do not correlate with infection" [13]. This stresses the need for combined serological and virological surveillance in humans exposed to pigs to gain this information. There have been recent developments in surveillance of influenza in European swine populations, which is an essential starting point for the monitoring of swine flu in humans. A fruitful initiative has been the "European Surveillance Network for Influenza in Pigs (ESNIP)" (2000-2009) a European Commission funded project that ends next month.

Even if the magnitude of the risk of swine influenza virus infections to human health is unknown, it seems unlikely to be high. Two factors are probably restricting infection of humans, though both are neglected research areas. Firstly, the host range of influenza viruses is generally very restricted by a limited fitness of a given virus in a different host species. Studies on the infectivity of animal influenza viruses for cells of the human respiratory tract, and the molecular determinants involved, have however so far focused almost exclusively on avian influenza viruses [16-18]. Secondly, immunity to human H1 or H3 influenza viruses may partially protect against infection with swine viruses. But animal model experiments on this issue are lacking. This type of research is needed if we want to understand the risk of zoonotic influenza based on scientifically proven facts rather than hypotheses.

The unknown element is the risk of reassortment to produce a novel virus, even a pandemic strain either in the pig "mixing vessel" or in a human dually infected with a human and pig strain. In the United States there have recently appeared triple reassortant swine influenza viruses with avian, human and swine genes and these have then transmitted to humans [19,20]. Fortunately, these and similar swine influenza viruses [21] that can infect humans have not yet met any of the criteria to cause a human pandemic. The true risk can only become clear if epidemiological investigations are combined with experimental research. Some scientists have advocated offering seasonal influenza vaccination to persons working with pigs to reduce their risk of getting infected [15]. However, experience with workers with domestic poultry on this point is not encouraging [22]. In one audit attempt in Europe uptake of the vaccine was low and those offered immunisation were confused as to what they were being protected against. The possible efficacy of human influenza vaccines against swine influenza virus infection, on the other hand, also remains unknown.

Following the discovery in Spain it seems likely that more human infections will be detected and reported as has happened in North America. While such events will mean an improvement in surveillance rather than an increased risk, they highlight another area where closer human and animal surveillance is needed around a poorly understood zoonosis.


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# Human case of swine influenza A (H1N1), Aragon, Spain, November 2008

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A human case of swine influenza A (H1N1) in a 50-year-old woman from a village near Teruel (Aragón, in the north-east of Spain), with a population of about 200 inhabitants, has been reported in November 2008.

On 8 November 2008, a 50-year old woman developed fever, cough, extreme tiredness, myalgia, irritation of the nasal/oral mucosae and shivers of sudden onset. During a medical visit on 12 November 2008, the general practitioner (GP) who treated the case and is a member of the sentinel influenza surveillance system, took a throat swab sample and sent it to the Microbiology Laboratory of the Miguel Servet University Hospital in Zaragoza, Aragón in the context of the Spanish Influenza Surveillance System. The patient, with no history of recent travel, did not need specific treatment or hospitalisation and recovered fully.

## Epidemiological investigation

The case worked on a family swine farm and had direct and close exposure to pigs. No other family members or co-workers reported flu-like symptoms before or after this case and no symptoms were observed in the pigs. However, the GP who took the throat swab sample reported influenza-like illness (ILI) after visiting the patient. No samples from the GP were taken at that time.

A low level influenza activity, with no activity for the geographical spread indicator, was reported in Spain and specifically in the province of Teruel during week 46/2009 when the case was notified. The GP did not report any other influenza case for the whole season up to week 53.

After the initial report of a possible case of A(H1N1) of swine origin from the National Influenza Reference Laboratory on 13 January, the following actions were taken: an active surveillance was implemented on site, including collection of blood samples for serological investigations from the case, the treating physician and the four household contacts of the case on January 20. Informed consent was required from all of them and a specifically designed questionnaire was used to interview the six mentioned people. So far, no more cases related to the farm have been detected.

Following the requirements of the International Health Regulations (IHR, 2005), this event was notified to the World Health Organization (WHO) as a human case of influenza caused by an influenza virus different from those circulating in humans.

## Laboratory investigation

Respiratory secretions were first inoculated in cell cultures (MDCK) at the Microbiology Laboratory of the Miguel Servet University Hospital. The cell cultures were positive for influenza A virus, but the assays routinely used in this laboratory (immunofluorescence with monoclonal antibodies and PCR assay) failed to subtype the virus. After consulting the National Influenza Reference Laboratory (National Influenza Centre-Madrid, Instituto de Salud Carlos III, Spain) the specimen and influenza isolate were sent to this laboratory for further characterisation. Different PCR approaches allowed to partially sequence and identify the haemagglutinin gene. On 13 January, 2009, the Reference Laboratory reported an influenza A subtype H1 phylogenetically close to the human isolate A/Switzerland/8808/2002 of swine origin [1] indicating a sporadic human infection of possible swine origin.

Other genes (NA, M, NP and NS) were also sequenced and analysed, which confirmed that the influenza A virus was phylogenetically related to swine H1N1 viruses. Partial sequences of the five genes have been submitted to the GenBank database (accession numbers from FJ713784 to FJ713788)PPB. Avian-like H1N1 swine influenza viruses are enzootic in the swine population of Western Europe. In order to undertake a serological survey and further virological studies the virus is being propagated in embryoned hen eggs.

## Discussion

The epidemiological and virological information points towards a human infection with an influenza virus of swine origin in a person with professional exposure to pigs. No further cases have been identified amongst family members or fellow workers. Sporadic human infections due to influenza viruses of swine origin have been described previously, mostly in young persons (<25 years) in contact with pigs [2-4]. Transmission to humans for unknown reasons seems to be inefficient. Although it is expected that similar

cases could appear in the future this event could not be considered unexpected. All these considerations have led us to investigate this case in order to contribute to a better knowledge of the interaction between swine and human influenza.

The treating physician reported mild influenza-like symptoms after contact with the patient. Based on the available information, human to human transmission could not be confirmed. Ongoing serological studies may be of help to determine whether further transmission of the swine virus has taken place. Human to human transmission has been reported before; however in these cases transmission was limited to one generation [5].

To conclude, this event cannot be considered unexpected and does not pose a public health risk which would require specific public health measures.


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# Mumps outbreak among the military in Luxembourg in 2008: epidemiology and evaluation of control measures

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In the last quarter of 2008, an outbreak of mumps occurred in Luxembourg affecting initially 10 young adults at a military centre. Following a mass vaccination campaign, no further clinical cases were observed. 90% of 136 vaccine recipients were IgG positive one month after vaccination compared to 54% before vaccination. Until 31 December 2008, 19 mumps cases were also reported from the community. The outbreak strain belonged to genogroup G.

## Introduction

During the last three months of 2008, an outbreak of mumps occurred in Luxembourg with 29 suspected clinical cases reported until 31 December 2008. Prior to this outbreak, the last time a mumps case was reported to the health authorities was in 2005.

Mumps is an acute viral infection characterised by swelling of the salivary glands and particularly the parotid glands. Asymptomatic cases occur quite frequently (up to 30% of all cases) and symptoms can be flu-like. The most frequently observed complications include inflammation of genital glands (testicles or ovaries), pancreatitis as well as aseptic meningitis. Mumps can be prevented by vaccination which was introduced to the routine schedule in Luxembourg in 1986-7 with trivalent measles, mumps, rubella vaccine (MMR) for children aged 15 to 18 months. A recommendation for a second dose at the age of 5-6 years was released in October 1994.

Following the incidence of 10 cases in different units at a military centre in Luxembourg in September and October 2008, the Military Command, the Army Health Service and the Health Inspection decided to organise a vaccination campaign for personnel in all units working on this particular military site, which also included personnel and trainees of the Luxembourg Police Force. At the same time it was decided together with the National Health Laboratory to conduct a sero-epidemiological survey with the aim to determine seroprevalence against mumps virus in this army population and to study risk factors for being seronegative.

## Methods

For the purpose of the outbreak investigation at the military centre, the following case definition criteria stated by the Centers for Disease Control and Prevention (CDC) were used [1]. A clinical case was defined as a patient with acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland(s), lasting at least two days, and without other apparent cause. Laboratory criteria for diagnosis were isolation of mumps virus from clinical specimen, detection of mumps nucleic acid by real-time PCR, or detection of mumps IgM antibodies.

Following the decision to hold a vaccination campaign, all army and police personnel working onsite were briefed about the cases and the current situation of the mumps epidemic, recommended to participate in the vaccination campaign (on a voluntary basis) and explained the reasons and usefulness of the sero-epidemiological study. The blood sample collection was organised at the Army Health Service onsite in collaboration with the National Health Laboratory upon receipt of written informed consent forms. The samples were immediately transported to the National Health Laboratory where they were prepared and stored for future analysis. A quantitative IgG and IgM assay (Genzyme Virotech, Rüsselsheim, Germany) was used to determine the presence of anti-mumps antibodies according to the manufacturer's instruction. A real-time PCR assay was implemented to detect mumps virus in throat swaps/oral fluid and followed by sequencing of the positive samples [2,3].

## Results

### The epidemic

Figure 1 shows the evolution of the mumps epidemic in Luxembourg up to the end of the year 2008. Following the vaccination campaign which began on 28 October 2008, no further clinical cases have been observed at the military centre, but several clinical cases were reported in the "civilian" population in Luxembourg.

The age distribution of reported cases shown in Figure 2 reveals that the large majority (23 of 29 or 79%) were aged between 15 and 34 years. Seven of the reported 29 (24%) cases were female.

Of 13 oral or throat swabs taken from suspected clinical mumps cases, six were positive by PCR (out of which five could also be cultured). Nucleotide sequencing showed that the strain belonged to genogroup G which has been observed recently in Bavaria, Germany (May-July 2008), the United States (2006) and the United Kingdom and Ireland (2004-05).

Detailed clinical data are available for the 10 cases reported at the military centre. Eight patients had a classical presentation with parotitis, predominantly right-sided. Of those eight cases, five had never been vaccinated, one had received a single dose and two had received two doses of a MMR vaccine. The two patients with non-specific symptoms and positive IgM test results had received two vaccine doses. Two patients hospitalised with suspected viral meningitis recovered without sequelae.

**Sero-epidemiological study at the military centre**

225 participants including 26 women (12%) agreed to give a blood sample prior to the vaccine administration by informed written consent. Of these, 134 (60%) had a positive IgG result, 37 (16%) had a borderline IgG result and 54 (24%) had a negative IgG result. The majority, 219 (97%) participants were IgM negative, five (2%) were IgM borderline, and one participant had a positive IgM result.

The IgG seroprevalence rate varied significantly with age – participants born before 1970 had higher seroprevalence (81%) compared to participants born after 1970 (53%, p=0.006).

For participants with a documented vaccination history, IgG seroprevalence did not vary significantly as a function of the number of received doses (p=0.19).

Of the 225 participants, 136 (60%) gave a second blood sample on average 31 days after administration of the Priorix® vaccine. 123 (90%) were IgG positive, six (4%) were IgG borderline and seven (5%) were IgG negative. Of 37 participants who were initially IgG negative, 24 (65%) became IgG positive, six (16%) were IgG borderline and seven (19%) remained IgG negative one month after vaccination. All 25 participants who were initially IgG borderline became IgG positive and all 74 participants who were initially IgG positive remained positive.

At the second sampling opportunity, four (3%) participants were IgM positive (they were initially IgG and IgM negative), three (2%) were IgM borderline (two had also been initially IgM borderline and one negative), and 129 (95%) participants were IgM negative.

FIGURE 2

**Age distribution of reported mumps cases in Luxembourg, 2008 (n=29)**

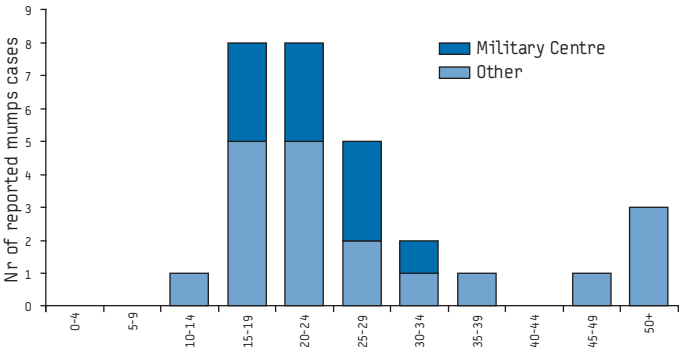


TABLE 1

**Sero-epidemiological study of mumps at a military centre in Luxembourg, 2008. IgG results by year of birth (chi2 test, p=0.006)**

| Year of birth | negative | borderline | positive |
|---|---|---|---|
| <1970 | 6 (11%) | 4 (7%) | 44 (81%) |
| 1970-83 | 19 (33%) | 8 (14%) | 30 (53%) |
| 1984-86 | 15 (27%) | 10 (18%) | 31 (55%) |
| 1987-90 | 14 (24%) | 15 (26%) | 29 (50%) |
| Total | 54 (24%) | 37 (16%) | 134 (60%) |

TABLE 2

**Sero-epidemiological study of mumps at a military centre in Luxembourg, 2008. IgG results by number of measles, mumps, rubella (MMR) vaccine doses received before the onsite vaccination campaign (chi2 test, p=0.19)**

| Number of doses | negative | borderline | positive |
|---|---|---|---|
| 0 | 24 (19%) | 19 (15%) | 81 (65%) |
| 1 | 14 (39%) | 5 (14%) | 17 (47%) |
| 2 | 14 (25%) | 11 (20%) | 31 (55%) |
| 3 | 0 (0%) | 1 (50%) | 1 (50%) |
| Total | 52 (23%) | 36 (16%) | 130 (59%) |

FIGURE 1

**Epidemic curve of reported mumps cases in Luxembourg, 2008 (n=29)**

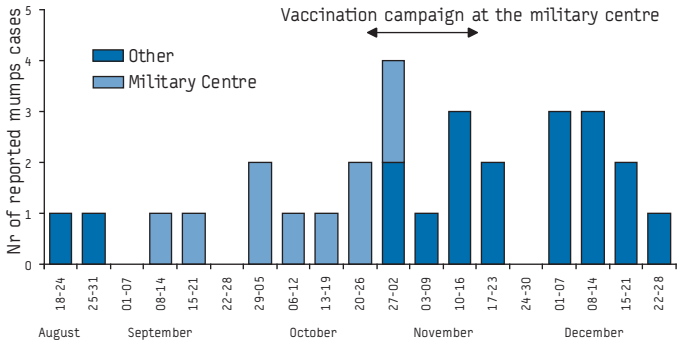


TABLE 3

**Sero-epidemiological study of mumps at a military centre in Luxembourg, 2008. Comparison of IgG results before and one month after the vaccination campaign**

| | IgG after vaccination | | | |
|---|---|---|---|---|
| IgG before vaccination | negative | borderline | positive | Total |
| negative | 7 | 6 | 24 | 37 |
| borderline | 0 | 0 | 25 | 25 |
| positive | 0 | 0 | 74 | 74 |
| Total | 7 | 6 | 123 | 136 |

## Discussion

Our study reveals that, following several years of absence, mumps virus has re-emerged in Luxembourg in the last term of 2008. This is not surprising as other countries in Europe and North America have also witnessed relatively sizable mumps outbreaks in recent years [4-13].

In our case, most reported cases occurred in young adults. More than half of the staff on the military site was born before the introduction of the combined MMR vaccine in 1986 and the majority of reported clinical mumps cases had never received vaccination. Whereas most persons born before 1970 have naturally acquired immunity, persons born between 1970 and 1985 have had less exposure to mumps virus (due to the reduction of mumps circulation after the MMR vaccine was introduced into the vaccination schedule in 1986) and have never been targeted by a "mop-up" vaccination campaign. Moreover, our data seem to suggest that a sizable fraction of persons born between 1986 and 1990 (49% of participants) have not received the recommended two doses of MMR vaccine. This could be explained by the fact that the official recommendation of a second dose of MMR was only issued in 1994, eight years after the introduction of MMR vaccine.

The vaccination campaign at the military centre appears to have led to a large reduction of viral transmission as no further clinical cases have been observed at the site. Following vaccination, 90% of the study participants were IgG positive compared with 54% before vaccination. Even if the sensitivity of our serological assay is slightly problematic (due to a high proportion of borderline results), a quantitative analysis seems to suggest that « borderline » results can be boosted by vaccination, from a mean of 10 Virotech units to 18 units.

Another interesting aspect of this incident is that the rapid implementation of the vaccination campaign at the military centre was an ideal real-life exercise for the influenza pandemic. Our experience suggests that in the right conditions, a doctor assisted by two technicians (one for the preparation of the vaccine and one for paper work) can administer vaccines to approximately 150 persons in half a day.

Although the sample size in our study is quite limited, our data suggest that a single dose of Priorix® vaccine could be immunogenic (i.e. induced a positive or borderline IgG result) in approximately 80% of previously seronegative adults. While some authors have suggested that waning immunity may contribute to mumps outbreaks in older vaccinated populations [6], the large majority of our cases have no history of vaccination. If waning of immunity was more prevalent, we would also expect the outbreak to spread to younger vaccinated generations (who go to secondary schools where a lot of mixing occurs [14]) and this has not (yet) been observed.

To stop the circulation of mumps virus in the long term in Luxembourg, we suggest that a MMR campaign aimed at all persons* born between 1970 et 1990 who have not received two doses of vaccine or who do not have protective antibody levels would be necessary to protect their health. Such a campaign could also have an additional advantage of increasing population immunity against rubella and measles which have been targeted for elimination by the World Health Organization (WHO) European Region by 2010. In addition, further measures are probably necessary to document and possibly raise levels of two dose coverage with the MMR vaccine in adolescents and children born after 1990.

*Note: While respecting vaccine manufacturer's contraindications, particularly in women: no current or pregnancy planned for 3 months after vaccination.


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# Treatment failure in case of typhoid fever imported from India to Czech Republic, December 2008 - January 2009

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In this report we describe a case of typhoid fever in a Czech patient with history of travel to India and discuss antibiotic treatment failure which led to the relapse of fever.

## Case report

### Travel history

A previously healthy 31-year-old man from the Czech Republic visited India from 2 October to 28 November 2008. Before leaving the Czech Republic he had received neither vaccination (travellers to India are advised to get vaccinated at least against viral hepatitis A and typhoid fever) nor antimalaric chemoprophylaxis. He climbed the Himalayas, and in the last week of his stay he visited Varanasi at the Ganga River. There, he drunk a soft drink from a cup washed in water of unsure origin at the market place. His travelling companion had the same food without this soft drink, and had no problems afterwards.

A week before returning home the man experienced fever (temperature 40°C), fatigue and vomiting without diarrhoea. While still in India he took ciprofloxacin bought at the chemist´s. He returned home on 28 November 2008. On 1 December the patient was examined by his general practitioner and sent to the Department of infectious diseases in Ostrava because of malaria suspicion.

### First hospitalisation

After admission malaria was excluded, and hepatosplenomegaly was proved by ultrasonography. Laboratory analyses showed increased C-reactive protein (109 mg/l), and alanine aminotransferase (ALT) was elevated (100.2 U/l). Widal test was repeatedly negative during hospitalisation. On 3 December Salmonella sp. was found in blood culture and in stool, and on the next day *Salmonella typhi (S. typhi)* was identified.

The patient was first treated by cefotaxime in a dose of 6 g per day. As fever continued, after five days of cefotaxime, ciprofloxacin of 800 mg per day was added. Although fever gradually dropped, the temperature stayed at 38.5°C for 10 days and at 37.5°C for next five days. Laboratory results were subsequently improving (a decline of C- reactive protein and ALT). Cefotaxime was administered for a total of 19 days, ciprofloxacin for a total of 15 days. The patient was discharged on 22 December 2008 after 21 days of hospitalisation and after seven days without fever.

### Second hospitalisation

At home the patient was feeling weak but his condition was gradually improving. On 31 December (nine days after leaving hospital), the patient had a new episode of fever (temperature 38.5°C) and on 1 January 2009 he was hospitalised again with the temperature of 39.5°C, fatigue and sweat. Malaria was excluded again. Ciprofloxacin was used in the therapy. As treatment showed no effect on the third day ciprofloxacin was replaced by meropenem, however, despite therapy change the patient´s temperature continued to peak daily at 39.5°C. Laboratory analyses showed increasing C-reactive protein (from 42 mg/l to 96 mg/l) and decreasing platelet count (from 195 to 83 x 109/l). Hepatosplenomegaly was proved by ultrasonography again. When *S. typhi* was detected in blood culture again on 5 January 2009 the patient was administered intravenous chloramphenicol in dose of 6 g per day for 17 days. Finally his temperature dropped within 36 hours and the patient started to feel better without further complications. Laboratory results were gradually improving. He was discharged home after 22 days.

## Discussion

In endemic areas typhoid fever occurs as asymptomatic or mild illness. According to the World Health Organization the case-fatality rates were 10-20% during the pre-antibiotic era, and can be reduced to less than 1%, with prompt and appropriate antibiotics therapy [1]. Fluoroquinolones had previously been very effective in the treatment of typhoid fever but in the past decade, progressive increase in the minimum inhibitory concentration (MIC) of ciprofloxacin and high incidence of clinical failures to quinolones have been described [2]. The third generation cephalosporins are now being increasingly used but they are associated with a long time of defervescence and high rates of relapses [2].

The annual incidence of typhoid fever in India is 493.5 per 100,000 inhabitants, and quinolones treatment failure is common there [3]. In India there have also been sporadic reports of high–level resistance to ceftriaxon in *S. typhi* and return of sensitivity to chloramphenicol [1,3]. Multi-drug resistance was seen in 32% of strains [4]. There are reports of the emergence of fluoroquinolone-resistant isolates in various part of Asia and descriptions of resistance to third-generation cephalosporins in the same region. However, many of these reports are coupled with evidence of re-

emergence of sensitive isolates in the same region [1]. In South America incidence of fluoroquinolone-resistant strains is low [5].

In the case described in this paper, sensitivity tests performed during the first hospitalisation showed that *S. typhi* had MIC of cefotaxime equal to 0.016 mg/l, of ciprofloxacin 0.250 mg/l and of meropenem 0.016 mg/l. *S. typhi* was sensitive to chloramphenicol, but MIC was not assessed. During the second hospitalisation *S. typhi* had MIC of cefotaxime 0.016 mg/l, of meropenem 0,016 mg/l, of ciprofloxacin 1.000 mg/l, of ampicilin >128.0 mg/l and of cotrimoxazol > 64.0 mg/l. MIC of 0.250 mg/l has been described as resistance to ciprofloxacin [6,7].

In our patient typhoid fever therapy with ciprofloxacin plus cefotaxime showed to be ineffective, despite of adequate dose, duration of therapy and susceptibility to cefotaxime in vitro. Even though the results of blood tests were improving, the temperature declined very slowly and a relapse of typhoid fever appeared two weeks after stopping the treatment. In spite of good sensitivity to meropenem, this agent was also ineffective. Only traditional chloramphenicol actually showed to be effective.

In typhoid fever diagnostics Widal test is very commonly used but has very variable sensitivity and specificity and problems in interpretation [2]. In our patient Widal test was repeatedly negative.

## Conclusion

The 2003 World Health Organization guidelines recommend treatment with fluoroquinolones for both complicated and uncomplicated cases of typhoid fever. However, sensitivity profiles of S. typhi vary geographiccaly, so the initial antibiotic choice for typhoid fever treatment should be based on the sensitivity data of the area in which the infection was acquired [5]. In a patient returning from India S. typhi resistance to quinolones has to be presumed. The third generation cephalosporins represent treatment alternative, although resistance to these drugs is gradually increasing [3]. Chloramphenicol can be an option of antibiotic choice for typhoid fever treatment when another therapy fails.

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# Risk factors for sporadic Campylobacter infection: an all-Ireland case-control study

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We report the findings of the first case-control study conducted in both the Republic of Ireland and Northern Ireland to determine risk factors for sporadic *Campylobacter* infections. A total of 197 cases and 296 case-nominated controls matched for age, were included. Based on Population Attributable Fraction (PAF), the most important risk factors were consuming chicken [adjusted matched (am) OR 6.8; 95%CI 2.1-21.9], consuming lettuce (amOR 3.3; 95%CI 1.5-7.1) and eating in takeaways (amOR=3.1; 95%CI 1.4-6.6). Contact with sheep (amOR=11; 95%CI 1.6-78), peptic ulcer (amOR=19; 95%CI 3.8-93.7), hiatus hernia (amOR=20.3; 95%CI 2.3-183.3), lower bowel problems (amOR=4.5; 95%CI 1.2-16.8) were also independently associated with infection. Mains water supply showed protective effect (amOR=0.2; 95 CI 0.1-0.9). The findings highlight the continued need for consumer food safety education and further control measures throughout the food chain on the island of Ireland.

## Introduction

In line with many western countries, *Campylobacter* is the most common cause of laboratory confirmed bacterial gastrointestinal disease in both the Republic of Ireland (ROI) and Northern Ireland (NI). Between 1999 and 2006 over 20,000 laboratory-confirmed cases were reported in the two jurisdictions, giving a mean incidence rate of 47 per 100,000 population per year and representing about two thirds of all acute reported gastroenteritis [1,2].

*Campylobacter* infection is of important public health concern as it can cause considerable illness and loss of productivity and may be associated with sequelae, such as reactive arthritis and Guillain Barré syndrome [3-7]. Different risk factors have been reported in various studies conducted in several developed countries, with the most common ones being: consumption and handling of chicken, and in particular undercooked chicken or commercially prepared chicken; unpasteurised milk and dairy products; consumption of untreated water; contact with domestic pets like dogs and cats; contact with farm animals; travel abroad [7-14]. However, differences between risk factors across studies may reflect either different study methodologies or variations in the sources of infection across different countries [6,8]. In addition, epidemiological studies conducted in the United Kingdom (UK) have suggested that there may be even regional differences in the contributing risk factors for infection [15].

Although the population health burden from *Campylobacter* is considerable, there have not been any analytical studies conducted in Ireland on the epidemiology of the disease in humans. This paper describes the first case-control study that was conducted in both ROI and NI, to identify risk and protective factors for sporadic *Campylobacter* infection on the island of Ireland and estimate the proportion of the risk attributable to the identified factors, in order to guide prevention efforts.

## Methods

### Study design

A prospective matched case-control study was conducted in all four Health Board areas in NI and the Health Service Executive (HSE) Eastern region in ROI (which includes the greater Dublin area and represents 36% of the ROI population). Data were collected over a 12-month period (from December 2003 to December 2004).

Two controls were nominated by each case matched for age group (0-5, 6-10, 11-20, 21-34, 35-49, 50-64 and 65+ years). Age was chosen as a matching variable because (i) potential high-risk exposures (e.g. food habits, leisure activities) vary considerably among different age groups and (ii) the age profile of campylobacteriosis in Ireland, both ROI and NI, peaks in some age groups, namely 0-4 and 20-34 years.

### Cases

A case was defined as a person of any age (living or visiting the study area) whose laboratory confirmed Campylobacter spp. infection was reported through the routine surveillance systems in the participating health authorities, during the 12-month study period. Cases were excluded if (i) they were associated with an outbreak reported to the health authority or the national surveillance centre or (ii) at least one matched control could not be identified.

### Controls

Cases (or adult respondents, in case of children patients aged less than 16 years) were asked to hand the questionnaires to

two controls matched for age group (such as neighbours, work colleagues, friends or schoolmates, but not household members).

Controls were excluded (i) if they had gastrointestinal symptoms in the 14 days prior to the completion of the questionnaire (ii) if they lived in the same household as the case or (iii) if the completed questionnaire of the matched case was not available.

### Sample size

To detect an association with a matched odds ratio (mOR) of 2 at the 5% significance level, with 80% power and a case-control ratio of 1:2, a sample size of 186 case-control sets (i.e. a case with at least one matched control) was required, assuming 70% chicken consumption among controls, as reported in the North/South Ireland Consumption Survey [16]. The calculation was performed by a software written by the Statistics Unit of the Health Protection Agency (HPA) [17].

### Study questionnaire

Information on exposures of the cases and their matched nominated controls was collected using a self-administered postal questionnaire. This gathered demographic data (age, gender, employment status, occupation), clinical details of cases (date of onset, duration and symptoms of the disease, if hospitalisation was required), and information on household contacts.

The 86 considered exposures were grouped into five categories:

- Food and drink history, including drinking water (type of water supply, bottled water, other sources), meat (beef, pork, lamb, sausage, ham, salami), fish, chicken, vegetables, fruit, milk and dairy products and eating out (type of restaurant or takeaway);
- Foreign travel (outside the island of Ireland);
- Contact with animals (pets and farm animals);
- Leisure activities (including swimming, gardening, visits to parks or farms, fishing and other sports);
- Medical history and medication (antacids, H2-receptor antagonists, antibiotics).

Dose-responses of the food and drink exposures (frequency of consumption) were investigated. All questions related to exposures in the seven days before the onset of symptoms for cases and seven days before the completion of the questionnaire for controls, except for medication (one month before illness onset/completion of questionnaire) and foreign travel (14 days before). Adult family members were asked to complete the questionnaires on behalf of children under the age of 16. The questionnaire was validated during a pilot study conducted in ROI that involved 20 cases. To increase the response rate, a reminder letter was sent to the cases that had not responded within 14 days.

The study received ethical approval by two Ethics Committees; the Faculty of Public Health Medicine Research Ethics Committee in ROI and the Queen's University of Belfast Research Ethics Committee in NI.

### Statistical analysis

Data were entered in a database designed using EpiInfo2003 software (version 3; Centers for Disease Control and Prevention) and were checked for mistakes and inconsistencies (consistency and range checks). Food/drink exposures were treated as dichotomous variables, whereas frequencies of food/drink consumptions were analysed as continuous variables. Age was grouped into the following age bands: 0-5, 6-10, 11-20, 21-34, 35-49, 50-64 and 65+ years. Initial univariate matched analysis was carried out to calculate age-group adjusted matched OR (mOR) and their 95% confidence intervals (95%CI). Age adjustment was performed to control for the potential residual confounding of age, as matching for age had not been successful in some young cases. Dose-response relationships were also examined between frequencies of food/drink consumptions and the disease.

Multiple conditional logistic regression models were constructed with Stata software (version 8, Stata Corporation, Texas). The initial regression model was developed including age, gender and all other variables for which (i) the p-value (for the OR) was less than 0.05, or (ii) the OR was more than 1.5 or less than 0.67 in the univariate analysis. These cut-off values were considered

**Table 1**

**Socio-demographic characteristics of cases and controls included in the final analysis. All-Ireland Campylobacter infection case-control study, 2004**

| | Cases (n=197) n (%) | Controls (n=296) n (%) |
|---|---|---|
| Sex | | |
| Males | 91 (46.4) | 101 (34.4) |
| Age group | | |
| 0-5 years | 26 (13.3) | 23* (8.0) |
| 6-10 years | 9 (4.6) | 9* (3.1) |
| 11-19 years | 25 (12.8) | 37 (12.9) |
| 20-34 years | 46 (23.4) | 78 (27.2) |
| 35-49 years | 47 (23.9) | 61 (21.3) |
| 50-64 years | 31 (15.8) | 58 (20.2) |
| 65+ years | 13 (6.6) | 21 (7.3) |
| Employment status | | |
| Employed | 98 (52.7) | 175 (61.8) |
| Unemployed | 8 (4.3) | 16 (5.7) |
| Student | 34 (18.3) | 48 (17) |
| Retired | 19 (10.2) | 22 (7.8) |
| Other (housewife, baby, etc.) | 27 (14.5) | 22 (7.9) |
| Food-handler | 13 (13.3)† | 28 (16.0)‡ |
| Contact with animals (as job) | 3 (3.1) | 7 (4.0) |
| Place of residence | | |
| City/town | 40 (90.9) | 62 (89.9) |
| Village/rural area | 4 (9.1) | 7 (10.1) |
| Type of house | | |
| Apartment | 14 (7.7) | 18 (6.8) |
| House | 163 (89.6) | 238 (90.5) |
| Farm | 5 (2.7) | 7 (2.7) |
| Household contacts | | |
| Mean number of people in household (standard deviation) | 3.5 (1.5) | 3.8 (2.2) |
| Child < 5 years in household | 44 (22.6) | 68 (23.1) |
| Mean number of children <5 years in household (standard deviation) | 0.31 (0.6) | 0.31 (0.7) |

* Five cases aged 0-5 years and five cases aged 6-10 years nominated controls that were older than 5 and 10 years, respectively
† Among the 98 employed cases
‡ Among the 175 employed controls

important for the specific exposures and the disease. To simplify the model, variables were removed one at a time depending on the significance testing ($p<0.05$) by the likelihood ratio (LR) test or the alteration of OR. Because of several missing values, frequency of food/drink consumption variables were not included in the models and food/drink items as dichotomous variables were included instead. Potential interactions among all variables in the final model, age and country (ROI vs NI) were also examined. The population-attributable fractions (PAF) for all risk factors in the final model were calculated, using the following formula for matched case-control studies: PAF = [ P' * (amOR -1) / amOR, where P' is the proportion of cases exposed and amOR is the adjusted matched OR which was derived from the final conditional regression model.

## Results

### Response rate

A total of 978 persons fulfilling the case definition were contacted and 402 (41.1%) (215; 37.7% in ROI and 187; 45.7% in NI) returned a completed questionnaire. Of these, 197 (49%;52.5% in ROI and 44.9% in NI) had at least one control that responded. The final analysis was made up of 197 cases (113 in ROI and 84 in NI) and 296 controls (172 in ROI and 124 in NI). Of the 197

**Table 2**

**Univariate analysis of risk and protective factors (travel, eating out, poultry, meat and fish, vegetables and fruit consumption) for campylobacteriosis. All-Ireland Campylobacter infection case-control study, 2004.**

| Exposure | Cases (n=197) † n (%) | Controls (n=296) † n (%) | Crude OR * (95% CI) | P-value |
|---|---|---|---|---|
| Male | 91 (46.4) | 101 (34.4) | 2.0 (1.2-3.2) | 0.005 |
| Foreign travel | | | | |
| Foreign travel (outside the island of Ireland) | 41 (20.8) | 22 (7.5) | 3.5 (1.7-7.3) | <0.001 |
| Travel to United Kingdom | 7 (3.6) | 8 (2.7) | 1.8 (0.6-5.7) | 0.34 |
| Travel to Europe | 29 (14.7) | 20 (6.8) | 2.8 (1.4-5.8) | 0.005 |
| Travel to places outside Europe | 12 (6.1) | 2 (0.7) | 17.8 (2.2-143) | 0.007 |
| Poultry and poultry products | | | | |
| Chicken | 181(92.3) | 251 (85.1) | 3.0 (1.5-6.1) | 0.002 |
| Undercooked chicken | 13 (6.7) | 2 (0.7) | 9.5 (2.1-43.5) | 0.004 |
| Duck | 10 (5.1) | 12 (4.1) | 2.0 (0.7-5.6) | 0.18 |
| Turkey | 11 (5.6) | 44 (14.9) | 0.3 (0.1-0.6) | 0.002 |
| Handle raw chicken bought from butchers | 9 (4.6) | 34 (11.5) | 0.4 (0.2-0.9) | 0.02 |
| Meat and fish | | | | |
| Any meat and fish | 189 (95.9) | 290 (98) | 0.4 (0.1-1.5) | 0.15 |
| Beef (including mince) | 143 (73) | 244 (82.7) | 0.6 (0.4-1) | 0.03 |
| Sausages | 114 (58.5) | 196 (60.2) | 0.6 (0.4-1) | 0.03 |
| Pate | 12 (6.1) | 13 (4.4) | 1.9 (0.7-4.8) | 0.25 |
| Salami | 17 (8.7) | 33 (11.2) | 0.6 (0.3-1.2) | 0.14 |
| Fresh fish | 40 (20.5) | 84 (28.5) | 0.5 (0.3-0.9) | 0.02 |
| Frozen fish | 42 (21.5) | 89 (30.2) | 0.6 (0.4-1) | 0.07 |
| Any meat cooked rare | 17 (8.8) | 14 (4.7) | 1.6 (0.7-3.6) | 0.26 |
| Handle raw meat | 73 (37.4) | 144 (49.5) | 0.6 (0.4-1) | 0.05 |
| Vegetables and fruit | 178 (90.4) | 281 (94.9) | 0.5 (0.2-1.1) | 0.07 |
| Lettuce | 124 (63.6) | 181 (61.4) | 1.6 (1.0-2.6) | 0.06 |
| Prepared salad - other than lettuce, e.g. coleslaw | 71 (36.4) | 147 (50.1) | 0.6 (0.4-0.9) | 0.01 |
| Milk and dairy products | 187 (94.9) | 283 (95.9) | 0.9 (0.4-2.3) | 0.88 |
| Cold milk | 87 (44.4) | 171 (58.2) | 0.5 (0.3-0.8) | 0.00 |
| Ice-cream | 86 (44.3) | 166 (56.5) | 0.6 (0.4-0.9) | 0.02 |
| Yoghurt | 99 (50.8) | 184 (62.8) | 0.6 (0.4-0.9) | 0.01 |
| Eating out | 143 (73) | 204 (69.2) | 1.4 (0.9-2.2) | 0.13 |
| Fish and Chip shop | 24 (12.2) | 64 (21.7) | 0.5 (0.3-0.9) | 0.03 |
| Indian Restaurant/ /takeaway | 12 (6.1) | 14 (4.7) | 1.3 (0.5-3.1) | 0.61 |
| Chinese Restaurant/ /takeaway | 61 (31.1) | 89 (30.2) | 1.1 (0.7-1.8) | 0.55 |
| Other Restaurant/takeaway | 54 (27.6) | 46 (15.6) | 2.6 (1.5-4.4) | <0.001 |
| Plane | 19 (9.7) | 5 (1.7) | 7.8 (2.2-27.1) | 0.001 |

* Matched odds ratio adjusted for age † For several variables answers were not available from all participants (denominators in percentages vary).

case-control sets, 101 cases were matched to one control each, 93 cases to two controls each, and three cases to three controls each (as these three cases handed questionnaires to three controls instead of two).

The participant (n=197) and non-participant cases did not differ significantly in terms of gender (p=0.24) and age group (p=0.13). In addition, the response rate of cases was similar in each season, suggesting that the number of participant cases by season reflected the seasonal distribution of reported campylobacteriosis cases (data not shown).

### Cases and controls

The main socio-demographic characteristics of cases and controls are shown in Table 1. The median age (32 years; range 0-76) of cases did not differ significantly from the median age (33 years; range 0-81) of controls (p=0.253). Regarding gender, 46.4% of cases and 34.4% of controls were male.

**Table 3**

**Univariate analysis of risk and protective factors (alcohol and drinking water, contact with animals, leisure activities, medical history) for campylobacteriosis. All-Ireland Campylobacter infection case-control study, 2004.**

| Exposure | Cases (n=197) † n (%) | Controls (n=296) † n (%) | Crude OR* (95% CI) | P-value |
|---|---|---|---|---|
| Alcohol | 98 (50.5) | 174 (59.4) | 0.7 (0.4-1.2) | 0.15 |
| Alcohol during meals | 59 (30.3) | 73 (24.9) | 1.8 (1-3.2) | 0.04 |
| Drinking water | | | | |
| Mains water supply | 184 (93.4) | 268 (96.3) | 0.4 (0.2-1.0) | 0.06 |
| Well | 4 (2.0) | 3 (1.0) | 2.4 (0.5-11.0) | 0.27 |
| Group water scheme | 2 (1.0) | 2 (0.7) | 1.5 (0.2-12.0) | 0.70 |
| Tap water | 151 (77.0) | 245 (83.6) | 0.8 (0.5-1.3) | 0.37 |
| Own pet(s) | | | | |
| Own any pet | 5 (2.5) | 5 (1.7) | 1.8 (0.5-7.1) | 0.38 |
| Dog (as pet) | 16 (8.1) | 36 (12.2) | 0.5 (0.2-1.1) | 0.08 |
| Cat (as pet) | 4 (2.0) | 11 (3.7) | 0.6 (0.2-2.1) | 0.46 |
| Fish (as pet) | 4 (2.0) | 10 (3.4) | 0.3 (0.1-1.4) | 0.12 |
| Pet ill with diarrhoea | 57 (28.9) | 110 (37.4) | 0.7 (0.4-1.1) | 0.09 |
| Contact with animals (other than pets) | | | | |
| Other dogs | 39 (19.3) | 93 (31.6) | 0.5 (0.3-0.8) | 0.01 |
| Horses | 4 (2.0) | 7 (2.4) | 0.5 (0. 1-2.6) | 0.39 |
| Sheep or lambs | 8 (4.1) | 5 (1.7) | 3.8 (0.7-19) | 0.11 |
| Outdoor and leisure activities | | | | |
| Swimming or water sports in the sea | 10 (5.1) | 8 (2.7) | 2.4 (0.7-8.6) | 0.18 |
| Running/Jogging/Athletics | 18 (9.2) | 38 (12.9) | 0.6 (0.3-1.1) | 0.12 |
| Play in a garden or park | 42 (21.4) | 90 (30.6) | 0.4 (0.2-0.7) | 0.00 |
| Own a garden | 175 (89.7) | 262 (89.4) | 1.4 (0.7-3.1) | 0.35 |
| Using manure in the garden | 6 (3.1) | 7 (2.4) | 1.4 (0.4-4.6) | 0.55 |
| Health and medical history | | | | |
| Any of the following health problems | 73 (37.1) | 63 (21.3) | 2.3 (1.42-3.6) | 0.00 |
| Stomach ulcer | 23 (11.7) | 8 (2.7) | 5.4 (2-14.7) | <0.001 |
| Gall stones or liver disease | 5 (2.6) | 2 (0.7) | 4.3 (0.8-24) | 0.10 |
| Hiatus hernia | 18 (9.2) | 4 (1.4) | 11.9 (2.7-52) | 0.00 |
| Lower bowel problems | 23 (11.7) | 14 (4.8) | 4.2 (1.8-9.6) | <0.001 |
| Lower bowel problems | 8(4.1) | 6 (2) | 2.7 (0.8-9.2) | 0.11 |
| Lower bowel problems | 12 (6.2) | 5 (1.7) | 3.8 (1.2-11.3) | 0.03 |
| Any of the following drugs in the month before | 47 (24) | 52 (17.7) | 1.4 (0.8-2.3) | 0.21 |
| Antacid medicines | 21 (10.8) | 34 (11.6) | 0.9 (0.5-1.7) | 0.70 |
| Ulcer medicines | 21 (10.8) | 4 (1.4) | 10.3 (3-35.7) | <0.001 |
| Steroid tablets | 4 (2.1) | 4 (1.4) | 1.7 (0.4-7.2) | 0.47 |
| Antibiotics | 17 (8.7) | 15 (5.1) | 1.4 (0.7-3) | 0.39 |

* Matched odds ratio adjusted for age † For several variables answers were not available from all participants (denominators in percentages vary).

Information on place of residence (city/village/rural area) was only available for 38.3% of the respondents. Of those, the majority (90.9% of cases and 89.9% of controls) reported living in a town or city.

There were no significant differences in the employment status between cases and controls (Pearson chi2 = 8.1712; p= 0.086). Among employed cases and controls, 13.3% and 16.0% respectively reported handling food as part of their occupation.

The median number of people living in the same household as the cases was three (range 1-8) compared to four (range 1-9) people living in the same household as controls (p=0.35). Of the cases, 22.6%, and of the controls, 23.1% had at least one child under five years of age in their household (p=0.47).

### Clinical features of cases

The main symptoms reported by the 197 cases were diarrhoea (99.1%) (including bloody diarrhoea reported by 39.1%), abdominal pain (89.3%) and fever (63.8%). Almost a fifth of cases were admitted to hospital, with the median duration of hospitalisation being fours days (range 1-14 days).

### Univariate and multivariate analysis of risk factors

The results of the univariate analysis for selected risk and protective factors are shown in Table 2 and Table 3. Cases were more likely than controls to have consumed chicken, and undercooked chicken in particular, duck, lettuce, to have eaten in a takeaway restaurant, to have eaten in a plane, to have travelled outside Ireland, to have drunk from a well, to have had contact with a sheep or lamb and to have swum in the sea. Cases were also more likely than controls to suffer from peptic ulcer, hiatus hernia or lower bowel problems.

**Table 4**

**Final conditional logistic regression model. All-Ireland Campylobacter infection case control study, 2004.**

| Risk and protective factor | Crude OR* (n=457) | Adjusted OR* (n=457) | PAF † |
|---|---|---|---|
| Chicken | 2.8 (1.4-5.7) | 5.6 (1.8-15.6) | 83.2 |
| Lettuce | 1.5 (0.9-2.5) | 2.6 (1.3-5.2) | 58.5 |
| Other restaurant/takeaway | 2.6 (1.5-4.4) | 3.1 (1.4-6.6) | 24.7 |
| Hiatus hernia | 11.9 (2.7-52.4) | 20.3 (2.3-183.3) | 21.6 |
| Peptic ulcer | 5.4 (2-14.7) | 19.0 (3.8-93.7) | 32.7 |
| Lower bowel problems | 4.2 (1.8-9.6) | 4.5 (1.2-16.8) | 14.4 |
| Contact with sheep | 3.8 (0.7-19.1) | 11.0 (1.6-78) | 14.5 |
| Turkey | 0.7 (0.5-1.1) | 0.2 (0.1-0.5) | -- |
| Beef | 0.6 (0.4-1) | 0.4 (0.2-0.8) | -- |
| Salad (other than lettuce) | 0.6 (0.4-0.9) | 0.4 (0.2-0.8) | -- |
| Mains water supply | 0.4 (0.2-1) | 0.2 (0.1-0.9) | -- |
| Contact with a dog other than one's own | 0.5 (0.3-0.8) | 0.4 (0.2-0.8) | -- |
| Playing in a park | 0.4 (0.2-0.7) | 0.3 (0.1-0.7) | -- |
| Male | 2.0 (1.2-3.2) | 2.4 (1.2-4.7) | -- |

* Crude and adjusted matched odds ratios (ORs) are calculated based on 457 subjects, due to missing values in some variables
† Population-attributable fraction

In the final conditional logistic regression model, seven variables remained significant independent risk factors for *Campylobacter* infection (consuming chicken, consuming lettuce, eating in a takeaway, contact with sheep, suffering from peptic ulcer, suffering from hiatus hernia and suffering from lower bowel problems) and six were protective factors (consuming turkey, consuming beef, consuming salad other than lettuce, having mains water supply at home, contact with dog other than one's own and playing in a park) (Table 4).

Eating chicken was the only risk factor that showed a dose-response relationship, as more frequent consumption of chicken increased the risk of infection by 20% per time of consumption (amOR 1.2 ; 95%CIs: 1-1.4). When we stratified the results by country (ROI versus NI), country-specific ORs were not found significantly different. However, the numbers in the strata were not large enough to allow safe conclusions and the corresponding 95% CIs were wide (data not shown).

## Discussion

### Risk factors for transmission of infection

This study identified some independent risk factors for *Campylobacter* infection that could account for the majority of sporadic cases on the island of Ireland. The most important, based on PAF, was eating chicken, consuming lettuce and eating from a restaurant takeaway (other than Chinese or Indian) in the seven days before onset of illness. The other risk factors identified were: contact with sheep, suffering from stomach ulcer, peptic ulcer or gastritis, suffering from hiatus hernia, suffering from lower bowel problems.

Our study showed an increased risk associated with chicken consumption in general, and an even (three times) higher risk associated with undercooked chicken consumption. This finding, which was also supported by an observed dose-response relationship, was not unexpected as chicken and, in particular, undercooked chicken has been the most consistent finding in studies of risk factors for campylobacteriosis [4,5,7,8,11,12,15,18,19,20]. However, the PAF suggests that the consumption of chicken may account for an unusually high proportion (i.e. the majority) of sporadic cases that occur in Ireland, both ROI and NI. Given that chicken consumption exceeds 70% among the Irish population, this finding receives more importance [16]. Recent microbiological studies of raw poultry conducted in NI and ROI have shown that 50%-70% of raw chickens tested at retail level, were contaminated with *Campylobacter* [21-26]. Those contamination rates were consistently the highest among all food items examined. Furthermore, the genotypic characterisation by Pulsed Field Gel Electrophoresis (PFGE) of both clinical and food isolates and comparative cluster analysis during a recent all-Ireland study, has revealed that a high proportion of indistinguishable *Campylobacter* isolates found in poultry products were also found in human cases [21], re-emphasising the significant role that chicken plays in the epidemiology of human *Campylobacter* infection in Ireland.

Although, in line with several other studies, our study has found negative associations with salad vegetables, lettuce was identified as an important risk factor for infection. Lettuce consumption has previously been described in association with outbreaks [27-29], but, to our knowledge, it has never been identified as a risk factor for sporadic cases. The consumption of lettuce was implicated as the likely vehicle of infection in a recent large *Salmonella* Newport outbreak in NI [30]. Lettuce could be contaminated

with *Campylobacter* before or after the point of sale. Contamination at source could occur through the presence of contaminated soil, the use of contaminated water during harvesting or even flies [31]. During food preparation, fresh lettuce may also be cross-contaminated by kitchen tools or surfaces already contaminated from previous contact with other food [32]. Cross-contamination was the most frequent contributory factor identified in a review of foodborne outbreaks in England and Wales (including five due to *Campylobacter*) linked with lettuce and other salad vegetables and fruit [28,29]. A recent study in ROI, in common with several other studies, has demonstrated that *Campylobacter* can easily spread from fresh food, mainly chicken, to domestic kitchen surfaces and tools and subsequently to lettuce and other salad vegetables [33]. This suggests that cross-contamination of fresh products is very likely to happen in kitchens, particularly through poor handling or storage practices.

Consumption of food from takeaways (other than Chinese or Indian) was an important risk factor, based on PAF (PAF=25). This association suggests that food-hygiene preparation practices in these settings may be poor. Several other studies have implicated exposure to food (most often poultry) prepared outside the home to be associated with campylobacteriosis [7,18,34]. However, it was not possible in this study to identify specific food items associated with infection, bought from takeaways. Further attention to sources of food and food-handling practices in these restaurants in Ireland are needed. Cross-contamination of ready-to eat foods may be an important source of infection, given evidence from experimental studies suggesting that *Campylobacter* is frequently present in a variety of foods and has a low infectious dose (ranging from 500-10,000 cells) [22,35].

A small proportion of cases could be explained by contact with sheep. This association, though apparently uncommon, is entirely plausible. Sheep are known to be carriers [36], excrete *Campylobacter* and therefore may transmit infection to humans. Previously, occupational contact with animal faeces, living on a farm and contact with cattle have all been described as risk factors for *Campylobacter* infection [15].

The association between campylobacteriosis and suffering from peptic ulcer or hiatus hernia yielded the highest amOR among all risk factors identified, although this factor explained a small percentage of cases, overall. Many of the patients who suffer from these gastrointestinal diseases may be receiving long-term treatment with acid suppressants, such as proton pump inhibitors (omeprazole) and H2 antagonists. These drugs have been previously reported to increase risk for *Campylobacter* infection probably by increasing gastric PH and therefore making the stomach a much less hostile environment for bacteria [37].

To our knowledge, the independent association between lower bowel problems and campylobacteriosis has not been previously reported. The biological plausibility of this finding is unclear, particularly, as data were not collected on specific diseases of the lower bowel. It is possible that some conditions or their treatment may lead to a prolonged gastrointestinal transit time and slow clearance of the organism. Alternatively, this finding may be due to a bias, as the case ascertainment for campylobacteriosis may have been higher for patients with pre-morbid bowel problems who may be more likely to submit a faecal stool sample. This bias may also apply to the previously mentioned diseases, i.e. peptic ulcer or hiatus hernia. However, more research is needed to clarify this apparent effect and the mechanisms behind it.

**Protective factors**

The role of mains water supply as a protective factor is interesting. It has been previously reported that inadequately treated water may cause Campylobacter infection in humans and this pathogen was implicated in several waterborne outbreaks in some countries [38-42]. In addition, a recent ecological study in Sweden indicated that water might be an important route of transmission for *Campylobacter* infection [43]. Water can be contaminated through animal faeces [44] and sewage and some *Campylobacter* strains can survive for long in untreated water sources [45]. In this study, cases were twice more likely to drink water from a source other than the mains water supply (e.g. wells or other water schemes). This association, however, was not statistically significant probably because this exposure was uncommon (reported only by 13 cases and 7 controls). It is possible that the protective effect of the public water supply reflects the association of infection with sources of untreated water.

Many of the other protective factors (mainly food items such as beef, turkey and salad vegetables other than lettuce) might indirectly confirm the association with chicken and lettuce as our data suggest that controls, who ate chicken or lettuce less frequently than cases, were more likely to replace those food items with another kind of meat (including poultry) or salad vegetable respectively.

The protective effect of playing in the park and of having contact with a dog other than one's own is less clear. It is possible that these individuals may have a healthier life-style and therefore be less prone to infections or may have engaged in some practices, not evaluated in the study, which protect them from *Campylobacter* infection.

**Limitations of the study**

The study only involved campylobacteriosis cases reported through the routine surveillance system, that constitute a subset of all cases occurring in the community. Epidemiological studies in the UK have shown that only one in eight cases of *Campylobacter* infections occurring in the community is reported through routine surveillance [15]. In addition, due to the relatively low response rate and the matched design of the study, cases that were included in the analysis may have not been representative of all reported cases. However, the available demographic data (age and gender), suggest that there were no statistically significant differences between participant and non-participant campylobacteriosis cases reported to the health authorities.

All *Campylobacter* species were included in the case-definition and no information on speciation was collected. It is possible that risk factors vary according to campylobacter species. Approximately 90-95% human infections are due to *C. jejuni* in the developed world [38], and sporadically available typing data suggest that Ireland has a similar distribution [1].

Controls were not randomly selected from the source population, which would have assured their representativeness in terms of the exposures, but were case-nominated. Choosing controls among friends, work colleagues and neighbours might lead to over-matching, as cases and controls may be similarly exposed to common risk factors (especially food). In addition, some of the controls may have come from the same household as the cases. This could have increased the risk of over-matching even more. This effect, however, may have only reduced the strength of

any association. We excluded those cases and controls from the analysis, whenever this was evident.

As in all case-control studies, cases as a result of their illness may be more able to recall exposures than controls, which may result in recall bias. However, cases that received their questionnaire long after their onset of symptoms in this study (median delay 16 days), may have reported a list of food preferences rather than their definite food exposures. This may have been less of a problem for controls, as exposure period referred to the week prior to their completing the questionnaire, i.e. a more recent period.

Information on place of residence was limited in this study, as only 38.3% of the respondents answered the relevant question. Surveillance data have shown increased incidence of *Campylobacter* infection in rural areas compared to urban areas and studies have suggested that exposure to risk factors may be different for people living in rural compared to those in urban areas [46]. Accurate knowledge of the geographical distribution of cases and controls would have been of added value, and it could have potentially resulted in different guidelines for rural and urban areas.

## Conclusion and recommendations

The study suggests that consumption of chicken, lettuce and food from takeaways accounts for the majority of *Campylobacter* infections in the island of Ireland, both ROI and NI. All these factors could be prevented using basic food-hygiene measures. The findings of this study therefore, highlight the need for an improved and more efficient approach to basic food-hygiene measures to prevent campylobacteriosis and other infectious gastrointestinal illnesses in the community. Further measures are needed throughout the food chain from production, transport, retail and catering to reduce the risk of contamination and cross-contamination. Improved catering practice, whether in the domestic or commercial setting, is an important last line of defense in reducing exposure to potentially *Campylobacter*-contaminated products. In addition, it is essential to raise awareness in the population of the importance of good basic food-hygiene practices, using means of communication easily and readily accessible. Further efforts are needed to identify the defective points in the food chain and enable appropriate measures to reduce the overall burden of this infection in the Irish community. Linkage of epidemiological data with *Campylobacter* speciation and the development of new molecular diagnostic tests will also provide a greater understanding of *Campylobacter* infection.


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