Outbreak of *Cryptosporidium hominis* in northern Sweden: persisting symptoms in a five-year follow-up

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Research note

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Abstract

Objectives

In 2010-2011, a waterborne outbreak of the parasite, *Cryptosporidium hominis*, affected approximately 27,000 inhabitants in the city of Östersund, Sweden. Previous research suggested that post-infectious symptoms, such as gastrointestinal symptoms and joint pain, could persist for up to two years after the initial infection. In this study, we investigated whether the parasite caused post-infectious sequelae for up to five years after the outbreak. This prospective cohort study examined whether individuals infected during the outbreak were more likely than uninfected individuals to report post-infectious symptoms five years later. The participants completed a questionnaire on whether they experienced a list of symptoms. We analysed data using logistic regression and calculated odds ratios with 95% confidence intervals.

Results

The analysis included 626 individuals. Among the 262 individuals infected during the outbreak, 56.5% reported symptoms at follow-up. Compared to uninfected individuals, infected individuals were significantly more likely to report watery diarrhoea, diarrhoea, swollen joints, abdominal pain, bloating, joint discomfort, acid indigestion, alternating bowel habits, joint pain, ocular pain, nausea, and fatigue at the follow-up, after adjusting for age and sex. Our findings suggested that cryptosporidiosis was mainly associated with gastrointestinal- and joint-related post-infectious symptoms for up to 5 years after the infection.

Introduction

Cryptosporidium is a protozoan parasite that can infect humans and animals. More than 20 species have been identified, but *C. hominis* and *C. parvum c*ause the majority of infections in humans [1, 2]. *Cryptosporidium* is mainly transmitted through the faecal-oral route, either through oocyst-contaminated water or food or through direct contact with an infected person or animal [3].

Cryptosporidiosis occurs worldwide and in all age groups [3]. Many small waterborne outbreaks have been reported globally, but only a few large outbreaks have been reported [4]. To date, the largest outbreak occurred in Milwaukee, Wisconsin, in 1993. In that outbreak, 400,000 people were infected through the public water supply [5]. In November 2010, Östersund, a city in northern Sweden, experienced a large outbreak of acute diarrhoea, caused by *C. hominis* IbA10G2, which was transmitted through the public water supply. Approximately 27,000 (45%) of 59,000 inhabitants reported symptoms compatible with cryptosporidiosis [6].

The most common symptoms of cryptosporidiosis are watery diarrhoea, nausea, vomiting, fever, and abdominal pain. The symptoms typically last a few days to 2–3 weeks [3], but the infection can also be asymptomatic. [2] Children, particularly those < 2 years old, often display more severe symptoms than adults [7].

Post-infectious symptoms after cryptosporidiosis have been described in several studies [8–10]. Long-term sequelae are common after *C. hominis* infections, including diarrhoea, abdominal pain, nausea, fatigue, and headache [11]. Among children in developing countries, cryptosporidiosis has been associated with increased mortality (12), impaired physical fitness, and impaired cognitive function [13]. Two years after the outbreak in Östersund, individuals that had been infected during the outbreak (cases) were more likely than those that had not been infected (non-cases) to report gastrointestinal symptoms, fatigue, headache, or joint-related symptoms [14]. Although a few small studies have followed young children for up to 9 years after sporadic cryptosporidiosis [13, 15], we lack large studies that followed cryptosporidiosis outbreak cohorts for more than 36 months.

The present study aimed to investigate whether post-infectious symptoms persisted for 5 years after a *Cryptosporidium* outbreak.

Methods

This retrospective cohort study was performed in 2016, 5 years after the outbreak of *C. hominis* IbA10G2 in Östersund, Sweden.

Study population and data collection

Two months after the outbreak in November 2010, we invited 1524 randomly selected inhabitants in Östersund, representing all ages, to complete a written questionnaire (outbreak questionnaire), which included questions on demographics, onset and symptoms of cryptosporidiosis, and underlying medical conditions. Among 1044 (69%) respondents, 481 (46.1%) were men and 563 (53.4%) were women. [6] The response rate was lowest among young adults (48.8%, age 20–29 years), and highest among older adults (> 87%, age > 60 years). Follow-ups were performed at 6 months and 2 years post-outbreak, and the results were reported in detail elsewhere [14, 16].

In mid-March 2016, we sent a 5-year follow-up questionnaire, developed for this study (Additional files 1 and 2), by post to the respondents of the outbreak questionnaire. We included a pre-paid envelope to return the completed questionnaire. For children < 15 years old, we asked parents or guardians to complete the questionnaire. A reminder was sent after one month. The respondents reported experiences in the three months prior to completing the questionnaire concerning the following post-infectious symptoms: loss of appetite, weight loss, diarrhoea, watery diarrhoea, bloody diarrhoea, abdominal pain, nausea, vomiting, acid indigestion, bloating, a change in bowel habits, headache, eye pain, fatigue, stiff joints, joint pain, swollen joints, and joint discomfort. A blank area was included for reporting any other symptoms. We scanned the returned questionnaires optically and transformed them into an electronic database.

Case and Non-case definitions

A “case” was defined as a respondent that lived in Östersund in mid-January, 2011, and reported, in the outbreak questionnaire, new episodes of diarrhoea (≥ 3 episodes daily), and/or watery diarrhoea, with an onset between November 2, 2010 and January 30, 2011.

A “non-case” was defined as any respondent that did not fulfil these criteria during the outbreak.

Exclusion criteria

We excluded respondents that, in the outbreak questionnaire, reported a prior diagnosis of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), or “other long-term bowel issues”. This exclusion obviated potential misclassifications.

Data analyses

The study population was stratified according to age and sex. Age was defined as the age at the time of the outbreak. The mean number of symptoms in each group was examined using the Student’s t-test. We examined associations between follow-up symptoms and case status with logistic regressions, adjusted for age and sex. The results are expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). Furthermore, associations between symptoms and case status were examined in different age groups (0–15 years, 16–40 years, 41–65 years, and > 65 years), with logistic regressions adjusted for sex. Missing values were excluded in the analyses. Analyses were performed with the statistical software, SPSS Statistic 24 (IBM, Armonk, NY, USA)

Results

Study population

A total of 675 (69.0 %) individuals responded to the 5-year follow-up questionnaire. Compared to responders, non-responders were younger (30.8 vs. 46.0 years, $p < 0.001$), and more often men (51.5% vs. 43.7%, $p = 0.014$). There were no differences concerning case status.

We excluded 2 individuals unable to answer due to dementia, and 47 individuals that reported IBD, IBS or other long-term bowel issues prior to the outbreak (Fig. 1).

The final analysis included 626 individuals: 280 (44.7%) men and 346 (55.3%) women. Of these, we defined 262 (41.9%) as cases and 364 (58.1%) as non-cases. The median ages at the time of the outbreak were 43 (range 0–80) years in the case group, and 54 (range 0–92) years in the non-case group (Table 1).

Table 1
Demographic characteristics of the study population, grouped by outbreak case status

Characteristic	Case n (%)	Non-case n (%)	Total n (%)
Sex			
Female	145 (55.3)	201 (55.2)	346 (55.3)
Male	117 (44.7)	163 (44.8)	280 (44.7)
Age group, y (at outbreak)			
0–15	44 (16.8)	50 (13.7)	94 (15.0)
16–40	72 (27.5)	68 (18.7)	140 (22.4)
41–65	109 (41.6)	152 (41.8)	261 (41.7)
> 65	37 (14.1)	94 (25.8)	131 (20.9)
Total Cases	262	364	626

Symptoms during follow-up

Five years after the outbreak, 56.5% of the case group and 41.2% of the non-case group reported symptoms during the follow-up period. The case group reported a higher mean number of symptoms (3.8; median = 2, range = 0–17), than the non-case group (2.0; median = 0, range = 0–15; $p < 0.001$). The case group reported that symptoms during the prior three months lasted 10 days, compared to 7 days for the non-case group (median). The most frequent symptoms in the case group were headache, fatigue, and bloating.

Compared to the non-case group, the case group was significantly more likely to report watery diarrhoea, diarrhoea, swollen joints, abdominal pain, bloating, joint discomfort, acid indigestion, changes in bowel habits, joint pain, ocular pain, nausea, and fatigue (Table 2). Symptoms associated with case status varied among age groups. Abdominal pain, acid indigestion, and alternating bowel habits were only observed in the > 65 year-old group; diarrhoea, swollen joints, and nausea were only observed in the 41–65 year-old group; and loss of appetite were only observed in the 16–40 year-old group. In the youngest age group (≤ 15 years), watery diarrhoea was the only symptom significantly associated with case status (OR: 11.1, 95% CI: 1.3–92.8).

Table 2
Symptoms reported at follow-up by respondents and associations with case status

	Total			**0–15 years**	**16–40 years**	**41–65 years**	**>65 years**
	N = 626			N = 94	N = 140	N = 261	N = 131
Symptom	Cases n (%)	Non-cases n (%)	OR (95% CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Watery diarrhoea	43 (16.8)	14 (4.0)	**4.5 (2.4–8.4)**	**11.1(1.3–92.8)**	2.5 (0.9-7.0)	**5.0 (2.0-12.5)**	.
Diarrhoea	52 (20.2)	23 (6.4)	**3.6 (2.2–6.2)**	3.7 (0.7–19.4)	2.4 (1.0-6.1)	**4.1 (1.9-9.0)**	5.7 (1.0–34.0)
Swollen joints	33 (12.9)	20 (5.8)	**3.0 (1.6–5.4)**	.	7.5 (0.9–63.4)	**2.7 (1.2–6.2)**	2.7 (0.9–8.1)
Abdominal pain	64 (25.1)	36 (10.1)	**2.6 (1.7–4.1)**	2.0 (0.8-5.0)	2.0 (0.9–4.5)	3.7 (0.7–8.1)	**4.8 (1.1–21.2)**
Bloating	102 (39.4)	73 (20.9)	**2.5 (1.7–3.6)**	2.8 (0.8–8.2)	2.1 (1.0-4.3)	**1.8 (1.1–3.4)**	**5.8 (2.3–14.6)**
Joint discomfort	82 (31.8)	62 (17.7)	**2.4 (1.6–3.6)**	2.7 (0.7–9.6)	**3.5 (1.5–8.4)**	**2.1 (1.2–3.8)**	1.7 (0.7–3.9)
Stiff joints	71 (27.5)	58 (16.7)	**2.3 (1.5–3.4)**	2.2 (0.4–13.0)	**5.8 (1.8–18.2)**	**2.1 (1.2–3.7)**	1.2 (0.5–2.9)
Acid indigestion	62 (23.9)	44 (12.8)	**2.3 (1.5–3.5)**	4.7 (0.9–24.2)	1.9 (0.8–4.6)	1.8 (0.9–3.3)	**3.4 (1.3–8.9)**
Changes in bowel habits	47 (18.1)	32 (9.3)	**2.2 (1.3–3.5)**	2.9 (0.7–11.9)	2.5 (0.9-7.0)	1.5 (0.8-3.0)	**4.3 (1.1–16.2)**
Joint pain	79 (30.4)	65 (18.7)	**2.2 (1.5–3.3)**	1.8 (0.5-7.0)	**4.6 (1.7–12.5)**	**2.5 (1.4–4.4)**	0.8 (0.3-2.0)
Ocular pain	49 (19.3)	33 (9.5)	**2.3 (1.4–3.7)**	2.4 (0.7–7.9)	2.3 (0.9–6.1)	2.1 (0.9–4.6)	2.8 (1.0-7.6)

Bolded values indicate a significant association

	Total			0–15 years	16–40 years	41–65 years	>65 years
Nausea	55 (22.0)	35 (9.9)	**2.2 (1.4–3.6)**	1.3 (0.5–3.3)	1.7 (0.7–3.9)	**4.0 (1.8–9.1)**	4.0 (0.8–19.1)
Fatigue	106 (41.4)	85 (24.3)	**2.0 (1.4–2.9)**	1.8 (0.7–4.3)	**2.1 (1.1–4.2)**	**2.2 (1.2–3.8)**	1.6 (0.6–4.2)
Headache	108 (42.2)	103 (29.3)	1.5 (1.0-2.1)	1.2 (0.5–2.8)	1.9 (0.9–3.8)	1.5 (0.8–2.6)	1.1 (0.4–3.4)
Loss of appetite	23 (8.9)	14 (4.1)	2.0 (1.0–4.0)	1.5 (0.4–5.2)	**12.1 (1.5–96.7)**	0.9 (0.2–3.3)	2.6 (0.3–19.5)
Vomiting	20 (7.9)	13 (3.7)	1.8 (0.9–3.7)	1.4 (0.4–4.5)	1.8 (0.5–6.5)	2.7 (0.6–11.5)	.
Weight loss	14 (5.5)	10 (2.9)	1.8 (0.8–4.1)	1.4 (0.3–6.8)	1.4 (0.2–8.9)	2.9 (0.5–16.4)	2.5 (0.5–13.3)
Bolded values indicate a significant association							

Discussion

In this retrospective cohort study, we demonstrated that post-infectious symptoms persisted for 5 years after a large waterborne outbreak caused by *C. hominis* in northern Sweden. Compared to the non-case group, the case group was more likely to report gastrointestinal symptoms, joint-related symptoms, ocular pain, and fatigue. Middle-aged individuals (41–65 years) seemed to be most affected, particularly by diarrhoea and different joint-related symptoms. The symptoms persisted to a lesser extent in children (≤ 15 years old) than in other age groups.

To our knowledge, no other large studies have conducted such a long follow-up after an acute cryptosporidiosis. Our research group previously reported similar data from the same cohort, where follow-ups after 6-11months [16] and 2 years [14] demonstrated that the case group was more likely to have gastrointestinal and joint-related symptoms, compared to the non-case group. In another Swedish study, 271 individuals with sporadic infections from different types of cryptosporidiosis were followed in 2006–2008. After 25 to 36 months, 15% reported intermittent diarrhoea and 9% reported abdominal pains [17].

Acute gastroenteritis is known to increase the risk of IBS [18, 19]. Follow-up studies on *Giardia*, another protozoan parasite that causes gastroenteritis, have shown similar post-infectious symptoms that persisted for up to 10 years [18]. Several putative factors have been implicated in the pathogenesis of

IBS, including dysfunction of the innate immune system or the enteric nervous system and alterations in the faecal microbiota [20]. However, additional studies are needed to clarify the interplay between these factors to reach a plausible hypothesis for the pathophysiologic mechanism of long-term symptoms after a *Cryptosporidium* infection.

Overall, the symptoms most frequently reported in our case group were headache, fatigue, and bloating. In the most affected age group (41–65 year-olds), diarrhoea, joint-related symptoms, nausea, and fatigue were most highly associated with cryptosporidiosis. These data were consistent with results reported in a systematic review based on pooled estimates from 8 studies on the health sequelae of cryptosporidiosis, with follow-up periods of 2—36 months. In that study, the most common long-term sequelae were diarrhoea (25%), abdominal pain (25%), nausea (24%), fatigue (25%), and headache (21%) [11].

The group of children (0–15 years old) in our study was small (n = 94), and this group reported watery diarrhoea, but no other persisting symptoms. However, previous studies have reported that particularly young children (< 2 years old) were vulnerable to acute infections and the consequences [7], and IBS or IBS-like symptoms after cryptosporidiosis occurred at a higher rate in children than in adults [9]. In contrast, in our cohort, at the two-year follow-up, the children did not report any significant persistent symptoms, other than headaches [14]. However, it is difficult to identify and define sequelae in young children, and adults have been over-represented in most large studies [11]. Thus, more research is needed with a particular focus on long-term persistent symptoms in children.

Conclusion

In summary, our findings indicated that post-infectious symptoms, due to cryptosporidiosis, could persist for up to 5 years, a longer time than any previous study has documented. This finding suggested that the long-term health consequences of cryptosporidiosis may be underestimated, both on an individual level and on the global level.

Limitations

One limitation of this study was that our case definition was based on self-reported symptoms, and we lacked laboratory confirmation. This limitation might have led to misclassification of case-status in some individuals. However, during the outbreak in 2010, cryptosporidium was detected in the drinking water; in addition, 149 stool samples were collected among individuals with diarrhoea, and all were positive *for C. hominis* and negative for other gastrointestinal pathogens [6].

Another limitation was that we did not determine whether participants had a chronic *Cryptosporidium* infection, which could potentially have caused the follow-up symptoms. However, during the 2-year follow-up, study participants were invited to submit stool samples (n = 183), and these were all negative for *Cryptosporidium*, based on a standard concentration determination technique with modified Ziehl–Neelsen staining [14].

Moreover, it is possible that individuals with chronic intermittent diarrhoea might have been misclassified as cases during the outbreak. These individuals might be more likely to have had similar symptoms at follow-ups, which could have led to an overestimation of the associations. However, we attempted to minimize this effect by excluding individuals that reported a pre-existing IBD or IBS diagnosis, or any other long-term gastrointestinal problems, prior to the outbreak. On the other hand, some participants might have had subclinical *Cryptosporidium* infections during the outbreak [2]. If these participants had experienced and reported post-infectious symptoms, they would have contributed to the prevalence of symptoms in the non-case group. That situation could have led to an underestimation of the associations.

Although the long-term gastrointestinal symptoms reported by many participants were likely to be due to IBS, we could not fully diagnose IBS. A validated questionnaire on the Rome IV criteria is typically used to diagnose IBS [21]. However, the questionnaire is lengthy, and we were concerned that including the full questionnaire might reduce the overall response rate. Therefore, we decided not to include it in full, but to base our questions concerning gastrointestinal symptoms on those criteria.

Lastly, there was a risk that individuals that were infected during the outbreak (i.e., cases) might be more prone to note, remember, and report on their symptoms, compared to individuals that were not infected.

Abbreviations

C. hominis
Cryptosporidium hominis
CI
Confidence interval
IBD
Inflammatory bowel disease
IBS
Irritable bowel syndrome
OR
Odds ratio

Declarations

Ethics approval and consent to participate

The Regional Ethical Review Board in Umeå approved this study (2015/495-31Ö). The respondents were given information about the study in a written letter, and participants provided consent by completing the written questionnaire.

Consent for publication

Not applicable.

Availability of data and material

The datasets used in the current study are available from the corresponding

author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

ML and MW were the main contributors to the design of the questionnaires. All authors contributed to the analysis and interpretation of the data. MS and MA were the major contributors to writing the manuscript. All authors read and approved the final manuscript.

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Figures

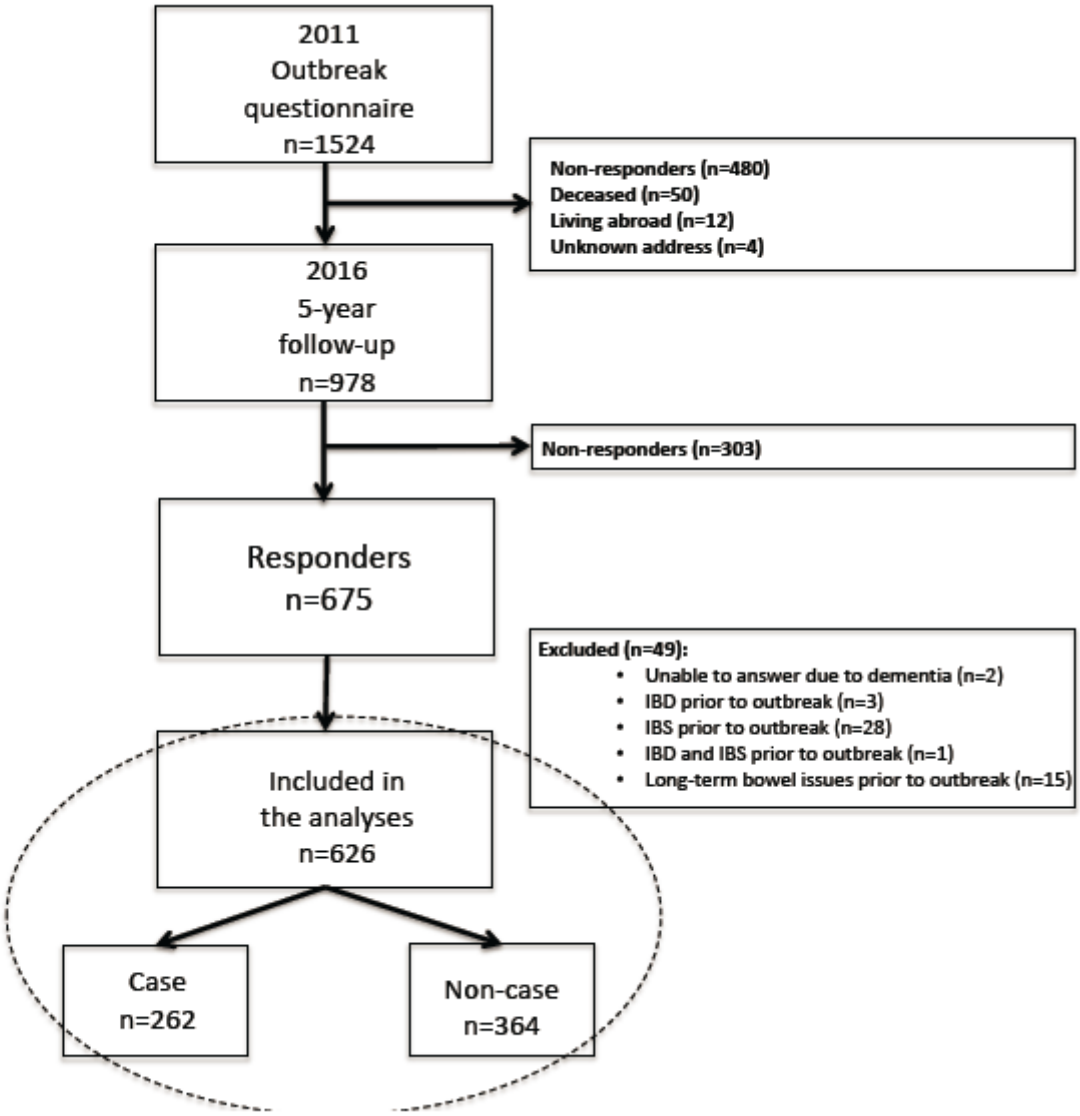

Figure 1

Flow chart of the case selection process Case = New episodes of diarrhoea (≥ 3 episodes daily), and/or watery diarrhoea between November 1, 2012 and January 31, 2011, in respondent residing in Östersund in mid-January 2011 Non-case = Any respondent not fulfilling the case criteria during the outbreak. IBD = Inflammatory bowel disease IBS = Irritable bowel syndrome

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile1Swe.pdf
- AdditionalFile2Eng.pdf