Urban–rural differences of age- and species-specific campylobacteriosis incidence, Hesse, Germany, July 2005 – June 2006

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Citation style for this article:

Fitzenberger J, Uphoff H, Gawrich S, Hauri AM. Urban–rural differences of age- and species-specific campylobacteriosis incidence, Hesse, Germany, July 2005 – June 2006. *Euro Surveill.* 2010;15(42):pii=19693. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19693>

Article published on 21 October 2010

Campylobacter infection is the most common cause of bacterial gastroenteritis worldwide. This study examines the association between campylobacteriosis incidence and degree of urbanicity in Hesse, Germany, by age and *Campylobacter* species. During a one-year period (July 2005–June 2006), Hessian local health authorities provided information on municipality of residence for 3,315 campylobacteriosis cases. We calculated age- and *Campylobacter* species-specific incidences for six levels of urbanicity, as defined by population density and accessibility of centres. For children under five years old, living in inner rural areas (incidence rate ratio (IRR): 2.9; 95% confidence interval (CI): 1.9 to 4.4) and for children aged 5–14 years living in inner rural (IRR: 2.1; 95% CI: 1.3 to 3.1) or intermediate areas (inner intermediate area IRR: 1.8; 95% CI: 1.2 to 2.7; outer intermediate area IRR: 2.1; 95% CI: 1.3 to 3.3) was associated with a statistically significantly higher campylobacteriosis risk (reference category: inner urban area). Calculations by *Campylobacter* species showed a higher risk of gastroenteritis due to *C. coli* for inhabitants (all ages) of non-urban areas. This study suggests that differences in risk factors by age, *Campylobacter* species and degree of urbanicity do exist. For children contact with animals or the environment may be responsible for a substantial proportion of sporadic *Campylobacter* infections.

Introduction

Campylobacter infections resulting in gastroenteritis are recognised as an emerging problem worldwide. With 47 cases per 100,000 population campylobacteriosis is the most commonly reported gastrointestinal disease in the European Union (data from 2007) [1]. Notification rates differ markedly, ranging from zero per 100,000 population in Romania to 95 per 100,000 population in the United Kingdom in 2007 [1]. In Germany, the annual number of reported cases rose from 47,937 in 2003 (58 per 100,000 population) to 62,807 in 2009 (79 per 100,000 population) [2]. A number of case–control studies identified travelling abroad, eating poultry, pork and sausages, drinking untreated water or unpasteurised milk, barbecuing

and having contact with domestic animals as risk factors for infection [3–5], but most infections are believed to result from the ingestion of contaminated food [6]. The primary source of food contamination is believed to be animal faeces. This is consistent with high *Campylobacter* carriage rates in poultry, pigs and cattle and the fact that similar *Campylobacter* genotypes have been identified in farm animals and humans [7–9]. Contamination of the environment by faeces of domestic and wild animals presents an alternative exposure pathway for human infection, for example, via contamination of drinking and recreational water sources [10]. Humans may also be exposed to animal faeces in the environment through other outdoor activities such as playing, camping, walking and picnicking.

Since 2001, when the country's disease reporting system was reorganised, specific notification data on human campylobacteriosis have been available in Germany. Using national case definitions [11], local health authorities verify locally identified notifiable diseases and send case reports electronically via state health departments to the national surveillance unit at the Robert Koch Institute in Berlin [12]. For campylobacteriosis, data collected in this system include demographic characteristics, dates of illness, county and – for internationally imported cases – country of infection, diagnostic procedure used (bacterial culture or enzyme-linked immunosorbent assay (ELISA)), and if performed, results of species differentiation, but not the techniques used) and association with outbreaks.

Hesse is one of the 16 German Laender, with a population of 6.1 million in 2007. In Hesse, the annual number of notified cases of campylobacteriosis rose from 3,000 in 2001 to 4,029 cases in 2009, corresponding to an incidence of 49 per 100,000 population and 66 per 100,000 population, respectively. County-specific incidence of *Campylobacter* infection in Hesse ranged from 19 per 100,000 inhabitants in 2001, 2002 and 2004 to 113 per 100,000 inhabitants in 2007. While the annual campylobacteriosis incidence varied widely between Hessian counties, intracounty incidence changed little

from 2001 to 2007. We investigated the association between campylobacteriosis incidence and living in

Hessian urban, intermediate and rural environments by cases' age, sex and *Campylobacter* species.

FIGURE 1

Geographical distribution of *Campylobacter* infections, by municipality, showing (A) degree of urbanicity, (B) incidence in children aged 0–14 years and (C) incidence in people aged 15 years and above, Hesse, Germany, July 2005 – June 2006

TABLE 1

Population density and percentage population, by degree of urbanicity, Hesse, Germany, July 2005 – June 2006

Degree of urbanicity	Population density (number of inhabitants per km ²)	Percentage of population
Inner urban area	1,441	35
Outer urban area	447	27
Inner intermediate area (has agglomeration tendencies)	274	16
Outer intermediate area (has low population density)	122	7
Inner rural area (has agglomeration tendencies)	136	11
Outer rural area (has very low population density)	66	4

Methods

Data on age, sex and *Campylobacter* species of all campylobacteriosis cases with disease onset (or if missing, date of diagnosis) from July 2005 to June 2006 were extracted from the state surveillance database. In addition, Hessian local health authorities provided information on the municipality of the cases' residence (postal code and/or name of municipality) for all cases included in the study. Population data were provided by the Hesse Statistical Office. The 426 Hessian municipalities were grouped into six categories according to their degree of urbanicity, as defined by the Federal Office of Building and Regional Planning based on population density (urban, intermediate and rural) and accessibility of centres (inner and outer) [13]. The spatial distribution of categories of urbanisation in Hesse

is shown in Figure 1. In Hesse, the total inner urban area (IUA) has a population density of 1,441 inhabitants per km². Some 35% of the Hessian population live in municipalities of the IUA (Table 1).

Age-specific campylobacteriosis incidences for the six categories of urbanisation and five age groups (under 5 years, 5–14 years, 15–44 years, 45–64 years, more than 64 years) were calculated. In our study, *C. coli* and *C. jejuni* together represent over 96% of campylobacteriosis reports with species information. Due to the small numbers of *C. coli* cases, species-specific campylobacteriosis incidences for *C. jejuni* and *C. coli* were calculated only for three categories of urbanisation (urban, intermediate and rural areas). We also

TABLE 2

Association between campylobacteriosis cases and degree of urbanicity, by age group, Hesse, Germany, July 2005 – June 2006 (n=2,710)

Age group and degree of urbanicity	Number of cases (n=2,710)	Population (N=6,097,765)	Incidence (per 100,000 population)	95% CI
0–4 years				
Inner urban area	51	100,800	51	37.7–66.5
Outer urban area	33	76,200	43	29.8–60.8
Inner intermediate area	26	42,700	61	39.7–89.1
Outer intermediate area	8	19,900	40	17.3–79.1
Inner rural area	44	30,000	147	106.8–197.2
Outer rural area	9	10,100	89	40.7–168.7
5–14 years				
Inner urban area	55	194,300	28	21.3–36.8
Outer urban area	47	174,700	27	19.8–35.8
Inner intermediate area	54	103,600	52	39.2–68.0
Outer intermediate area	30	50,400	60	40.2–85.0
Inner rural area	43	74,100	58	42.0–78.2
Outer rural area	12	26,700	45	23.2–78.5
15–44 years				
Inner urban area	479	901,000	53	48.5–58.1
Outer urban area	374	671,500	56	50.2–61.6
Inner intermediate area	231	388,000	60	52.1–67.7
Outer intermediate area	115	174,700	66	54.3–79.0
Inner rural area	145	264,300	55	46.3–64.6
Outer rural area	41	93,000	44	31.6–59.8
45–64 years				
Inner urban area	236	558,300	42	37.1–48.0
Outer urban area	153	437,800	35	29.6–40.9
Inner intermediate area	94	244,600	38	31.1–47.0
Outer intermediate area	36	114,300	31	22.1–43.6
Inner rural area	49	174,400	28	20.8–37.1
Outer rural area	19	60,800	31	18.8–48.8
>64 years				
Inner urban area	128	385,600	33	27.7–39.5
Outer urban area	71	281,400	25	19.7–31.8
Inner intermediate area	56	170,100	33	24.9–42.8
Outer intermediate area	26	85,200	31	19.9–44.7
Inner rural area	37	138,800	26	18.8–36.7
Outer rural area	8	50,100	16.0	6.9–31.4

CI: confidence interval.

calculated 95% confidence intervals (CI) for incidence rates and incidence rate ratios (IRRs) and the attributable fraction among the exposed and the population attributable fraction for living in non-urban areas according to Boice and Monson, using the incidence in urban areas as reference for calculation [14].

As species information was not available for all cases and in order to take into account variation in the frequency of species differentiation according to degree of urbanicity, the number of species-specific cases was estimated using the formula: corrected number of species-specific cases = (number culture confirmed/number differentiated to species level) x (reported number of species-specific cases). Corrected incidence

rates and IRRs were then calculated. For corrected incidences, 95% CI were not calculated, due to the additional uncertainty resulting from incompleteness of species differentiation. Data were analysed with Stata version 10.0.

Results

From July 2005 to June 2006, 3,331 campylobacteriosis cases were reported in Hesse. Of these, 2,710 cases (81.4%) were reported to have acquired their infection in Hesse. Of the remaining 621 campylobacteriosis cases, 377 (60.7%) were infected outside Germany, 74 (11.9%) were infected in German Laender other than Hesse, and for 170 (27.4%) details of the place of infection were not available. Only the 2,710 cases reported

FIGURE 2

Age-specific incidence rate ratios and 95% confidence intervals, by degree of urbanicity, Hesse, Germany, July 2005 – June 2006

I: intermediate; IA: inner area; OA: outer area; R: rural U: urban.

TABLE 3

Association between campylobacteriosis cases and degree of urbanicity, by *Campylobacter* species, Hesse, Germany, July 2005 – June 2006

<i>Campylobacter</i> species and degree of urbanicity	Population	Reported cases			Corrected estimate of cases ^a		
		Number of cases	Incidence (per 100,000 population)	Incidence rate ratio (95% CI)	Number of cases	Incidence (per 100,000 population)	Incidence rate ratio
<i>Campylobacter coli</i>							
Urban areas	3,781,800	88	2	1 (reference)	164	4	1 (reference)
Intermediate areas	1,393,600	91	7	2.8 (2.1–3.8)	115	8	1.9
Rural areas	922,400	64	7	3.0 (2.1–4.2)	90	10	2.3
<i>Campylobacter jejuni</i>							
Urban areas	3,781,800	698	18	1 (reference)	1,300	34	1 (reference)
Intermediate areas	1,393,600	352	25	1.4 (1.2–1.6)	443	32	0.93
Rural areas	922,400	232	25	1.4 (1.2–1.6)	325	35	1.1

CI: confidence Interval.

^a Number of cases corrected for incomplete differentiation to species level, which differed by level of urbanicity.

to have acquired their infection in Hesse were included in this study. Of these, 2,673 (98.6%) were laboratory confirmed, for 1,581 (58.3%) species information was available, and 43 (1.6%) cases were part of nine small clusters, each of three to six cases.

Campylobacteriosis incidence for Hesse and all age groups was 44 per 100,000 population, (2,710 of 6,095,055) and did not differ by degree of urbanicity (urban area: 43.0, 95% CI: 41.0–45.2; intermediate area: 48.5, 95% CI: 44.9–52.3; rural area: 44.1, 95% CI: 40.0–48.7). Of the 2,710 infections acquired in Hesse, 53.3 % (1,445) were male and 46.5% (1,259) were female. For six cases details of their sex were not available. For males and females campylobacteriosis incidence did not vary by degree of urbanicity (data not shown).

Campylobacteriosis incidence was highest in children under five years of age (annual incidence: 61 per 100,000 population) and in people aged 15–44 years (annual incidence: 56 per 100,000 population), and lowest in people older than 65 years (annual incidence: 29 per 100,000 population). In the age groups under five years and 5–14 years, campylobacteriosis incidence varied largely by degree of urbanicity (Table 2). When compared with living in IUAs, living in IRAs was significantly associated with a higher campylobacteriosis incidence in children aged under five years of age (IRR: 2.9, 95% CI: 1.9–4.4). For children aged 5–14 years, living in IRAs (IRR: 2.1, 95% CI: 1.3–3.1) and in intermediate areas (IIA IRR: 1.8, 95% CI: 1.2–2.7; OIA IRR: 2.1, 95% CI: 1.3–3.3) was significantly associated with a higher campylobacteriosis incidence. For children aged under five years and those aged 5–14 years, the association between living in the ORAs and higher campylobacteriosis incidence was not statistically significant (children under five years IRR: 1.8, 95% CI: 0.8–3.6; children aged 5–14 years IRR: 1.6, 95% CI: 0.8–3.0) (Figures 1 and 2).

We then calculated the attributable risk of living in non-urban areas for children aged 0–14 years. In the exposed children, the risk was 46%; the population attributable risk was 25%.

While urban–rural differences were most pronounced in children 14 years of age and younger, they were also seen in the three older age groups. In these age groups there was a tendency towards lower campylobacteriosis incidences for persons living in more rural areas (Figure 2). However, only for those aged 65 years and above living in ORAs did this difference reach statistical significance (IRR: 0.5, 95% CI: 0.2–1.0).

Of 1,581 cases with species information, 15% (n=243) were infected with *C. coli*, 81% (n=1,282) with *C. jejuni*, 3% (n=49) with *C. lari*, and less than 1% (n=7) with other *Campylobacter* species. The proportion of culture-confirmed cases did not differ by degree of urbanicity: 88.7%, 87.4% and 89.4% of cases were

culture confirmed in urban, intermediate and rural areas, respectively. However, a higher proportion of isolates from patients in non-urban areas were differentiated to species level: 53.7%, 79.4% and 71.3% of culture-confirmed cases were differentiated to species level in urban, intermediate and rural areas, respectively (Pearson's chi-square test $p < 0.001$). When compared with urban areas, species-specific incidences for *C. coli* and *C. jejuni* were higher in rural and intermediate areas. However, when the number of *C. coli* and *C. jejuni* cases was corrected for incomplete differentiation to species level, only incidence of *C. coli* infections differed by degree of urbanicity (Table 3). In addition, a relatively higher proportion of *C. coli* cases lived in non-urban areas: the ratio of the *C. coli* to *C. jejuni* cases (corrected) was 0.13 in urban areas, 0.26 in intermediate areas and 0.28 in rural areas.

Discussion

In this analysis, degree of urbanisation was found to be associated with campylobacteriosis in children under 15 years of age. Calculation of the attributable risk indicated that 25% of all reported cases of campylobacteriosis aged under 15 years were associated with living in non-urban areas. These attributable risk calculations reflect the degree to which the true, unknown sources of infection are more abundant in non-urban areas than in urban areas.

Recent studies investigated urban–rural differences in campylobacteriosis incidence in Canada [15], the Netherlands [16], Scotland [17], Denmark [18] and Sweden [19]. Four of these studies found higher incidences in rural environments [15, 17–19] and one in urban and urbanised environments [16]. The authors of the last study suggested the higher incidence of campylobacteriosis in urban and urbanised areas could be related to higher consumption of ready-to-eat foods. Of the two studies that presented age-specific data, one reported the greatest urban–rural differences for children 0–4 years-old [15] and one that urban–rural differences were limited to children 0–14 years of age [18]. Authors of both studies suggested that contact with farm animals and the environment were the source of a substantial proportion of sporadic *Campylobacter* infections.

When interpreting age-specific differences in urban–rural gradients of campylobacteriosis incidence, two main factors need to be considered: age-specific risk factors for infection and immunity acquired during childhood towards local, i.e. rural sources of *Campylobacter* infection. Few studies reported on age-specific risk factors for campylobacteriosis [20–25]. However, in case–control studies on risk factors for the disease in infants and young children food exposures explained less than 40% of the infections [20,22,23]. *Campylobacter* infections in these age groups have been associated with contacts with diarrhoeic pets [20,23,24] and live chickens [24,25], drinking water from a well, lake or river [20,23], riding in a shopping

trolley next to meat or poultry [23], visiting or living on a farm [23], ownership of farm animals or visiting farm animals outside the household [22] as well as different food exposures. Among these food exposures were the consumption of fruits and vegetables prepared at home [23], mayonnaise [24], butter [25], porridge [25], undercooked meat [22], products containing raw eggs [22] and grilled meat [20,22]. In contrast to many other published case–control studies [4–5], these studies did not find an association between eating chicken and *Campylobacter* infection. In the light of these findings we believe that environmental exposure accounts for a considerable part of *Campylobacter* infections in children and that children living in non-urban areas have more opportunities for direct or indirect contact with animals or their excrement. In addition, children living in urban and rural environments may differ in their eating and drinking habits. *C. jejuni* outbreaks, for example, have been repeatedly related to the consumption of raw milk [26]; children living in non-urban areas may drink raw milk more frequently.

The absence of urban–rural differences in campylobacteriosis incidence in persons aged 15 years and above may be related to differences in behaviour and/or a higher level of immunity from previous exposures [27]. In developing countries, clinical disease due to *C. jejuni* is common among children younger than two years, but rare among individuals later in life [28]. This relative absence of disease is thought to be related to acquired immunity [29]. If a higher proportion of inhabitants of Hessian rural areas aged 15 years and above are immune to *Campylobacter* infection, then the association between living in rural areas and campylobacteriosis may be decreased or even reversed. These questions should be addressed in *Campylobacter* seroprevalence studies or the inclusion of only non-immune controls in future case–control studies for the identification of risk factors.

In our study, 15% of all campylobacteriosis cases with species information were due to *C. coli*. Germany is one of the European Union Member States with the highest proportion of cases due to *C. coli* [30]. Within Germany, the proportion of cases due to *C. coli* differs widely between States and is higher in the former East German or new Laender (in 2006, 14% of all cases (n=7,494) with species information) than in the former West German or old Laender (in 2006, 6% (n=26,205). For whole of Germany, the proportion in 2006 was 8% (n=33,699) [2]. The new Länder are more rural, i.e. the population density is lower [31], a greater proportion of the total area is agricultural [32] and a smaller proportion of the total area is inhabited [33].

When analysing species–specific differences in campylobacteriosis incidence in urban, intermediate and rural areas and correcting for differences in frequency of species differentiation, we found a higher incidence for *C. coli* in non-urban areas. Microbiological data show that the prevalence of different *Campylobacter* species

varies between different potential sources of infection, including animal species, food and water [10,34,35]. Poultry has been recognised as the primary reservoir of *C. jejuni*, while pigs are mostly implicated as reservoirs of *C. coli* [36–38]. Differences in food-borne exposures between *C. coli* and *C. jejuni* have been shown to exist [22,39] and differences in consumption habits between persons living in urban and rural areas may contribute to the observed difference in species distribution. However, it has been suggested that *C. coli* may survive in the environment better than *C. jejuni* [10] and people living in non-urban areas may be exposed more frequently to environmental sources of *C. coli*.

This study is limited by constraints inherent to all ecological analyses: a sample size limiting detailed subgroup analysis and a limited availability of further data on municipality level (for example, information on water supply, animal density or consultation of health services and diagnostic practices). However, our analysis suggests that differences in risk factors by *Campylobacter* species, cases' age and degree of urbanicity do exist.

Acknowledgements

We thank the Hessian Public Health Offices for providing, in addition to case reports, data on municipality of campylobacteriosis cases. We are also grateful to Thomas Pütz, Federal Office of Building and Regional Planning, Bonn, Germany, for providing data on degree of urbanicity for the Hessian municipalities.

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