

A case-cohort study to investigate concomitant waterborne outbreaks of *Campylobacter* and gastroenteritis in Söderhamn, Sweden, 2002–3

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ABSTRACT

Increased domestic, laboratory confirmed, *Campylobacter* notifications were reported in Söderhamn municipality, December 2002 and January 2003. Concurrently, during preliminary investigations a large outbreak of acute gastroenteritis was detected. Simultaneously, two studies were completed to identify risk factors for infection with *Campylobacter* and acute gastrointestinal infection (AGI): (1) a case-cohort study using *Campylobacter* cases ($N = 101$) with a large random sample from the municipal population as referents ($N = 1000$) and (2) a retrospective cohort study for the outcome AGI using the same sample. A postal questionnaire was used to collect demographic, clinical, water and food consumption data. Measures of association (risk ratio (RR), odds ratio (OR)) and 95% confidence intervals (CI) were calculated. Stool, environmental and water samples were tested by standard methods at Gävle Hospital and SMI laboratories respectively. In the case-cohort study, *Campylobacter* cases were more likely than referents to consume communal water ($OR = 12.6$ (95% CI 1.7–92.3)). In the cohort study, risk of gastroenteritis was 2.3 times higher in those who consumed water ($AR = 27.3\%$) than others ($AR = 12\%$). Risk of illness was associated with the amount of water consumed in both studies. *Campylobacter* was detected in stools and *Escherichia coli* (*E. coli*) from routine communal water (CW) samples. Results suggest both Söderhamn outbreaks of *Campylobacter* and AGI were associated with consumption of CW. The method used strengthened epidemiological evidence and was efficient in the use of time and resources.

Key words | case-cohort study, concomitant water-borne outbreaks

INTRODUCTION

Sweden has a long tradition in the surveillance of waterborne outbreaks. The first Swedish outbreaks of reported waterborne diseases were the cholera outbreaks between 1834–1874 (Arvidsson 1972). The pattern of the outbreaks has changed with time.

Between 1880 and 1979, 77 waterborne outbreaks, including 26 867 cases and 789 deaths were reported. Of these cases, 88% were due to known agents, such as typhoid fever, shigellosis, hepatitis and polio (Andersson & Bohan 2001).

During the period 1980–2003, 142 waterborne outbreaks were reported, involving 63 000 people. About 80% of the outbreaks were due to unknown agents. The most common agents reported were *Campylobacter*, *Norovirus* and *Giardia intestinalis*.

Between 1980–2003 there have been 20 waterborne *Campylobacter* outbreaks reported, involving 11 608 cases. The three largest reported *Campylobacter* outbreaks in Sweden occurred in 1980, 1994 and 1995 with, respectively, 1000, 2500 and 3000 affected people (Stanwell-Smith *et al.* 2003).

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Swedish drinking water is comprised of 50% groundwater (which includes bank filtered water) and 50% surface water. Most groundwater is non-chlorinated. Surface water is chlorinated but at a low concentration (0.1–0.3 mg/l).

The port of Söderhamn lies on the east coast of Sweden, 250 km north of Stockholm. The municipality of Söderhamn covers an area of 1062 km² and has a population of 27 765.

In January, 2003, the County Medical Officer (CMO) for Gävleborg noticed an increased incidence of domestic, laboratory confirmed cases of *Campylobacter* in the municipality of Söderhamn. At the same time cases of acute gastroenteritis infection (AGI) were reported in the community. In order to identify the sources, modes of transmission and vehicles for the outbreak, the Swedish Institute for Infectious Disease Control (SMI) was invited to take part in the investigation along with the Environmental Health Protection Board at Söderhamn.

An initial rapid assessment based on 750 telephone interviews indicated that 24% of the population self-reported AGI, potentially affecting some 6–7000 members of the population.

The water supply was suspected as the source of the outbreak for the following three reasons.

1. There had been a previous waterborne outbreak in the municipality at a similar time of year (Sandarne, November 1998).
2. A contaminated routine well water sample with one *E. coli* had been analysed two weeks prior to our arrival (15 January 2003).
3. It was felt that the 24% attack rate of self-reported AGI in the community, and the increased reported cases of *Campylobacter*, were probably associated and that more than one pathogen may be involved.

As water supplies were suspected to be at the origin of both outbreaks (*Campylobacter* and AGI), preliminary and immediate measures of intervention included:

- intensification of water sampling;
- chlorination of the water supplies of the municipality; and
- holding a press conference to inform the population.

No advice on boiling water was issued.

METHOD

Epidemiology

We thus found two simultaneous outbreaks, which may overlap to some extent. One was the outbreak of verified *Campylobacter* infections, while the second was the larger outbreak of self-reported acute intestinal illness. Since most of the patients in the latter outbreak were not tested for *Campylobacter*, there may well have been unidentified *Campylobacter* cases in this group as well.

Two epidemiological investigations were simultaneously completed to identify the role of the water supply and other risk factors in both outbreaks: a case-cohort study, using laboratory reported cases of *Campylobacter* infection and a large random sample of the community as referents, and – using the same random community sample – a retrospective cohort study to identify the risk factors for self-diagnosed AGI.

Case-cohort study

A case of *Campylobacter* infection was defined as a person living in the Söderhamn municipality during December 2002 and January 2003 with laboratory verified *Campylobacter*, grown from a stool sample, using standard methods laid down by The Swedish Institute of Infectious Disease Control (SMI) (Referensmetodik 2002). Cases were identified from the laboratory notifications.

The reference cohort consisted of 1000 residents randomly selected from the municipal population register of Söderhamn.

Information requested from cases and referents by postal questionnaire included demography, clinical signs and symptoms, food outlets, food items and type and amount of water consumed.

Cohort study

The expected high incidence of AGI in the population allowed us to use the random sample of 1000 controls in the previous study as a retrospective cohort. The same questionnaire was used as the case-cohort study, with the objective of assessing if water consumption was also the

vehicle of transmission for the concomitant outbreak of AGI.

A case was defined as a person living in the Söderhamn municipality during December 2002 and January 2003 with self-diagnosed AGI. Attack rates of AGI were compared by the amount of water consumed. The chi squared value for trend was used.

Sample size

The number of estimated cases and a planned size of 1000 people in the random sample of the cohort allowed for a power of 80% for the cohort study (alpha = 5%, detectable $RR = 12$) and 80% for the case-cohort study (alpha = 5%, detectable $OR = 12$) plus an estimated 80% rate of response.

Data management and analysis

Epidemiological data were entered and analysed using Epi Info 2003 version 3.2 (Center for Disease Control, Atlanta, GA).

Microbiological investigation

The Gävleborg county surveillance system first noticed the increase of domestic *Campylobacter* cases. The Gävle hospital laboratory use standard methods described by SMI to cultivate *Campylobacter* from stool samples (Referensmetodik 2002).

Molecular typing of *Campylobacter* was completed using pulse field gel electrophoresis (PFGE) and restriction fragment length polymorphism (RFLP) analysis of the flagellin gene *flaA* in *C. jejuni* (Nachamkin et al. 1993).

Environmental investigation

Water was sampled using routine methods as described by the National Food Administration Guidelines (Livsmedelsverket 2002).

Analysis for *Campylobacter* in the water samples was completed using modified guidelines SS 0281 65 /NMKL 119 (Livsmedelsverket 2002).

RESULTS

Epidemiology

Case-cohort study

In all, 101 cases of *Campylobacter* infection were reported during the study period. Of these 68 (68%) responded to the questionnaire and were included in the case-cohort study.

Of the 1000 questionnaires sent 563 were returned (56%). The age and sex distribution of the sample and the Söderhamn population were similar (Table 1).

Forty-eight (48%) of the *Campylobacter* cases gave a date of onset of symptoms from which an epidemic curve was constructed (Figure 1).

The epidemic curve extends from 11 December 2002 to 28 January 2003, a duration of 48 days. The majority of cases occur during the relevant 28 days of January. There is no clear peak.

Overall, 67 of the 68 cases (98.5%), and 461 of 548 (84.1%) controls for whom information was available, had consumed communal water during the study period ($OR = 12.6$; 95% $CI (1.7-92.3)$) (Table 2).

Estimated from the OR , the relative risk of illness increased with the amount of water consumed (Table 3).

Analysis of exposure to other food items, food outlets and pets did not increase the risk of illness (data not shown).

Retrospective cohort study

The retrospective cohort study was conducted using the 563 randomly selected individuals from the case-cohort study. Among them 130 met the case definition ($AR = 23.1\%$, similar to the figure gained from the telephone interviews).

Of them 86 (66%) gave a date for the onset of symptoms from which an epidemic curve was constructed (Figure 1). The epidemic curve extends from 1 December 2002 until 28 January 2003, a duration of 59 days. The peak appeared in mid-January and coincided with the period during which the maximum number of *Campylobacter* cases also occurred.

Of the 439 residents who had consumed communal water during the study period, 120 (27%) developed AGI compared to 10 of the 83 residents who did not consume communal water (12%) ($RR = 2.3$; 95% $CI (1.2-4.1)$) (Table 4).

Table 1 | Age and sex distribution of *Campylobacter* cases, cohort group (for December 2002–January 2003), compared with Söderhamn municipal population 2002

Age	Cases (%)			Cohort sample (%)			Population (%)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
0 to 6	4 (15.4)	1 (2.9)	5 (8.2)	10 (4)	9 (3.5)	19 (3.7)	7	6	6
7 to 24	1 (3.8)	4 (11.4)	5 (8.2)	35 (13.9)	38 (14.6)	73 (14.3)	22	20	22
25 to 44	6 (23.1)	7 (70)	13 (21.3)	33 (13.1)	37 (14.2)	70 (13.7)	25	23	24
45 to 64	10 (38.5)	14 (40)	24 (39.2)	79 (31.5)	81 (31.2)	160 (31.3)	28	27	28
65 +	5 (19.2)	9 (25.7)	14 (23)	94 (37.5)	95 (36.5)	189 (37)	18	24	20
Total	26 (100)	35 (100)	61 (100)	251 (100)	260 (100)	511 (100)	100	100	100

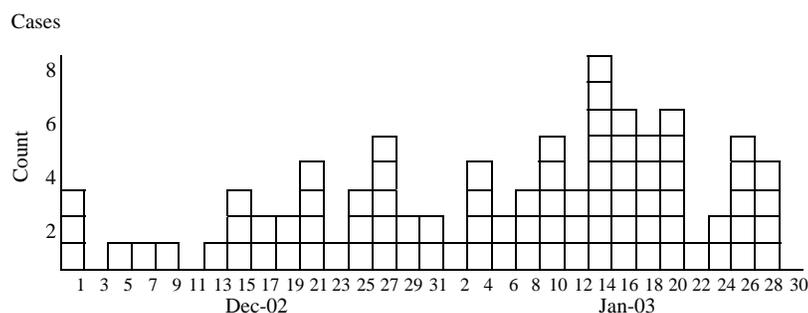
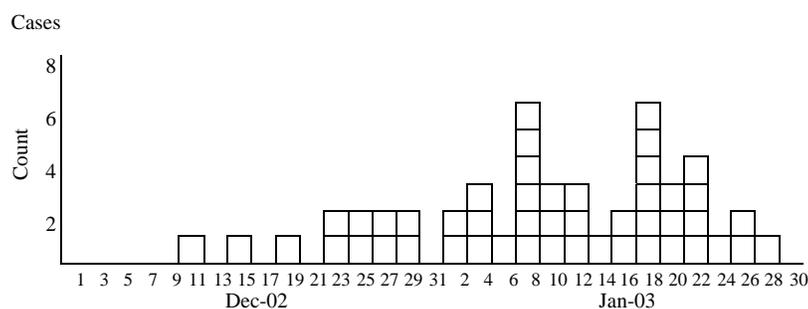
There was an increased risk of illness associated with the amount of water consumed ($p = 0.05$) (Table 5).

Microbiology results

From the 101 cases, *Campylobacter* was the only pathogen isolated. Patients were sampled once.

Eleven of the human *Campylobacter* strains were typed showing five different subtypes. With respect to this outbreak, using the SMI typing system, these were named one to five.

Three campylobacter subtypes were grown from six sewage water samples taken from a single inspection point on the mains sewage pipeline. They are the same sub-type as three of the human strains.



□ = 1 Case

Figure 1 | Top: reported cases of *Campylobacter* in Söderhamn municipality by date of onset December 2002–January 2003 ($N = 68$, data missing on 20 cases). Bottom: reported cases of AGI in Söderhamn municipality by date of onset December 2002–January 2003 ($N = 130$, data missing on 40 cases).

Table 2 | Water consumption among cases of *Campylobacter* infection and a random sample of residents of Söderhamn municipality December 2002–January 2003 (data missing for 15 subjects)

	Campylobacter cases	Random sample	Total	OR	95% confidence interval
Communal water	67	461	528	12.6	(1.7–92.3)
No communal water	1	87	88	Ref	
Total	68	548	616		

Table 3 | Amount of communal water consumed per day by *Campylobacter* cases and a random sample of Söderhamn municipal population December 2002–January 2003

Water amount	Cases	Random sample (+ case)	OR	OR 95% CI
None	0*	44 (45)	Ref	
<0.5 L	13	165 (178)	3.47	0.45–72.8
>0.5 L	53	333 (386)	7	1.01–139.59
Total	66	542 (609)		

Chi squared for trend $p < 0.01$.

*For the purposes of calculating the odds ratios a figure of one was inserted in the category None = 'No communal water consumed'.

Table 4 | Risk of AGI according to the amount of communal water consumed by a random sample of Söderhamn municipality, December 2002–January 2003 (data missing for 26 subjects)

	Cases of AGI	Total	Attack rate	Risk ratio	95% confidence interval
Communal water	120	439	0.27	2.3	(1.2–4.1)
No communal water	10	83	0.12	Reference	
Total	130	522	0.24		

Three further strains were typed from samples taken at a suspected source. They were not the same as the human strains.

Neither *Campylobacter* or viral matter was found in the water.

DISCUSSION

In this study we describe an outbreak that is likely to have involved at least two pathogens causing *Campylobacter* infection and AGI, affecting over 6000 residents of the Söderhamn municipality (25%) and our data suggest it is

epidemiologically associated with the communal water system.

These findings are consistent with other Swedish waterborne outbreaks involving *Campylobacter*, which generally affect about 20% of the community. *Campylobacter* is an exception, as waterborne outbreaks involving other pathogens in Sweden generally affect between 40–80% of the community.

Influences which could have occurred and distorted our results include information and selection biases.

Information bias is common in the investigation of waterborne outbreaks (Craun *et al.* 2001) and cannot be excluded from this investigation. The outbreak had been

Table 5 | Risk of AGI according to the amount of communal water consumed by a random sample of Söderhamn municipality, December 2002–January 2003

Water amount	AGI cases	Total	AR (%)	RR	RR 95% CI
None	5	41	12	Ref	
<0.5 L	37	159	23	1.92	0.8–4.55
>0.5 L	85	317	27	2.25	0.95–5.1
Total	127	517			

Chi squared for trend $p = 0.05$.

well publicised via the media and it was known that chlorination was being used as a precautionary measure. Unlike some European countries, drinking unchlorinated tap water in Sweden is considered safe: it is estimated 96% of Swedes regularly drink such tap water (Socialstyrelsen 2001)

Regarding selection bias, the cohort was randomly selected from the population register and should therefore be representative of the source population exposed to the communal water (which gave rise to both *Campylobacter* and AGI).

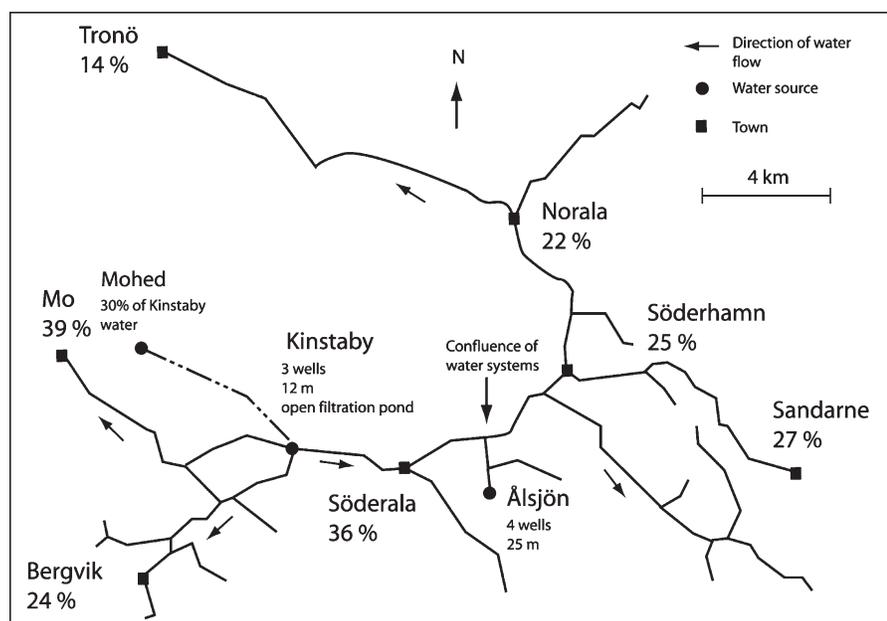
The telephone survey indicated a 24% incidence of AGI in the community, which was almost identical to the figure

yielded by the postal questionnaire. This indicates that a rapid telephone survey is a reliable and quick method.

The case-cohort methodology was used for two reasons: (1) the combination of preliminary evidence from the telephone survey of a 24% incidence of AGI, in comparison to the relatively few cases of *Campylobacter*, suggested that at least two pathogens may be involved, and (2) because the communal water system was suspected, it naturally defines a cohort.

Using this study design, it was possible to amass two bodies of evidence from one study, the case-cohort and the retrospective cohort. Both of these suggested that the outbreaks of *Campylobacter* and AGI were associated with the consumption of municipal communal water. The dual association, combined with the absence of evidence from other exposures, gave increased proof in the absence of pathogens being isolated from water samples.

Epidemiological evidence and the absence of a detected pathogen by the laboratory in the implicated vehicle is a common occurrence in the investigation of waterborne outbreaks, especially in association with *Campylobacter*, *Norovirus* and *Giardia* where there is no correlation between indicator bacteria and pathogens (Mentzing 1981; Carrique-Mas *et al.* 2003).

**Figure 2** | Diagram of mains water system in Söderhamn and ARs of AGI in Söderhamn municipality December 2002–January 2003.

This is the second waterborne outbreak to occur in this municipality in the last five years.

There was no history of disruption, or major works of maintenance, to the water system during or preceding the outbreak. Routine maintenance protocols had been adhered to fastidiously. The only two anomalies were: (1) the contaminated routine water sample in January 2003, containing one *E. coli* 35 per 100 ml and (2) the dry summer and autumn, which had caused a reduction in the volume of water from Mohed to Kinstaby (Figure 2) with the result that the filtration pond had only been partially covered, though maintained as required. This created a possibility for contamination by wild animals or during the maintenance process. But this was unlikely as it had been fully covered since October.

Most regulations rely on the absence of indicator bacteria as a definition of water safety. But these indicators do not exclude the presence of viral material which may induce AGI, e.g. Norwalk-like virus (NLV), which has a low infective dose, is difficult to detect and remarkably robust (Kukkula *et al.* 1999; Wyn-Jones *et al.* 2000).

NLV is found in contaminated surface and groundwaters. The US Environmental Protection Agency (EPA) is interested in preventing NLV contamination in treated water used for consumption, and these viruses are on the EPAs "contaminant candidate list" for regulatory consideration in drinking waters (Craun 1992). Future drinking-water regulations may need to ensure that treatments are adequate to remove NLV from source waters.

Waterborne outbreaks continue to occur in countries with advanced economies and access to proven drinking-water treatment technologies (Hrudey *et al.* 2003). Such outbreaks inflict suffering and cost on society (Andersson *et al.*, 1997) and question public confidence in the management of the public utilities and public health services.

As previously mentioned there is a changing pattern and nature to waterborne outbreaks (Craun 1992) in Sweden. The Walkerton Inquiry (Hrudey *et al.* 2003) in Canada demonstrated that in many waterborne outbreaks the circumstances are specific, but many of them also have common and recurring themes.

The pattern has changed from that of untreated ground-water with an identified agent, to inadequate, or interrupted, disinfection with rarely identified agents, despite a growing

list of water contaminants (Craun 1992) and methods for detection. The consequence of the lack of hard evidence is an unwillingness to accept or apportion responsibility.

This pattern may create a tendency to rely primarily on compliance monitoring as a mechanism for managing drinking-water quality. Although this is a necessary part of drinking-water quality management, it is not sufficient to guarantee the safety and quality of drinking-water supplies.

With the changing nature of waterborne outbreaks and the increasing absence of a detectable pathogen, there is a greater need for epidemiological methods to provide the evidence.

By identifying the source epidemiologically, research can then be directed towards identifying the circumstances surrounding the outbreaks and the results of that research can be translated into more effective policy, regulatory standards and management, which may address the specific circumstances of an outbreak and also contribute to the broader issues of drinking-water quality raised.

CONCLUSION

The case-cohort approach was efficient in its use of time and resources and appropriate for this situation, where a communal distribution system is suspected as the source of the outbreak and naturally defines a cohort.

The method produces two bodies of evidence, which in this case corroborate. They demonstrated that both *Campylobacter* and AGI cases were associated with the consumption of communal water from the municipality, in the absence of an identified pathogen from water samples.

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