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Cryptosporidiosis in Wisconsin: A case-control study of post-outbreak transmission

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SUMMARY

During March–April 1993, an estimated 403000 residents of the 5-county greater Milwaukee, Wisconsin area developed cryptosporidiosis after drinking contaminated municipal water. Although the number of cases dropped precipitously after the implicated water plant closed on 9 April, cases continued to occur. To investigate risk factors for post-outbreak cryptosporidiosis, 33 Milwaukee-area residents who had laboratory-confirmed *Cryptosporidium* infection with onset of diarrhoea between 1 May and 27 June 1993 were interviewed by telephone. Of these, 28 (85%) had onset of diarrhoea during May, 12 (36%) had watery diarrhoea during the outbreak, and 5 (15%) were HIV-infected. In a neighbourhood-matched case-control study, immunosuppression (matched odds ratio (MOR) not calculable, 95% confidence interval (CI) 3·0, infinity) and having a child less than 5 years old in the household (MOR = 17·0, CI 2·0, 395·0) were independently associated with infection. When persons who had diarrhoea during the outbreak were excluded, immunosuppression remained significantly associated with illness (MOR not calculable, CI 1·6, infinity). *Cryptosporidium* transmission continued after this massive waterborne outbreak but decreased rapidly within 2 months.

BACKGROUND

Within the past few years, *Cryptosporidium parvum* has emerged as an important cause of sporadic diarrhoeal illness [1–3] and outbreaks of waterborne disease [1, 4–6]. Within 2–14 (median 6–7) days after exposure to the organism, immunocompetent persons typically develop self-limited watery diarrhoea that lasts from 3–9 days [1, 7–9]. Asymptomatic infections have been documented and may occur frequently [10]. Persons with immunosuppressive conditions, particularly those with the acquired immunodeficiency syndrome (AIDS), may develop severe protracted diarrhoea that results in weight loss, chronic wasting, and death [11, 12]. A pattern of recurrent, intermittent, or 'waxing and waning' diarrhoea has been noted [13, 14], but this pattern has not been well-characterized, particularly in immunocompetent persons.

During March and April 1993, an estimated 403000 persons living in the 5-county area of greater Milwaukee, Wisconsin experienced diarrhoeal illness. An investigation by the Wisconsin Division of Health

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and the Milwaukee City Health Department established *Cryptosporidium* as the causative agent and implicated water from one of the two Milwaukee Water Works treatment plants [4]. This plant, located in southern Milwaukee, supplied drinking water primarily to southern and central Milwaukee [4].

On 7 April 1993, an advisory to boil water was issued by the mayor of Milwaukee. On 9 April the South Milwaukee Water Works treatment plant was temporarily closed and the entire city was supplied with water from the North plant. The South water treatment plant was put back into service on 1 June 1993. Telephone surveys conducted by the Wisconsin Division of Health and the City of Milwaukee Health Department from 12 April to 20 May 1993 indicated that the number of cases of watery diarrhoea dropped sharply after 15 April [4, 8]. However, laboratory-confirmed causes of *Cryptosporidium* infection continued to occur, and the source of transmission for these cases was unknown. Because of concern about ongoing transmission of *Cryptosporidium* in the Milwaukee area, an investigation was conducted to assess the magnitude of the problem, to identify possible risk factors for secondary transmission, and to characterize clinical and epidemiologic features of cryptosporidiosis following the outbreak.

MATERIALS AND METHODS

Case finding

Shortly after *Cryptosporidium* was identified as the cause of the outbreak, the City of Milwaukee Bureau of Laboratories established active surveillance for laboratory-confirmed cases. Medical laboratory directors in the Milwaukee area were asked to test all submitted stool specimens for *Cryptosporidium* and report by facsimile or telephone the number of stool specimens tested and the number positive for *Cryptosporidium*. In addition, the Milwaukee city epidemiologist received communicable disease case reports of cryptosporidiosis from physicians, hospital infection control personnel, public health officials and local health departments.

Case definition

A case was defined as a laboratory-confirmed *Cryptosporidium* infection in a resident of the 5-county greater Milwaukee area who had diarrhoea that began between 1 May and 27 June 1993, i.e., at least 3 weeks after the implicated water treatment plant was closed. The presence of oocysts in stool was microscopically confirmed by local laboratories using a modified acid fast stain or direct fluorescent antibody assay. To reduce the likelihood that persons with recrudescence of outbreak-associated cryptosporidiosis were classified as having post-outbreak *Cryptosporidium* infection, persons who had diarrhoea before 1 May were excluded from the study unless they reported having had at least 7 consecutive days of normal stools before onset of illness on or after 1 May. Diarrhoea was defined as two or more loose or watery bowel movements within a 24-h period. The outbreak interval was considered to be the period between 15 March and 15 April 1993.

Epidemiologic investigation

All laboratory-confirmed cases reported to the City of Milwaukee Health Department between 1 May and 27 June 1993 were reviewed. Attempts were made to contact the case-patients by telephone to determine eligibility.

Case-patients who agreed to participate were interviewed using a standardized questionnaire. We obtained information on signs and symptoms of illness and possible risk factors for secondary transmission of *Cryptosporidium*. Possible risk factors during the 2 weeks before onset of illness included immunosuppression, residential area, drinking water supplied by the Milwaukee Water Works, attending or working at a child day-care centre, changing diapers, swimming in a lake, pool, or river, bathing in a whirlpool or hot tub, drinking water in restaurants or using ice made from water supplied by the Milwaukee Water Works, drinking unpasteurized milk or eating unpasteurized cheese, having household pets, number of household members, number of children in the household, and having close contact with persons with diarrhoea. Reported HIV status was not verified by examination of medical records.

During the outbreak, residence in southern or central Milwaukee, a proxy for exposure to water supplied by the South water treatment plant, was a strong risk factor for cryptosporidiosis [4]. Between 9 April and 1 June however, the North plant was the only source of Milwaukee Water Works, and water from the South plant repeatedly tested negative for *Cryptosporidium* after it reopened on 1 June. There-

fore, we did not assess exposure to the water supplied by the South plant during the post-outbreak period. Instead, persons were considered exposed to Milwaukee Water Works water if they lived anywhere within the service area and reported drinking tap water at home during the 2 weeks before onset of diarrhoea.

Illness characteristics

Physicians in Milwaukee reported that cases of cryptosporidiosis occurring during the outbreak period appeared to be unusually severe, an impression that was supported by data collected during the outbreak. Of 739 persons who had laboratory-confirmed *Cryptosporidium* infection reported to the City of Milwaukee Health Department during the outbreak, 285 were interviewed by MacKenzie and colleagues, who described the clinical characteristics of these cases [4]. To determine whether reported cases of post-outbreak cryptosporidiosis were similar in severity to cases reported during the outbreak interval, we compared clinical characteristics (e.g., diarrhoea, abdominal cramps, fatigue, fever, and hospitalization) of post-outbreak cases with those of confirmed outbreak cases [4].

Household and neighbourhood controls investigation

To identify possible risk factors for cryptosporidiosis during the post-outbreak period, we conducted household and neighbourhood case-control studies. Each case was matched with one household control and one neighbourhood control. The household control was the member of the case-patient's household who was closest in age to the case-patient and who had had no diarrhoea since 1 May 1993. The neighbourhood controls were selected by systematic use of a computerized cross-index directory of telephone numbers and residential addresses in Milwaukee County. Control subjects who agreed to participate were interviewed by telephone to obtain information on possible risk factors for secondary transmission of cryptosporidiosis during the 2 weeks before the onset of diarrhoea in the matched case. With regard to risk factor assessment, the control questionnaire was identical to that used to interview the case-patients.

Two analyses of the data were performed. In part to assess whether diarrhoea during the outbreak (i.e., 15 March–15 April) was associated with post-outbreak diarrhoea (i.e., 1 May–27 June), the first analysis did not exclude either case-patients or controls who reported having had diarrhoea during the outbreak. In the second analysis, these persons were excluded.

Statistical methods

A matched case-control analysis was performed. Matched odds ratios (MOR) and 95% confidence intervals (CI) are reported for comparisons of cases and controls. If MORs were non-calculable, exact lower confidence intervals were calculated [15]. Differences in unmatched proportions were tested using the χ^2 with Yates correction and Fisher's exact test where appropriate.

RESULTS

Of 96 confirmed cases reported to the City of Milwaukee Health Department between 1 May and 27 June 1993, 36 (37%) had onset of symptoms before 1 May and were therefore not included in this analysis. The remaining 60 were considered potential post-outbreak cases. Of the 60 potential post-outbreak case-patients, 37 (62%) had telephone numbers available from the case report form or other sources; of these, 33 (90%) were interviewed. These 33 persons did not differ by age, sex, or residential location from the 27 post-outbreak case-patients who could not be reached for an interview (Table 1).

Characteristics of post-outbreak cases

Of 33 case-patients, 58% were female. Patients ranged in age from 6 months to 83 years (mean, 36 years). Twelve (36%) case-patients had immunosuppressive conditions or were taking immunosuppressive medications. Of these, 5 (42%) were HIV-positive.

Compared with persons who had *Cryptosporidium* infection during the outbreak, those with post-outbreak cryptosporidiosis were less likely to live in southern or central Milwaukee, the area that had been served by the South treatment plant before 9 April (54% *vs.* 39%, $P = 0{\cdot}15$) (Table 2). The clinical characteristics of illness in both groups of patients were similar (Table 2). Twelve (36%) case-patients with post-outbreak cryptosporidiosis reported having had watery diarrhoea during the outbreak interval. Of 12 immunocompromised case-patients, 5 (41%) gave a history of having had watery diarrhoea during the outbreak. Clinical characteristics of post-outbreak

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Table 1. *Demographic characteristics of 60 patients with post-outbreak laboratory-confirmed* Cryptosporidium *infection, Milwaukee, Wisconsin, May–June 1993*

	Interviewed and included in study	Unable to contact for interview
Number	33	27
Mean age, years (range)	36 (0·5–83)	34 (1–87)
Female gender	19 (58%)	16 (59%)
Residence in city of Milwaukee [4]	21 (64%)	19 (70%)
Southern Milwaukee	11 (33%)	10 (37%)
Northern Milwaukee	8 (24%)	6 (22%)
Central (mid-zone)	2 (6%)	3 (11%)

Table 2. *Demographic and clinical characteristics of laboratory-confirmed outbreak-associated and post-outbreak cases of cryptosporidiosis, 5-county greater Milwaukee area, 1993*

		Post-outbreak cases	
	Outbreak cases $n = 285$	Total $n = 33$	No diarrhoea during outbreak ($n = 21$)
Demographic characteristics			
Mean age, years (range)	41 (1–93)	36 (0·5–83)	34 (1–83)
Female gender	171 (60%)	19 (58%)	15 (71%)
City of Milwaukee residence*	209 (73%)	21 (64%)	13 (62%)
Southern Milwaukee	115 (40%)	11 (33%)	7 (33%)
Northern Milwaukee	55 (19%)	8 (24%)	5 (24%)
Central (mid-zone)	39 (14%)	2 (6%)	1 (5%)
Clinical characteristics			
Diarrhoea†	285 (100%)	33 (100%)	21 (100%)
Mean duration, days	12	10	10
Abdominal cramps	238 (84%)	28 (85%)	16 (76%)
Loss of appetite	230 (81%)	27 (82%)	16 (76%)
Fatigue	247 (87%)	29 (88%)	18 (86%)
Hospitalized	130 (46%)	15 (45%)	13 (62%)
Mean maximum measured temperature (°F)	101	102	102
Immunosuppressed	48 (17%)	12 (36%)	7 (33%)
HIV-infected	Unknown	5 (15%)	5 (24%)

* When both Milwaukee Water Works treatment plants are functioning simultaneously, persons in southern Milwaukee are supplied by water treated in the South plant, persons in northern Milwaukee are supplied by water treated in the North plant, and persons in central Milwaukee are supplied by water from both plants [4]. Between 9 April and 1 June the entire service area was supplied by the North plant.

† $\geqslant 2$ loose or watery bowel movements within a 24 h period.

cryptosporidiosis were similar for persons who had diarrhoea during the outbreak and for those who did not; however, persons who reported having had diarrhoea during the outbreak were less likely to be hospitalized (17% *vs.* 62%, $P = 0{\cdot}03$) and tended to be less likely to have AIDS ($P = 0{\cdot}13$, Table 2).

The number of post-outbreak cases declined linearly during the months of May and June (Fig. 1). Nineteen (55%) cases had onset of illness during the first 2 weeks of May, compared with nine (27%) cases during the last 2 weeks. Five cases were reported with onset during the first 3 weeks of June.

Twenty-eight (85%) case-patients lived in households with a total of 86 other persons. Of these, 25 (29%) household members had diarrhoea during the outbreak. Two (3·3%) of the remaining 61 household

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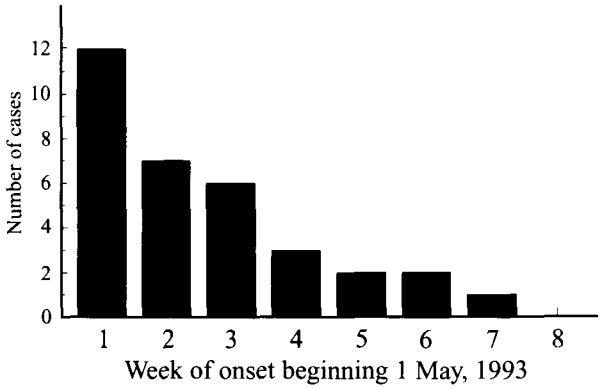

Fig. 1. Number of post-outbreak laboratory confirmed cases of cryptosporidiosis, by week of onset, Metropolitan Milwaukee, 1 May–17 June 1993.

members developed watery diarrhoea 4–5 days after exposure to a case-patient during the post-outbreak period. Illness in these two household members was not confirmed as cryptosporidiosis, nor was transmission from the index case-patient documented.

Case-control studies

Case-patients and controls were similar in age but 19 (58%) of 33 case-patients and 19 (34%) of 56 controls were women ($P = 0{\cdot}05$) (Table 3). In the household case-control study, 28 case-patients had matched controls. Of these 10 (36%) case-patients were immunosuppressed, compared with 2 (7%) of 28 household controls (MOR = 9·0, 95% confidence interval [CI] = 2·0, 43·0, $P = 0{\cdot}01$). No other variables were significantly associated with *Cryptosporidium* infection.

In the neighbourhood case-control study, immunosuppression and having a child under 5 years of age within the household were significantly associated with cryptosporidiosis. Ten (36%) of 28 case-patients and none of 28 neighbourhood controls were immunosuppressed ([MOR not calculable, CI = (3·0–infinity, $P = 0{\cdot}001$). Fifteen (54%) case-patients and one (4%) neighbourhood control had a child less than 5 years of age in the household (MOR = 17·0, CI = 2·0, 395·0, $P < 0{\cdot}001$). These two variables were independent; only two immunosuppressed case-patients had children less than 5 years old in the household. Although drinking municipal water during the post-outbreak period tended to be protective (MOR = 0·1, CI = 0·01, 0·99, $P = 0{\cdot}06$), no other factors were significantly associated with cryptosporidiosis during the post-outbreak period, even when household and neighbourhood controls were combined.

When the 12 case-patients, 7 household controls, and 6 neighbourhood controls who had diarrhoea during the outbreak were excluded from the analysis, immunosuppression remained significantly associated with illness in both the household and neighbourhood case-control analyses (MORs not calculable, CI 1·6, infinity, $P = 0{\cdot}01$); living with a child less than 5 years old was not significantly associated with illness in this analysis (MOR not calculable, $P = 0{\cdot}3$).

DISCUSSION

Following a massive outbreak in Milwaukee during March–April 1993, laboratory-confirmed cases of cryptosporidiosis continued to occur throughout May and June, although the occurrence of these cases decreased rapidly during this period. The greater geographic dispersion of these post-outbreak cases relative to cases during the outbreak and the inverse association between post-outbreak cryptosporidiosis and drinking Milwaukee municipal water suggest that modes of transmission other than drinking contaminated municipal water were responsible for cases occurring during the post-outbreak period. Both post-outbreak and outbreak-associated cases of laboratory-confirmed cryptosporidiosis appeared to be more severe than those reported in previous case series, with a greater reported frequency of abdominal cramps and anorexia [8]. The clinical similarity of post-outbreak and outbreak-associated illness is consistent with the notion that post-outbreak cases resulted from secondary transmission of the outbreak strain or strains of *Cryptosporidium*.

Despite efforts to avoid including persons with outbreak-related cryptosporidiosis in this study, 12 (36%) case-patients reported having had watery diarrhoea during the outbreak. Their post-outbreak diarrhoea began 3–10 weeks after the implicated water plant was shut down. None of these persons were tested for *Cryptosporidium* during the outbreak. Intermittent diarrhoea associated with *Cryptosporidium* infection has previously been reported, primarily in persons with HIV infection [9, 11, 12]. During the Milwaukee outbreak, however, recurrence of diarrhoea was a significant clinical feature among immunocompetent persons; 39% of persons with laboratory-confirmed cryptosporidiosis reported recurrence of diarrhoea after 2 or more days of normal stools [8].

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Table 3. *Selected characteristics of 33 persons with laboratory-confirmed cryptosporidiosis and household and neighbourhood controls, 1 May–27 June 1993*

	Cases	Household controls	Neighbourhood controls
Number	33 *	28	28
Mean age (range), in years)	36 (0·5–83)	35 (1–81)	43 (1–82)
Sex (no. [%] female)	19 (58%)	7 (25%)	12 (43%)
No. (%) with diarrhoea during the outbreak interval	12 (36%)	7 (25%)	6 (21%)
Immunosuppressed	12 (36%)	2 (7%)	0
HIV-infected	5 (15%)	0	0
Child < 5 years old in household	15 (45%)	13 (46%)	1 (4%)
Drank municipal water at home during post-outbreak period	22 (67%)	22 (79%)	23 (82%)

* In both the household and neighbourhood case-control studies, matched controls were identified for only 28 cases.

Only 6% of these persons had recurrence of symptoms after $\geqslant$ 5 days of normal stools. By definition, post-outbreak cryptosporidiosis in this study began after $\geqslant$ 7 days of normal stools. Thus, it seems unlikely that recurrence of outbreak-related cryptosporidiosis can explain post-outbreak cryptosporidiosis in all 12 case-patients who reported diarrhoea during the outbreak. Nonetheless, this possibility cannot be excluded. In fact, MacKenzie and colleagues reported a significant association between having had watery diarrhoea during the outbreak and new onset of diarrhoea during the post-outbreak period [8].

Although case-control studies of sporadic cryptosporidiosis have implicated drinking untreated surface water [16] and contaminated spring water [17], the relative importance of waterborne, person-to-person and foodborne transmission in sporadic cryptosporidiosis is unclear. Similarly, risk factors for post-outbreak cryptosporidiosis have not been well-characterized. Increased awareness and surveillance for *Cryptosporidium* infections in other parts of Wisconsin following the outbreak resulted in the identification of several outbreaks associated with public swimming pools [18, 19]. However, no such outbreaks were identified in Milwaukee, and swimming was not identified as a risk factor for post-outbreak cryptosporidiosis in this study.

Two independent risk factors, immunosuppression and having a child under the age of 5 years in the household, were significantly associated with post-outbreak cryptosporidiosis in the neighbourhood case-control study. Although difficult to document because of the relatively high possibility of exposure from other sources following this massive outbreak, the latter risk factor suggests that person-to-person transmission may have played a role in at least some of the post-outbreak cases. However, in both this study and a study of adults living outside the Milwaukee area who became infected while visiting Milwaukee during the outbreak [8], secondary attack rates within households appeared to be relatively low (i.e., 3–5%). This is in contrast to reported transmission rates of 12–22% from infected children to their household members and caregivers during outbreaks in day-care centres [20].

When persons who reported diarrhoea during the outbreak were excluded from the analysis, only immunosuppression was significantly associated with post-outbreak cryptosporidiosis. This finding seems to suggest that the attack rate of cryptosporidiosis in the Milwaukee area was higher among immunosuppressed persons than in the general population, but detection bias may account for this association. Immunosuppressed persons are probably over-represented among persons with laboratory-confirmed cryptosporidiosis because they tend to seek medical care for diarrhoeal illness, their illness tends to be more severe, and their physicians are more likely to

order diagnostic tests for *Cryptosporidium*. It is also possible that HIV-infected case-patients were more likely than controls to divulge their HIV infection status. Nonetheless, our findings suggest that immunosuppressed persons who do not become ill during large community-wide outbreaks of cryptosporidiosis may remain at risk during the post-outbreak period. Thus, preventive measures taken by such persons to avoid exposure during the outbreak should be continued during the immediate post-outbreak period. It is possible that some of the immunosuppressed persons in our study were infected with *Cryptosporidium* during the outbreak but developed diarrhoea during the post-outbreak period. Data from one outbreak suggested that the mean incubation period for cryptosporidiosis in persons with HIV infection is 13 days, about twice that of HIV-negative persons [21].

Despite the high quality of water treatment in Milwaukee following the outbreak, public concerns about the safety of the municipal water supply persisted after the outbreak. We found no evidence that drinking municipal water was associated with post-outbreak cryptosporidiosis.

Our study was limited by the small sample size and by our inability to interview many potential post-outbreak case-patients because telephone numbers were not provided on the case report form. In addition, although persons were included as controls only if they had no post-outbreak diarrhoea, they were not tested for *Cryptosporidium* infection, and some may have had asymptomatic or subclinical infection. Accurate determination of risk factors for *Cryptosporidium* infection was also complicated by the possibility that persons who were exposed to the organism during the outbreak may have acquired partial immunity that could have prevented infection or attenuated the severity of symptoms on reinfection during the post-outbreak period.

In summary, continued active laboratory surveillance and case-investigation enabled us to document a continued decline in the occurrence of laboratory-confirmed cryptosporidiosis during the 2 months following a massive community-wide outbreak of cryptosporidiosis in Milwaukee. No new point sources were identified. Some post-outbreak cases may have resulted from person-to-person transmission or from recrudescence of infections acquired during the outbreak. Immunosuppressed persons remained at risk. To document the effectiveness of control measures and to rapidly identify and control new sources of transmission, we recommend that active surveillance and case investigation be continued for at least 2 months after large community-wide outbreaks of cryptosporidiosis.

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