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ORIGINAL RESEARCH ARTICLE

Epidemiology of *Campylobacter jejuni* infections in Sweden, November 2011–October 2012: is the severity of infection associated with *C. jejuni* sequence type?

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Background: *Campylobacter jejuni* is among the most frequent causes of bacterial gastroenteritis in Europe. Over 8,000 *C. jejuni* multilocus sequence typing sequence types (STs) have been described; ST-21 and ST-45 have been identified as the most frequent types in all human studies so far. In contrast to other STs, ST-22 has been associated with the Guillain–Barré syndrome and ST-677 was recently linked to severe systemic infections in Finland. We investigated risk factors associated with hospitalisation in individuals with *C. jejuni* infections acquired in Sweden.

Methods: A total of 1,075 individuals with domestically acquired *C. jejuni* infection diagnosed between November 2011 and October 2012 in Sweden were included in this retrospective cohort study. Typing data for the isolates as well as clinical data including hospitalisation dates and diagnosis codes for individuals with *C. jejuni* infection were obtained. Factors associated with hospitalisation and length of hospitalisation were investigated by multivariable analysis.

Results: A total of 289 individuals were hospitalised due to *C. jejuni* infection (26.8%); those with co-morbidities were over 14 times more likely to become hospitalised than those without (odds ratio [OR]: 14.39, 95% confidence interval [CI]: 6.84–30.26). Those with underlying co-morbidities were also hospitalised longer than those without (4.22 days vs. 2.86 days), although this was not statistically significant. *C. jejuni* ST-257 (OR: 2.38; CI: 1.08–5.23), but not ST-22 or ST-677, was significantly associated with hospitalisation.

Conclusion: ST-677 was not associated with increased hospitalisation or a longer hospital stay in our study whilst ST-257 was. However, individuals with *C. jejuni* infections were generally more frequently hospitalised than previously demonstrated; this requires further consideration including possible targeted interventions.

Keywords: *gastrointestinal pathogens*; *epidemiology*; *sequence type*; Campylobacter

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Campylobacter is the most common zoonotic bacterial cause of gastroenteritis in Europe with over 200,000 laboratory-confirmed cases occurring yearly (1). Although the prognosis of *Campylobacter* gastroenteritis is typically good, infections have been linked to systemic invasive disease and post-infectious complications such as reactive arthritis and Guillain–Barré syndrome (GBS) (2, 3). Data on campylobacteremia are rare, but it is known to occur mostly in the elderly and immunocompromised individuals (4, 5). In Sweden, more than 90% of the human *Campylobacter* gastroenteritis cases are due to *C. jejuni* (6).

Genotyping has shown *C. jejuni* to be genetically diverse (7). Multilocus sequence typing (MLST) is used to characterise *C. jejuni* into arbitrary sequence types (STs), which can be further grouped into clonal complexes (CCs) (7, 8). MLST measures the DNA sequence variations in a set of housekeeping genes and characterises strains according to their sequencing profile; sequences differing at even a single nucleotide are assigned as different alleles

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and thus as different ST. The genotyping data are stored in an online database facilitating international comparisons (www.pubmlst.org/campylobacter/) (8). To date, more than 8,000 *C. jejuni* STs have been identified. Some genotypes are more frequently isolated from human than the others; ST-21 and ST-45 have been identified as the most frequent types in all human studies so far (9–14).

As most *Campylobacter* infections are thought to be sporadic in industrialised countries, the sources of infections remain mostly uninvestigated (15). Based on epidemiological studies, eating improperly cooked meat, handling raw chicken meat, contact with pets, drinking untreated water, and swimming in contaminated natural water have been associated with acquiring *Campylobacter* infection (9, 15–19). Previous MLST-based source attribution studies have shown that a majority of human *C. jejuni* isolates are attributable to chicken (20–23), whereas the minority of infections have also been linked to cattle, water, and wild birds (21, 24). Although very little is known about risk factors associated with the severity of infection (25), certain *C. jejuni* types have been reported to be associated with severe infections. A link between ST-22 and GBS has been proposed (7, 26), and ST-677 was recently linked to severe systemic infections (27). Furthermore, the infections caused by ST-677 *C. jejuni* have been previously shown to be associated with more frequent hospitalisation and a longer hospital stay than infections caused by other STs (13). Old age has also been generally associated with a longer hospital stay (28).

In Sweden, it is mandatory to report all laboratory-confirmed *Campylobacter* infections to the Public Health Agency (www.folkhalsomyndigheten.se). Currently more than 8,000 cases are notified per year and 40% of those are of domestic origin. *Campylobacter* in broilers has been monitored since 1991 in Sweden (29), and a significant decrease in prevalence of *Campylobacter*-positive broiler flocks has been seen since the 1990s. However, the incidence of human campylobacteriosis has not followed that trend (30). The objective of our study was to determine the risk factors associated with the hospitalisation linked to domestically acquired *C. jejuni* infections in Sweden in order to better target the future *Campylobacter* interventions. From that, we have also estimated the total number of hospital bed days due to domestic *Campylobacter* infections in Sweden.

Material and methods

Study design

We performed a retrospective study of individuals with domestically acquired *C. jejuni* infection in order to assess factors associated with related hospitalisations in Sweden between November 2011 and October 2012.

Description of cohort

A total of 8,585 notifications of cases with laboratory-confirmed *Campylobacter* infection were received at the Public Health Agency of Sweden during the study period, and 3,434 from those were classified as having been acquired in Sweden. Clinical microbiological laboratories in Sweden were asked to submit all isolates obtained from domestically acquired *Campylobacter* cases to the National Veterinary Institute (SVA) in Uppsala for MLST typing during the study period; a total of 1,914 samples were received from 25 laboratories. From these samples, 1,139 were selected for typing by stratified random sampling to generate an equal sampling fraction through the year and the region.

Microbiological data

A total of 1,139 *C. jejuni* stool isolates obtained from domestically acquired cases between November 2011 and October 2012 were included in our study. These isolates had already been typed at the SVA according to the previously published MLST protocol (7). Data collected included Swedish personal identification number, age, sex, and name of the laboratory where primary diagnostic testing was performed as well as the date of sampling and MLST type.

Clinical data

The personal identification numbers from all 1,139 *C. jejuni* cases were used to match the microbiological data to the registry of hospitalisation from the Swedish Board of Health and Welfare. Clinical data obtained included all hospitalisation events for these patients from January 2011 to December 2012, including admission and discharge dates, primary diagnosis, and other diagnosis encoded with the ICD-10 system. Hospitalisation events occurring within 2 weeks from the *C. jejuni* isolation were considered potentially related to the *Campylobacter* infection; these diagnostic codes were checked individually and if unlikely to be related to *Campylobacter* infection (i.e. road traffic accident or burns), hospitalisation was considered as non-related. In addition, patients without matching hospitalisation records or hospitalisation outside the window period were considered not having been hospitalised due to *Campylobacter* infection.

Definitions

Campylobacter infection was defined as domestic if the individual had not travelled abroad in the 2-week period before the laboratory diagnosis. Co-morbidity was defined as having a chronic underlying health condition, including chronic heart, lung, kidney, and liver disease, or being immunocompromised (any form of neoplasm or acquired immunodeficiency) based on provided ICD-10 codes. Typed isolates were excluded from this study if it was not possible to match the sample identifier to a

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record from registry of hospitalisations from the Swedish Board of Health and Welfare.

Statistical analysis

The factors associated with two separate outcome measures, hospitalisation (yes/no) and length of hospitalisation (in days), were investigated. The factors included *C. jejuni* ST, county of residence, age, sex, and co-morbidity. Variables which were present in less than 33 cases (i.e. detection frequency $<3\%$) were omitted from the analysis; *P*-values under 0.05 were considered statistically significant.

a. **Hospitalisation.** Univariable analyses to investigate associations between the risk factors and hospitalisation were performed using the 2×2 chi-square test. Risk ratios (RRs) with 95% confidence intervals [CI] were calculated. To adjust the RRs for potential confounders such as age, sex, and co-morbidity, a multivariable analysis using a logistic regression model was performed. Risk factors with $P < 0.20$ in the univariable analysis were included in a multivariable model built through stepwise forward selection using the likelihood ratio test.
b. **Length of hospitalisation.** Univariable analysis to assess the association between the risk factors and length of hospitalisation (i.e. time to discharge) was performed using a Cox proportional hazard model. Hazard ratios with a 95% CI were calculated. Risk factors with $P < 0.20$ in the univariable analysis were included in a multivariable model built through stepwise forward selection using the likelihood ratio test.
c. **Estimation of hospitalisation linked to *Campylobacter* infections in Sweden.** Based on the reported numbers of *Campylobacter* infections and the hospitalisation rate obtained in this study, we have estimated the total number of hospitalisations linked to domestic *Campylobacter* infections in Sweden during the 1-year study period.

Ethics

The confidentiality of study subjects was protected via anonymisation of the data at the SVA. The study was approved by the Uppsala Regional Ethics Committee (2011/306).

Results

A total of 1,139 *C. jejuni* isolates were included in this study, but 64 of these were excluded as it was not possible to match their sample identifiers to the data from the Swedish Board of Health and Welfare. The remaining 1,075 *C. jejuni* isolates consisted of 119 distinct *C. jejuni* STs and 26 CCs. The most frequent STs identified and included in statistical analyses were ST-21 (139 isolates; 12.9% [belonging to the CC-21]), ST-50 (116; 10.8% [CC-21]), ST-19 (104; 9.7% [CC-21]), ST-45 (105; 9.8% [CC-45]), ST-677 (90; 8.4% [CC-677]), ST-48 (88; 8.2% [CC-48]), and ST-257 (41; 3.8% [CC-257]); all the remaining STs were identified in less than 33 cases and were clustered into their own group named 'other' (392 isolates; 36.5%) (Table 1). Although STs were further grouped into CCs, analyses have been performed based on STs as genetic diversity is less within STs than within the CCs (and results based on the CC were in line with the results based on STs; data not shown). Overall, 76 STs were represented by only one or two isolates in the collection. Samples were obtained from all 21 Swedish counties; those counties which had less than 33 *Campylobacter* cases in total (i.e. frequency $<3\%$ regardless of ST) were further clustered into their own group named 'other' for multivariable analysis. The sample was geographically and temporally representative of all domestic cases reported in Sweden during the study period (data not shown).

Table 1. The frequency of detection and hospital admission, length of hospital admission and mean age of individuals infected with *C. jejuni* MLST sequence types (ST) in Sweden, between November 2011 and October 2012

	Identified in this study			Admitted to hospital			
C. jejuni type	Number	Percentage	Mean age (range)	Number	Percentage	Mean age (range)	Length of hospitalisation (days)
ST-21	139	12.9	37.3 (0–87)	28	9.7	45.2 (0–87)	3.04
ST-50	116	10.8	39.1 (1–88)	37	12.8	42.7 (2–85)	2.51
ST-45	105	9.8	48.1 (1–87)	34	11.8	57.3 (1–87)	3.41
ST-19	104	9.7	41.6 (2–73)	20	6.9	48.7 (16–73)	3.15
ST-677	90	8.4	50.5 (1–86)	25	8.7	57.9 (1–86)	3.28
ST-48	88	8.2	40.6 (0–89)	24	8.3	44.9 (1–89)	4.21
ST-257	41	3.8	39.8 (0–77)	17	5.9	45.2 (10–77)	2.65
Other[a]	392	36.5	43.0 (0–95)	104	36.0	51.9 (2–95)	3.28
All	1,075		42.5 (0–95)	289		50.0 (0–95)	3.20

[a]Sequence types which were identified in les s than 33 isolates have been combined into this 'other' group.

A total of 289 individuals with *C. jejuni* infection were hospitalised (26.9%; Table 1): the smallest proportion of hospitalisation was noted for those infected with *C. jejuni* ST-19 (19.4%) and highest for those infected with ST-257 (40%). Most individuals (98%; 292/298) were hospitalised within 7 days (from 2 days before to 5 days after) from microbiological diagnosis of *C. jejuni*; the remaining six were hospitalised either 4 days (three individuals) or 5 days (three individuals) before the diagnosis. Most individuals hospitalised with *C. jejuni* infection were admitted either with the diagnosis of enteritis or colitis ($n = 265$) or with symptoms of diarrhoea and abdominal pain ($n = 6$), and the reason for admission was not given for five individuals. However, *Campylobacter*-specific ICD-10 diagnostic code was used for 148 hospitalised individuals (A405; 51%). A total of seven individuals with colitis were known to have either ulcerative colitis ($n = 4$), diverticular disease ($n = 1$), or Crohn's disease ($n = 2$). Furthermore, one individual was admitted with GBS and one with defined *Campylobacter* sepsis. Isolates from gastroenteritis were represented in all STs, whereas most isolates obtained from individuals with inflammatory bowel disease were found in ST-45 (4/6), GBS in ST-22 (1/1), and sepsis in ST-677 (1/1).

Mean age of individuals infected with *C. jejuni* was 42.5 years, whereas individuals hospitalised with *C. jejuni* infections were generally older with a mean age of 50 years (Table 1). The mean age of individuals infected and hospitalised with certain *C. jejuni* ST varied. The individuals infected and hospitalised with *C. jejuni* ST-677 were the oldest (mean age of 50.5 and 57.9 years, respectively). Furthermore, individuals infected with *C. jejuni* ST-21 (37.3 years) and individuals hospitalised with *C. jejuni* ST-50 (mean age of 42.7 years) were the youngest.

Risk factors associated with hospitalisation and the length of hospitalisation

Infection with *C. jejuni* ST-257 (RR: 1.57; 95% CI: 1.08–2.30), an age of 60 years or older (RR: 2.13; 95% CI: 1.76–2.57), and underlying co-morbidity (RR: 4.49; 95% CI: 2.91–6.92) were factors significantly associated with hospitalisation among patients who had *C. jejuni* infection in Sweden based on univariable analysis (Table 2). Most of the cases with reported co-morbidities, including being immunocompromised and those with chronic underlying conditions admitted to hospital, also had a laboratory-confirmed *C. jejuni* infection (83%; 80/97), whereas a smaller proportion of individuals without these co-morbidities were hospitalised with *C. jejuni* infection (22%; 209/978). Furthermore, age under 20 years (RR: 0.69; 95% CI: 0.50–0.95) or between 40 and 60 years (RR: 0.69; 95% CI: 0.55–0.87) as well as being diagnosed in Halland and Skåne counties (RR: 0.45; 95% CI: 0.21–0.97 and RR: 0.67; 95% CI: 0.46–0.97, respectively) were identified as statistically significant protective factors for hospitalisation coinciding with *C. jejuni* infection. No significant differences in proportion of individuals with co-morbidities or in age distribution of individuals were observed between counties.

After correction for potential confounders, co-morbidity (OR: 13.89; 95% CI: 7.88–24.46), an age of 60 years or older (OR: 1.98; 95% CI: 1.22–3.25), and *C. jejuni* ST-257 (OR: 2.35; 95% CI: 1.15–4.81) were found to be independently associated with hospitalisation (Table 3). In addition, Västra Götaland (OR: 0.59; 95% CI: 0.36–0.96), Halland (OR: 0.30; 95% CI: 0.21–0.97), and Skåne (OR: 0.43; 95% CI: 0.46–0.97) counties were identified as statistically significant protecting factors for hospitalisation with *C. jejuni* infection in multivariable analysis.

None of the factors investigated were significantly associated with duration of hospitalisation based on univariable analysis (Table 4) or multivariable analysis (data not shown). Duration of hospitalisation was not statistically different between cases infected with ST-677 or any other *C. jejuni* STs. It varied from 2.51 days (ST-50) to 4.21 days (ST-48), with the mean hospital stay of 3.20 days. Duration of hospitalisation was not statistically significant between different age groups, but those older than 60 years were hospitalised longer than those under 60 years of age (4.07 days vs. 2.53 days [< 20 years], 2.14 days [20–39 years], and 3.12 days [40–59 years]). Furthermore, those infected with *C. jejuni* who had underlying co-morbidities were also hospitalised for longer than those without (4.16 days vs. 2.84 days).

Estimation of hospitalisation linked to the domestic C. jejuni *infections in Sweden*

As the mean length of hospitalisation was 3.2 days, and 289 individuals with domestically acquired *C. jejuni* infections were hospitalised, it can be calculated that a total of 925 hospital bed days were used (95% CI: 879–971). As only a proportion of domestic *C. jejuni* infections were included in our study (1,075 from 3,434), the true numbers would be bigger (estimated around 2,954 bed days). Furthermore, one case of GBS among our study population would translate into three cases among all hospitalised individuals due to domestic *C. jejuni* infections in Sweden during the study period.

Discussion

This is the first study to determine the risk factors associated with the hospitalisation and the length of hospitalisation of individuals with domestically acquired *C. jejuni* infections in Sweden. Our study included 1,075 *C. jejuni*–infected individuals, representing approximately 30% of all reported domestic *C. jejuni* cases in Sweden during the 1-year study period. A high diversity of MLSTs among human *C. jejuni* isolates with a total of 119 distinct STs were observed, from which the seven frequent STs (ST-21, ST-50, ST-19, ST-45, ST-677, ST-48, and ST-257)

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Table 2. Potential covariates and their association with hospitalisation evaluated in univariable analysis using a 2×2 chi-square test in laboratory-confirmed domestic cases of *C. jejuni* in Sweden, November 2011–October 2012

Variable	Hospitalised/total	Percent	RR	95% CI	*P*
C. jejuni sequence type					
ST-21	28/139	20.1	0.72	0.51–1.02	0.07
ST-50	37/116	31.9	1.21	0.91–1.61	0.24
ST-19	20/104	19.2	0.69	0.46–1.04	0.08
ST-45	34/105	32.4	1.23	0.02–1.66	0.22
ST-677	25/90	27.8	1.04	0.73–1.47	0.92
ST-48	24/88	27.3	1.02	0.71–1.45	1.00
ST-257	**17/41**	**41.5**	**1.57**	**1.08–2.30**	**0.049**
Other[a]	104/392	26.5	0.98	0.79–1.20	0.89
County					
Södermanland	10/34	29.4	1.09	0.65–1.87	0.89
Dalarna	12/38	31.6	1.18	0.73–1.91	0.63
Gävleborg	13/35	37.1	1.40	0.90–2.18	0.23
Västra Götaland	46/214	21.5	0.76	0.57–1.01	0.06
Halland	**6/48**	**12.5**	**0.45**	**0.21–0.97**	**0.03**
Jönköping	6/28	21.4	ND[b]		
Kalmar	8/22	36.4	ND[b]		
Blekinge	5/16	31.3	ND[b]		
Värmland	6/33	18.2	0.67	0.32–1.39	0.35
Östergötland	11/35	31.4	1.18	0.71–1.94	0.67
Norrbotten	6/18	33.3	ND[b]		
Skåne	**24/128**	**18.8**	**0.67**	**0.46–0.97**	**0.04**
Stockholm	67/238	28.2	1.06	0.84–1.34	0.68
Västernorrland	5/13	38.5	ND[b]		
Västerbotten	13/36	36.1	1.36	0.87–2.12	0.28
Uppsala	9/29	31.0	ND[b]		
Gotland	7/12	58.3	ND[b]		
Västmanland	7/25	28.0	ND[b]		
Kronoberg	7/19	36.8	ND[b]		
Örebro	17/46	37.0	1.40	0.95–2.07	0.16
Jämtland	4/8	50.0	ND[b]		
Male gender					
No	169/638	26.5	–	–	–
Yes	120/437	27.5	1.04	0.85–1.27	0.78
Age (years)					
<20	**33/169**	**19.5**	**0.69**	**0.50–0.95**	**0.02**
20–39	66/292	22.6	0.80	0.63–1.02	0.07
40–60	**74/358**	**20.7**	**0.69**	**0.55–0.87**	**0.0015**
>60	**116/256**	**45.3**	**2.13**	**1.76–2.57**	**<0.0001**
Co-morbidity					
No	209/978	21.4	–	–	–
Yes	**80/97**	**82.5**	**4.49**	**2.91–6.92**	**<0.0001**

Variables with more than two categories (ST, county, and age group) were dichotomised by category, using all the remaining observations were as the reference group (e.g. ST-21 vs all other STs). Results for variables shown to be statistically significantly associated with hospitalisation ($P > 0.05$) are shown in bold face.

[a]Contains all other *C. jejuni* sequence types identified in this study.

[b]ND = not determined for variables with prevalence <3%.

covered 64% of all isolates in accordance with previously published studies from the United Kingdom, Finland, Denmark, and Canada (9–14, 24, 26). These STs were recently shown to have been responsible for a large proportion of domestic *C. jejuni* infections in Sweden already in 2000, and have also been isolated from Swedish broilers (23).

Table 3. Result of multivariable logistic regression analysis of variables associated with hospitalisation of laboratory-confirmed domestic cases of *C. jejuni* in Sweden, November 2011–October 2012

Variable	OR	95% CI	*P*
C. jejuni sequence type	0.98	0.93–1.05	0.62
ST-21	0.81	0.48–1.37	0.43
ST-50	1.59	0.96–2.62	0.07
ST-19	0.71	0.39–1.28	0.25
ST-45	1.14	0.67–1.94	0.63
ST-677	0.99	0.56–1.77	0.98
ST-48	1.28	0.72–2.29	0.40
ST-257	**2.35**	**1.15–4.81**	**0.017**
County	1.02	1.00–1.04	0.12
Södermanland	0.89	0.65–1.87	0.81
Dalarna	0.74	0.73–1.91	0.50
Gävleborg	1.09	0.90–2.18	0.85
Västra Götaland	**0.59**	**0.36–0.96**	**0.033**
Halland	**0.30**	**0.21–0.97**	**0.018**
Värmland	0.59	0.32–1.39	0.30
Östergötland	0.86	0.71–1.94	0.72
Skåne	**0.43**	**0.46–0.97**	**0.007**
Stockholm	0.76	0.84–1.34	0.24
Västerbotten	1.14	0.87–2.12	0.75
Örebro	1.31	0.95–2.07	0.48
Age (years)	**1.22**	**1.05–1.43**	**0.012**
20–39	0.99	0.61–1.62	0.61
40–60	0.79	0.48–1.27	0.33
>60	**1.98**	**1.22–3.25**	**0.006**
Co-morbidity (yes)	**13.89**	**7.88–24.46**	**<0.0001**

The 'other' categories were used as a reference groups for ST and county variables. Results for variables shown to be statistically significantly associated with hospitalisation ($P > 0.05$) are shown in bold face.

It has been suggested that the poultry is likely the most important source of domestic *C. jejuni* infections (19).

Although *Campylobacter* infections are usually considered mild and self-limiting, they can also lead to more severe infections requiring hospitalisation (3–5, 31). Up to 26.9% of individuals included in this study were admitted to hospital with the domestically acquired *C. jejuni* infection. We have matched the data on *Campylobacter* infections obtained from the Public Health Agency of Sweden and from the registry of hospitalisations from the Swedish Board of Health and Welfare. Based on our data, only 50% of hospitalisations were registered with *Campylobacter*-specific ICD-10 coding (A04.5), and the remaining were registered with non-specific gastroenteritis and colitis coding. The numbers on the hospitalisations related to *Campylobacter* infections are likely underestimated in studies where only specific ICD-10 codes are used without matching (31–34). Only 5% of reported *Campylobacter* cases were hospitalised according to the review of three national databases over a 4-year period in Canada (32), whereas an annual hospitalisation rate of 12.3% was obtained in a Danish registry-based study (33) and 10% in US surveillance study (34). As all the studies have used different methods to obtain the hospitalisation estimates, we cannot state if the hospitalisation rates are truly increasing, if they are higher since a smaller proportion of milder infections have been sampled, or simply more accurately estimated than recorded previously. This needs to be investigated further.

The correlation between co-morbidities and hospitalisation due to domestic *C. jejuni* infection is not surprising, given that most co-morbidities result in decreased immune function and thus more likely will lead to symptomatic *C. jejuni* enterocolitis. Co-morbidity category also included all known immunocompromised individuals (i.e. those with known malignancy). Furthermore, individuals with co-morbidities are more likely to seek health care with gastrointestinal symptoms and are more likely to be tested for *Campylobacter* than those without co-morbidities. There was also a trend towards more severe infections among the individuals with co-morbidities; they were hospitalised for longer than those without (4.16 days vs. 2.84 days). Although these differences were not statistically significant, they suggest more severe infections in those with co-morbidities. In a previous study, a high hospitalisation rate of 47.6% was described in patients with ulcerative colitis (35). However, the main focus of the Arora study (35) was to determine the risk factors for *C. jejuni* infection and not to investigate the risk factors associated with hospital admissions due to *Campylobacter* infections. Furthermore, previous studies have shown that those aged over 60 years are three times more likely to be hospitalised with *Campylobacter* infection than younger individuals (34), and that age >60 years can be a risk factor for a longer hospital stay (28). It is most likely that the older individuals have more diagnosed co-morbidities than the younger ones; the factor not considered in those studies. We clearly demonstrate that co-morbidity is the most significant risk factor for hospitalisation while having *C. jejuni* infection, not old age. Indeed, over 60% of all those hospitalised were younger than 60 years of age.

It is not fully understood why the hospitalisation rates were lower in the southwestern parts of Sweden (Västra Götaland, Halland, and Skåne counties) than elsewhere. None of the Swedish microbiology laboratories were using molecular methods for *Campylobacter* detection during the study period. A potential explanation could be differences in study population, such as overrepresentation of the elderly or those with co-morbidities, but no significant differences were observed between counties. The lower hospitalisation rates in these counties could also reflect differences between counties in primary health care policies with regard to testing patients with

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Table 4. Variables investigated for their association with length of hospitalisation evaluated in univariable analysis using Cox regression in laboratory-confirmed domestic cases of *C. jejuni* in Sweden, November 2011–October 2012

Variable		Me an stay (median)	HR	95% CI	*P*
C. jejuni sequence type	Other	3.28 days (3 days)	–	–	–
	ST-21	3.04 days (2 days)	1.12	0.74–1.71	0.56
	ST-50	2.51 days (2 days)	1.34	0.92–1.95	0.13
	ST-19	3.15 days (2 days)	1.01	0.63–1.63	0.97
	ST-45	3.41 days (3 days)	0.85	0.58–1.26	0.42
	ST-667	3.28 days (3 days)	0.98	0.63–1.51	0.91
	ST-48	4.21 days (4 days)	0.96	0.62–1.49	0.86
	ST-257	2.65 days (2 days)	1.49	0.89–2.50	0.13
County	Other	3.25 days (2.5 days)	–	–	–
	Eskilstuna	2.30 days (2 days)	1.31	0.67–2.56	0.42
	Falun	2.92 days (3 days)	0.97	0.53–1.81	0.94
	Gävle	2.77 days (2 days)	1.07	0.59–1.95	0.82
	Göteborg	3.28 days (3 days)	0.89	0.61–1.30	0.56
	Halmstad	3.83 days (4 days)	0.89	0.39–2.06	0.79
	Karlstad	2.67 days (2.5 days)	0.84	0.36–1.93	0.68
	Linköping	4.18 days (3 days)	0.77	0.40–1.45	0.42
	Malmö	3.54 days (2.5 days)	0.85	0.52–1.34	0.46
	Stockholm	2.81 days (2 days)	1.30	0.92–1.84	0.13
	Umeå	2.69 days (2 days)	1.22	0.68–2.23	0.50
	Örebro	4.71 days (3 days)	1.05	0.62–1.81	0.84
Male gender	No	3.11 days (2 days)	–	–	–
	Yes	3.34 days (3 days)	1.01	0.80–1.27	0.95
Age (years)	<20	2.53 days (2 days)	–	–	–
	20–39	2.14 days (2 days)	1.02	0.67–1.54	0.92
	40–60	3.12 days (2 days)	0.83	0.56–1.25	0.38
	>60	4.07 days (3 days)	0.73	0.50–1.07	0.11
Co-morbidity	No	2.84 days (2 days)	–	–	–
	Yes	4.16 days (3 days)	0.92	0.73–1.17	0.51

gastrointestinal illness for *Campylobacter,* where counties with a more liberal testing policy would be identified as 'protective' in this literature due to the relatively larger number of cases detected, and not hospitalised. The finding could also be due to differences in hospitalisation policy (i.e. stricter criteria for hospital admissions).

Only one study has previously investigated the association between *C. jejuni* STs and hospitalisation; based on that it was expected that *C. jejuni* ST-677 would be associated with more frequent hospitalisations and also with increased length of hospitalisation than other *Campylobacter* types (13). This hypothesis was also supported with more recent evidence demonstrating that *C. jejuni* ST-677 is specifically associated with invasive infections (i.e. campylobacteremia) (27). In our study, the association between *C. jejuni* ST-677 and the increased hospitalisations or a longer hospital stay could not be demonstrated. However, it should be noted that the Feodoroff study investigated blood culture isolates of *C. jejuni* collected over a 10-year study period, whereas the number of invasive *C. jejuni* infections during our 1-year study period would have been minimal (36). Interestingly, individuals infected with another less common *C. jejuni* type, ST-257, were shown to be at increased risk of hospital admissions in our study. Although ST-257 was recently isolated from domestic dogs in Sweden (37), only 4% of dogs were positive for *C. jejuni* and thus the importance of dogs as a source of human infections needs to be clarified further. In addition, ST-50 was linked to the highest number of *Campylobacter*–related hospitalisations in Sweden (37/289). Both of these types, ST-257 and ST-50, have been previously identified from Swedish broilers (23).

Although the pathogenesis of *C. jejuni* remains poorly understood, some *C. jejuni* types have been associated with severe infections. In our study, one individual was diagnosed with GBS and *C. jejuni* ST-22 infection, whereas another individual with systemic invasive infection had *C. jejuni* ST-677, consistent with the previous literature (7, 26, 27). Furthermore, we identified another *C. jejuni* type, ST-257, as a risk factor significantly associated with hospitalisation. This ST has not been linked to a specific disease outcome and thus the reason(s)

for the observed increased rate of hospitalisation is not currently known. However, *C. jejuni* ST-257 was shown to be the most virulent type measured as larval survival in the insect *Galleria mellonella* model (38). It is likely that the genetic differences between *C. jejuni* types will determine their pathogenicity, as previously demonstrated by combining the data from whole-genome sequencing and phenotypical characterisation of *C. jejuni* ST-677 (27, 39).

Although most *Campylobacter* infections are self-limiting and do not require treatment, antibiotics are often given to immunocompromised individuals (25), and thus it is important to consider possibility of resistance. In that context, it is important to note that a previous study from Slovakia demonstrated equally high frequency of antibiotic resistance among isolates obtained from humans, animals, and food. These included universal persistence of ciprofloxacin-resistance among *C. jejuni* ST-50 isolates (40); the second most common *C. jejuni* type in Sweden. High levels of ciprofloxacin resistance were also previously identified not only among *C. jejuni* ST-50 isolates but also among ST-257 isolates in Belgium (41). However, much lower levels of ciprofloxacin-resistance was observed among these types in the United Kingdom (10). Data on antibiotic resistance in human *Campylobacter* isolates is not routinely collected in Sweden, but a high level of ciprofloxacin resistance for untyped human *Campylobacter* isolates was reported in 2002–2011 (49%; (42)). For these reasons, further systematic monitoring of antimicrobial resistance in Sweden for human *Campylobacter* should also be considered.

Limitations

The clinical data obtained in this study were based on the diagnostic codes used and reported. As they have been assigned by individual doctors, they might differ according to the doctor and hospital practice. In addition, since only the diagnostic codes were used, we do lack other information on disease severity (i.e. data on ITU admission, need for IV fluids, antibiotic treatment, and resistance). It should also be noted that only individuals who have been diagnosed with certain disease entities will have been given the diagnostic codes (i.e. young individuals with newly diagnosed neoplasm might still be under ongoing investigations and thus definite diagnosis may not have been reported as yet). However, these limitations are likely to result in underestimation of associations and cannot be minimised within this study design. In addition, only *Campylobacter* cases who sought medical care could be included in this study (prerequisite for sampling) and thus milder infections that did not require medical attention were not included in this study. This may result in an under- or over-estimation of the effect of genotype on hospitalisation since cases of mild illness may not be uniformly distributed among genotypes of *C. jejuni*, as well as over-estimation of the population proportion of hospitalised cases.

Recommendations

We have demonstrated that over a quarter of all individuals diagnosed with domestic *C. jejuni* infection are hospitalised in Sweden, and that those infected with ST-50 or ST-257 are slightly more likely to be subject to hospital care than those infected with other STs. Although over 50% of all hospitalised individuals were less than 60 years of age and did not have any co-morbidities and were not known to be immunocompromised in this study, the biggest risk factors for hospitalisation identified included co-morbidities and old age. We have shown that individuals with co-morbidities are at a 14-time higher risk of becoming hospitalised with a domestic *C. jejuni* infection than those without. As these co-morbidities are often seen in older people, the burden of domestic *C. jejuni* infections is likely to increase even further in the future, considering the ageing population trend. Targeted public health messages including strict advice on kitchen hygiene and safe drinking water sources for those with co-morbidities as well as further investigations on antimicrobial resistance in *Campylobacter* in humans in Sweden are required.

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References

1. EFSA, ECDC. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2014. EFSA J 2015; 13: 4329. doi: http://dx.doi.org/10.2903/j.efsa.2015
2. Hannu T, Mattila L, Rautelin H, Pelkonen P, Lahdenne P, Siitonen A, et al. Campylobacter-triggered reactive arthritis: a population-based study. Rheumatology 2002; 41: 312–18.
3. McCarthy N, Giesecke J. Incidence of Guillain-Barré syndrome following infection with *Campylobacter jejuni*. Am J Epidemiol 2001; 153: 610–14.
4. Pacanowski J, Lalande V, Lacombe K, Boudraa C, Lesprit P, Legrand P, et al. Campylobacter bacteremia: clinical features and factors associated with fatal outcome. Clin Infect Dis 2008; 47: 790–6. doi: http://dx.doi.org/10.1086/591530

5. Louwen R, van Baarlen P, van Vliet AH, van Belkum A, Hays JP, Endtz HP. Campylobacter bacteremia: a rare and under-reported event? Eur J Microbiol Immunol 2012; 2: 76–87.
6. Gillespie IA, O'Brien SJ, Frost JA, Adak GK, Horby P, Swan AV, et al. A case-case comparison of *Campylobacter coli* and *Campylobacter jejuni* infection: a tool for generating hypotheses. Emerg Infect Dis 2002; 8: 937–42.
7. Dingle KE, Colles FM, Wareing DR, Ure R, Fox AJ, Bolton FE, et al. Multilocus sequence typing system for *Campylobacter jejuni*. J Clin Microbiol 2001; 39: 14–23.
8. Colles FM, Maiden MC. Campylobacter sequence typing databases: applications and future prospects. Microbiology 2012; 158: 2695–709.
9. Dingle KE, Colles FM, Ure R, Wagenaar JA, Duim B, Bolton FJ, et al. Molecular characterization of *Campylobacter jejuni* clones: a basis for epidemiologic investigation. Emerg Infect Dis 2002; 8: 949–55.
10. Cody AJ, McCarthy NM, Wimalarathna HL, Colles FM, Clark L, Bowler IC, et al. A longitudinal 6-year study of the molecular epidemiology of clinical campylobacter isolates in Oxfordshire, United Kingdom. J Clin Microbiol 2012; 50: 3193–201.
11. Sopwith W, Birtles A, Matthews M, Fox A, Gee S, Painter M, et al. *Campylobacter jejuni* multilocus sequence types in humans, northwest England, 2003–2004. Emerg Infect Dis 2006; 12: 1500–7.
12. Schouls LM, Reulen S, Duim B, Wagenaar JA, Willems RJ, Dingle KE, et al. Comparative genotyping of *Campylobacter jejuni* by amplified fragment length polymorphism, multilocus sequence typing, and short repeat sequencing: strain diversity, host range, and recombination. J Clin Microbiol 2003; 41: 15–26.
13. Kärenlampi R, Rautelin H, Schönberg-Norio D, Paulin L, Hänninen ML. Longitudinal study of Finnish *Campylobacter jejuni* and C. coli isolates from humans, using multilocus sequence typing, including comparison with epidemiological data and isolates from poultry and cattle. Appl Environ Microbiol 2007; 73: 148–55.
14. Sheppard SK, Dallas JF, MacRae M, McCarthy ND, Sproston EL, Gormley FJ, et al. Campylobacter genotypes from food animals, environmental sources and clinical disease in Scotland 2005/6. Int J Food Microbiol 2009; 134: 96–103.
15. Wilson DJ, Gabriel E, Leatherbarrow AJ, Cheesbrough J, Gee S, Bolton E, et al. Tracing the source of campylobacteriosis. PLoS Genet 2008; 4: e1000203.
16. Kapperud G, Espeland G, Wahl E, Walde A, Herikstad H, Gustavsen S, et al. Factors associated with increased and decreased risk of *Campylobacter* infection: a prospective case-control study in Norway. Am J Epidemiol 2003; 158: 234–42.
17. Wolfs TF, Duim B, Geelen SP, Rigter A, Thomson-Carter F, Fleer A, et al. Neonatal sepsis by *Campylobacter jejuni*: genetically proven transmission from a household puppy. Clin Infect Dis 2001; 32: E97–9.
18. Schönberg-Norio D, Takkinen J, Hänninen ML, Katila ML, Kaukoranta SS, Mattila L, et al. Swimming and Campylobacter infections. Emerg Infect Dis 2004; 10: 1474–7.
19. EFSA Panel on Biological Hazards (BIOHAZ). Scientific opinion on Campylobacter in broiler meat production: control options and performance objectives and/or targets at different stages of the food chain. EFSA J 2011; 9: 2105–246. doi: http://dx.doi.org/10.2903/j.efsa.2011.2105
20. Sheppard SK, Dallas JF, Strachan NJ, MacRae M, McCarthy ND, Wilson DJ, et al. Campylobacter genotyping to determine the source of human infection. Clin Infect Dis 2009; 48: 1072–8.
21. Lévesque S, Fournier E, Carrier N, Frost E, Arbeit RD, Michaud S. Campylobacteriosis in urban versus rural areas: a case-case study integrated with molecular typing to validate risk factors and to attribute sources of infection. PLoS One 2013; 8: e83731.
22. de Haan CP, Lampén K, Corander J, Hänninen ML. Multilocus sequence types of environmental *Campylobacter jejuni* isolates and their similarities to those of human, poultry and bovine *C. jejuni* isolates. Zoonoses Public Health 2013; 60: 125–33.
23. Griekspoor P, Engvall EO, Åkerlind B, Olsen B, Waldenström J. Genetic diversity and host associations in *Campylobacter jejuni* from human cases and broilers in 2000 and 2008. Vet Microbiol 2015; 178: 94–8.
24. Cody AJ, McCarthy ND, Bray JE, Wimalarathna HM, Colles FM, Jansen van Rensburg MJ, et al. Wild bird-associated *Campylobacter jejuni* isolates are a consistent source of human disease, in Oxfordshire, United Kingdom. Environ Microbiol Rep 2015; 7: 782–8.
25. Kaakoush NO, Castaño-Rodríguez N, Mitchell HM, Man SM. Global epidemiology of campylobacter infection. Clin Microbiol Rev 2015; 28: 687–720.
26. Nielsen LN, Sheppard SK, McCarthy ND, Maiden MC, Ingmer H, Krogfelt KA. MLST clustering of *Campylobacter jejuni* isolates from patients with gastroenteritis, reactive arthritis and Guillain-Barré syndrome. J Appl Microbiol 2010; 108: 591–9.
27. Feodoroff B, de Haan CP, Ellström P, Sarna S, Hänninen ML, Rautelin H. Clonal distribution and virulence of *Campylobacter jejuni* isolates in blood. Emerg Infect Dis 2013; 19: 1653–5.
28. Schönberg-Norio D, Sarna S, Hänninen ML, Katila ML, Kaukoranta SS, Rautelin H. Strain and host characteristics of *Campylobacter jejuni* infections in Finland. Clin Microbiol Infect 2006; 12: 754–60.
29. Hansson I, Forshell LP, Gustafsson P, Boqvist S, Lindblad J, Engvall WO, et al. Summary of the Swedish Campylobacter program in broilers, 2001 through 2005. J Food Prot 2007; 70: 2008–14.
30. National Veterinary Institute (2014). Surveillance of infectious diseases in animals and humans in Sweden. Uppsala, Sweden: SVA. SVA Rapport Serie 31 ISSN 1654-7098.
31. Toljander J, Dovärn A, Andersson Y, Ivarsson S, Lindqvist R. Public health burden due to infections by verocytotoxin-producing *Escherichia coli* (VTEC) and Campylobacter spp. as estimated by cost of illness and different approaches to model disability-adjusted life years. Scand J Public Health 2012; 40: 294–302.
32. Ruzante JM, Majowicz SE, Fazil A, Davidson VJ. Hospitalization and deaths for select enteric illnesses and associated sequelae in Canada, 2001–2004. Epidemiol Infect 2011; 139: 937–45.
33. Helms M, Simonsen J, Mølbak K. Foodborne bacterial infection and hospitalization: a registry-based study. Clin Infect Dis 2006; 42: 498–506.
34. Samuel MC, Vugia DJ, Shallow S, Marcus R, Segler S, McGivern T, et al. Epidemiology of sporadic Campylobacter infection in the United States and declining trend in incidence, FoodNet 1996–1999. Clin Infect Dis 2004; 38: S165–74.
35. Arora Z, Mukewar S, Wu X, Shen B. Risk factors and clinical implication of superimposed *Campylobacter jejuni* infection in patients with underlying ulcerative colitis. Gastroenterol Rep 2015. pii: gov029.
36. Harvala H, Ydring E, Brytting M, Söderblom T, Mäkitalo B, Wallensten A, et al. Increased number of campylobacter bacteraemia cases in Sweden, 2014. Clin Micro Inf 2015; pii: S1198-743X(15)00995-7.
37. Holmberg M, Rosendal T, Engvall EO, Ohlson A, Lindberg A. Prevalence of thermophilic *Campylobacter* species in Swedish dogs and characterization of *C. jejuni* isolates. Acta Vet Scand 2015; 57: 19.
38. Senior N, Bagnall M, Champion O, Reynolds S, La Ragione R, Woodward M, et al. *Galleria mellonella* as an infection model for *Campylobacter jejuni* virulence. J Gen Micro 2011; 60: 661–9.

39. Skarp C, Akinrinade O, Nilsson A, Ellström P, Myllykangas S, Rautelin H. Comparative genomics and genome biology of invasive *Campylobacter jejuni*. Sci Rep 2015; 25: 17300.
40. Kovač J, Cadež N, Lušicky M, Nielsen EM, Ocepek M, Raspor P, et al. The evidence for clonal spreading of quinolone resistance with a particular clonal complex of *Campylobacter jejuni*. Epidemiol Infect 2014; 142: 2595–603.
41. Habib I, Miller W, Uytttendaele M, Houf K, de Zutter L. Clonal population structure and antimicrobial resistance of *Campylobacter jejuni* in chicken meat from Belgium. Appl Environ Microbiol 2009; 75: 4264–72.
42. Swedres-Svarm (2012). Use of antimicrobials and occurrence of antibiotic resistance in Sweden. Solna, Uppsala: Swedres-Svarm. ISSN 1650-6332.

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