

Outbreak of toxoplasmosis associated with municipal drinking water

Victoria evidence
water

William R Bowie, Arlene S King, Denise H Werker, Judith L Isaac-Renton, Alison Bell, Steven B Eng, Stephen A Marion, for the BC Toxoplasma Investigation Team*

Summary

Background Outbreaks of toxoplasmosis are recognised infrequently. In March, 1995, a sudden increase of serologically diagnosed cases of acute toxoplasmosis was noted in the Greater Victoria area of British Columbia, Canada. Concurrently, but independently, seven cases of acute toxoplasma retinitis were diagnosed against a background of no cases in the previous 5 years.

Methods Cases were defined by serological testing, clinical presentation, and residence in Greater Victoria. A screening programme for women who were or had been pregnant was started. Geographical mapping of cases, and case-control studies of symptomatic cases and of women enrolled in the screening programme were done.

Findings 100 individuals aged 6 to 83 years met the definition for an acute, outbreak-related case. 94 resided in Greater Victoria and six had visited it; 19 had retinitis, 51 had lymphadenopathy, four others had symptoms consistent with toxoplasmosis, seven had other symptoms, 18 were symptom-free, and one would not provide information. 36 (0.9%) of 3812 screened pregnant and postnatal women were cases. Excess cases were not detected outside Greater Victoria and no conventional source of toxoplasmosis was implicated. Mapping studies of cases and of the screened women, and both case-control studies showed significant associations between acute infection and residence in the distribution system of one reservoir supplying water to Greater Victoria (ORs or RRs: 3.53, 3.05, 8.27, and 5.42, respectively). The epidemic curve appeared bimodal, with peaks in December, 1994, and March, 1995, that were preceded by increased rainfall and turbidity in the implicated reservoir.

Interpretation A municipal water system that uses unfiltered, chloraminated surface water was the likely source of this large community-wide outbreak of toxoplasmosis.

Lancet 1997; 350: 173-77

*Listed at the end of the paper

Division of Infectious Diseases (W R Bowie MD), Department of Pathology and Laboratory Medicine (J L Isaac-Renton MD), and Department of Health Care and Epidemiology (S A Marion MD), University of British Columbia, Vancouver, British Columbia, Canada; Epidemiology Services (A S King MD, D H Werker MD, A Bell MD) and Provincial Laboratory (J L Isaac-Renton), BC Centre for Disease Control, Vancouver; Field Epidemiology Training Program, Laboratory Centre for Disease Control, Health Canada, Ottawa (D H Werker); and Capital Regional District Health, Victoria, British Columbia (S B Eng MPH)

Correspondence to: Dr William R Bowie, Room 452, D Floor, 2733 Heather Street, Vancouver, BC V5Z 3J5, Canada (e-mail: bowie@unixg.ubc.ca)

Introduction

Toxoplasmosis is endemic throughout most of the world, and can infect a large proportion of the adult population.^{1,2} It is frequently symptomless or mild, but if infection occurs during pregnancy it can have devastating consequences for the fetus.^{1,2} Early treatment of infected pregnant women and their offspring is effective in preventing disease or reducing its severity. Toxoplasmosis can also cause serious disease among immunodeficient people. The causative parasite is *Toxoplasma gondii*, and the definitive hosts are felines.³ Outbreaks of toxoplasmosis involving more than a single family or small group are infrequent.⁴⁻⁷ We describe a widespread outbreak of toxoplasmosis, the largest known to us, and the first to be linked to municipal water.

Methods

Description of the outbreak

In March 1995, the British Columbia Centre for Disease Control became aware of a sudden increase in acute toxoplasmosis in one area of the province, Greater Victoria (figure 1), which includes the City of Victoria and adjacent areas of Vancouver Island, and which is a mixture of urban, suburban, and rural areas. This increase was noted by the Provincial Laboratory, the only laboratory in the province performing serological testing for *T gondii*. There had been no notable increase in testing and no change in testing procedures. Concurrently, but independently, two Victoria ophthalmologists diagnosed seven cases of acute toxoplasmosis with retinitis. Neither ophthalmologists had detected any acquired retinal toxoplasmosis in the previous 5 years.

More infections were detected, which continued to be strongly associated with exposure within Greater Victoria. No producer or distributor of meat, vegetables, or dairy products that uniquely supplies Greater Victoria was identified. There was no evidence of excess cases occurring in the rest of British Columbia, Alberta, or adjacent parts of Washington State, USA. Extensive investigations into potential exposures, including foods, beverages, and attendance at events or restaurants, failed to identify a source that fitted the observed pattern of cases.

Mapping showed an apparent clustering of cases in the central area of Greater Victoria. In the absence of any other plausible source, the municipal water supply was considered as a possible explanation for the spatial distribution of cases. At the time of the outbreak, the Greater Victoria Water District operated two disinfection plants supplying unfiltered, chloraminated surface water to 292 000 people from a total population of 321 585 (1994 estimate). Each disinfection plant supplied water to different areas of Greater Victoria, and to a common area receiving a mixture of water from each plant. The plant apparently associated with the outbreak distributed water from the relatively small Humpback reservoir (118 million gallons). The Humpback reservoir has a retention time of about 8 days in the winter and receives water from two unique watersheds as well as from another larger reservoir.

Serological detection

Sera were initially processed at the Provincial Laboratory with the Platelia (Sanofi Diagnostics Pasteur, Marnes-La-Coquette, France) solid-phase immunoassay for IgG and indirect sandwich type immunoassay for IgM. If IgM results were equivocal or positive, the sera were sent to the Toxoplasma Serology Laboratory, Research Institute, Palo Alto Medical Foundation, California, USA for confirmation and additional testing by

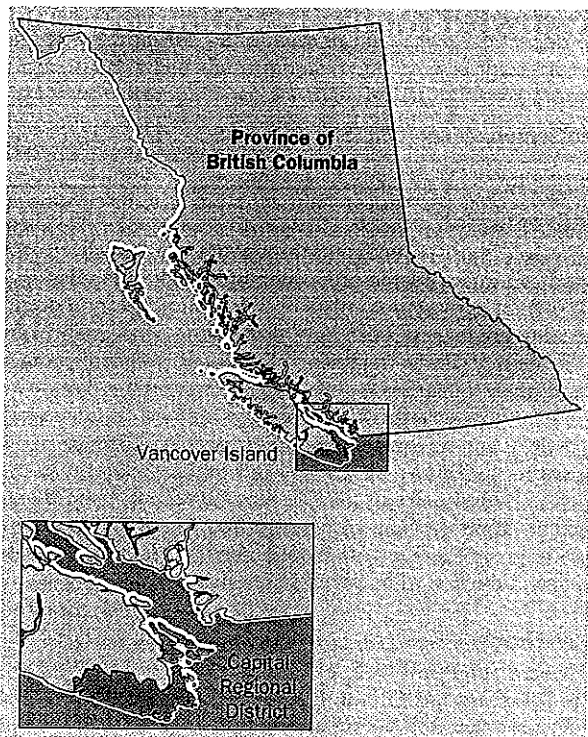


Figure 1: British Columbia and the Greater Victoria region methods described previously.^{2,8,9} All sera tested there and found positive for IgM antibody were also tested by differential agglutination to assess the acuteness of the serological reactivity.¹⁰

Case definitions

Individuals were categorised as acute, equivocal, non-acute, and never infected by standard serological criteria.^{2,8-10} Acute cases were further categorised on the basis of clinical findings between Oct 1, 1994 and the date of initial serological testing as: eye, where a diagnosis of retinal lesions consistent with retinitis caused by *T gondii* was made by an ophthalmologist; node, where there were one or more enlarged lymph node(s) of recent onset reported by the patient with or without physician confirmation; symptoms consistent with toxoplasmosis, where neither of the above criteria were met but fever or sweats plus one or more of headache, feeling ill, or feeling tired were reported; other, where none of the above criteria were met but other symptoms were reported; and symptomatic-free, where no symptoms were reported. An acute eye or node case was considered outbreak related if: the first serum sample demonstrating acute seropositivity was drawn in 1995; the onset of symptoms was between Oct 1, 1994, and June 30, 1995; there was exposure (through residence or travel) to Greater Victoria between Oct 1, 1994, and April 30, 1995; and exposure

occurred at least 4 days before the date of onset of symptoms. A non-eye or non-node acute case was considered outbreak related if: the first serum sample demonstrating acute positivity was drawn between Jan 1, 1995, and June 30, 1995; there was exposure to Greater Victoria between Oct 1, 1994, and April 30, 1995; and the exposure occurred at least 4 weeks before the date of blood sampling.

Case-control study of symptomatic cases

Cases were defined as being IgG and IgM positive at the Provincial Laboratory in a specimen collected between Jan 1 and May 31, 1995; having lived in greater Victoria for 3 months before the onset of symptoms; and having onset of retinitis or lymphadenopathy since Oct 1, 1994. Pregnancy-related cases were excluded. Controls were recruited through the offices of the physicians associated with the cases and were the same sex and age (± 5 years) as the case, had lived in Greater Victoria from July 1, 1994, and were ultimately shown to have no detectable IgG or IgM antibody to *T gondii*. A standardised 17 page questionnaire* seeking information about exposure to all known sources of toxoplasma infection, as well as exposure to various types of water, was administered in the home.

Case-control study in pregnant and postnatal women

Serological screening was offered to women residing in Greater Victoria who were pregnant at any time between Oct 1, 1994, and April 30, 1995. A second (independent) case-control study was conducted among women who participated in the screening programme. Cases met the definition criteria of an acute case, and had been pregnant at any time between Oct 1, 1994, and April 30, 1995. Controls were randomly selected from screened women who were IgG and IgM negative at the Provincial Laboratory, and were matched by expected day of confinement or date of delivery plus or minus 30 days. A 13 page questionnaire*, which sought information on a wide range of exposures including any found significant in the first case-control study, was administered by telephone.

Geographical mapping study

Administrative areas of Greater Victoria were classified into three levels according to degree of exposure to water from the Humpback reservoir. Screened women were assigned to area of residence using MapInfo,¹¹ a geographical mapping program, and attack rates for each area were calculated and compared.

Statistical analyses

For the first case-control study, Mantel-Haenszel matched odds ratio estimates with exact 95% mid-p confidence intervals were generated. For multivariate analyses and for the second case-control study, where age adjustment was required throughout, conditional logistic regression was used. For continuous exposures, means for cases and controls, controlling for the matching factor, were compared. To evaluate trends in proportions, a Mantel-Haenszel trend test was used.¹² For the mapping study, similar but unmatched analyses were carried out.

Results

Number of cases

100 people aged 6 to 83 years met the definition for an acute, outbreak-related case. Of these, 94 resided in Greater Victoria, and the other six were in Greater Victoria at some time during the outbreak before the onset of their disease. (In addition, 12 infants born to mothers with acute toxoplasmosis and considered to have congenital infection are excluded from these analyses.)

Of the 100 cases, 37 women were detected through the screening programme. Of the remaining 63, most were identified because they sought medical attention for symptomatic disease that was ultimately shown to be due to toxoplasmosis (table 1). 51 cases were classified as node, 19 as eye, four as having symptoms consistent with

	Clinical classification				
	Eye	Node	Symptoms compatible with toxoplasmosis	Other symptoms	Symptom free
Total	19	51	4	7	18
Pregnancy screening programme/other	0/19	15/36	2/2	4/3	15/3
Female (n=78)/male (n=21)	10/9	40/11	4/0	7/0	17/1
Age (years)					
Mean	56.1*	28.1	28.5	26.6	27.7
Median	56	28	30	29	27
Range	15-83	6-53	19-35	12-34	17-39

*Age of eye cases versus the rest $p < 0.0001$

Table 1: Means of ascertainment, sex, and age of acutely infected outbreak-related cases

*Available on request from the authors

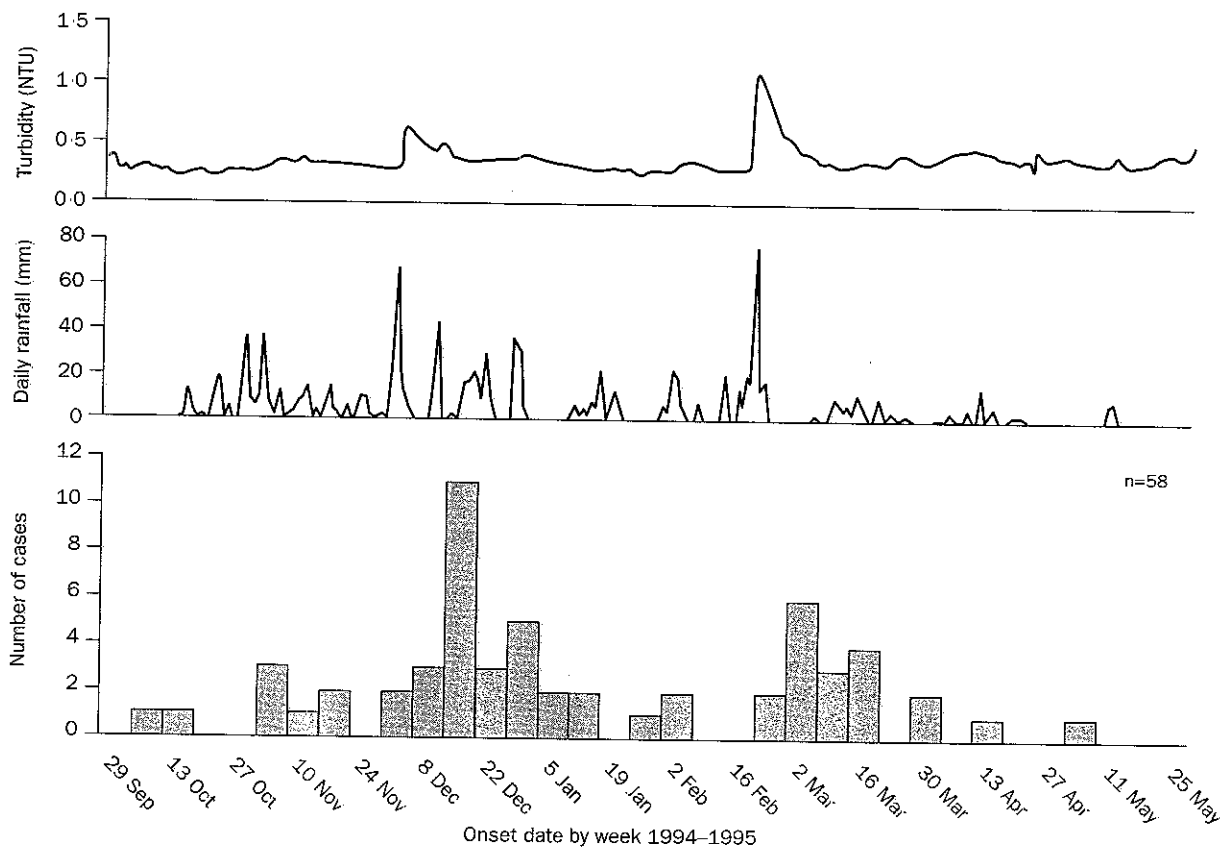


Figure 2: Daily rainfall (mm/day) and turbidity (nephelometric turbidity units) at the Humpback reservoir, and the weekly number of acute cases of toxoplasmosis in Greater Victoria

toxoplasmosis, seven as having other symptoms, and 18 as being symptom free. One case refused to provide information. Eye cases were significantly older than other cases ($p < 0.0001$).

Epidemic curve

Clinical data from the 100 cases were reviewed to develop the final epidemic curve. Data from ocular cases were used only if there were other symptoms consistent with toxoplasmosis because the median (range) interval between onset of symptoms and recognition of ocular disease was 31 (14–87) days for the eight cases with such symptoms. For the 31 node cases with other symptoms, the median interval between onset of symptoms and detection of nodes was 0 (0–64) days. The epidemic curve (figure 2) shows the date of onset of symptoms consistent with toxoplasmosis for eight eye and 31 node cases, plus the date of detection for the 19 node cases who did not meet the criteria for having symptoms consistent with toxoplasmosis. The epidemic curve shows peaks in Dec, 1994, March, 1995, and, possibly, Nov, 1994.

Initial observations

When residences were classified (based on location) as receiving high, intermediate, and no exposure to water from the distribution system of the Humpback reservoir, 83 of the 94 outbreak-related cases who resided in the Greater Victoria were found to live in the area served by the Humpback distribution system (figure 3). The incidence rate of acute toxoplasma infection in people residing in areas served by the Humpback reservoir (83 cases among about 219 000 people served) was more than three times that for areas with other sources of drinking water (11 cases

among 102 585 people) (RR 3.53, 95%CI 1.88–6.63; $p = 0.0003$).

Geographical mapping study

3812 women, about 85% of those estimated as eligible for screening, were tested and mapped. Of these, 36 (0.9%) had serological results consistent with acute infection, two (0.1%) had equivocal results, 216 (5.7%) had a non-acute pattern, and 3558 (93.3%) were never infected. Rates of infection in women living in the area served by the Humpback reservoir were three times higher than in women not living in the Humpback distribution system

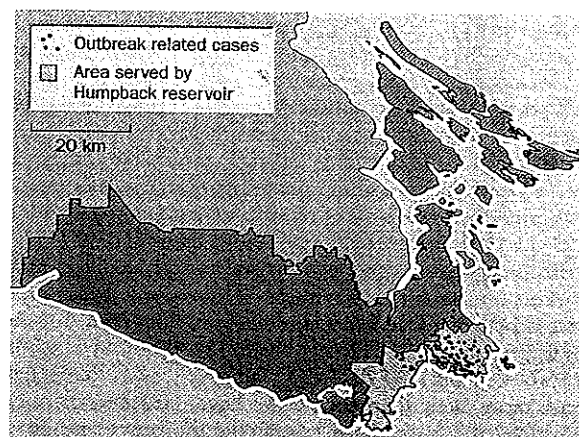


Figure 3: Place of residence of toxoplasma outbreak-related cases and area served by the Humpback reservoir in Greater Victoria

Exposure to Humpback reservoir water based on residential location	Laboratory classification					Acute infection rate (%)*
	Never infected	Non-acute	Acute	Equivocal	Total	
No exposure	983	64	4	1	1052	0.41
Intermediate exposure	1078	71	10	1	1160	0.92
High exposure	1497	81	22	0	1600	1.45
Total	3558	216	36	2	3812	1.00

*Calculation: acute/[acute+never infected]×100

Table 2: Geographical distribution of women screened during pregnancy according to residence and serologic status

(OR 3.05, 1.08–11.92). By contrast, serological evidence of non-acute infection with *T. gondii* was not associated with residence (OR 0.91, 0.67–1.25). When categorised by residence as having high, intermediate, and no exposure to Humpback water (table 2), rates of acute infection in those at risk (acute plus never infected) were 22 of 1519 (1.45%), ten of 1088 (0.92%), and four of 987 (0.41%), respectively (linear trend in proportions of acute infections, $p=0.01$).

Case-control study of symptomatic cases

123 potential controls were identified initially. Three (2.4%) had serological evidence of acute toxoplasmosis. 13 cases with retinitis, 26 cases with lymphadenopathy, and 88 matched controls were included in the final analysis. Illness was not associated with exposure to cats or cat litter, foreign travel, country of birth, exposure to a common event or restaurant, or with activities such as gardening, hiking, or horseback riding. Consumption of unpasteurised milk, game meat, raw meat, pork, lamb, sausage, or hamburger was not associated with illness. Illness was associated with residing in the area served by the Humpback distribution system (37/39 [95%] vs 68/88 [77%]; OR 8.27, 1.72–224; $p=0.025$) and with residing or working in this area (39/39 vs 75/88 [85%]; OR=infinity, 2.49–infinity). These associations remained significant when controlling for other potential risk factors in a conditional logistic regression model. When comparing persons residing in areas receiving high, intermediate, and no water from the Humpback reservoir, a dose-response relationship was found (matched Mantel-Haenszel χ^2 for linear trend=15.1, $p<0.005$).

Case-control study of pregnant and postnatal women

31 cases and 69 controls were included in the final analysis. Controls were slightly older than cases (mean [SD] age 29.8 [4.94] vs 27.4 [4.50] years, $p=0.03$). There were no differences between cases and controls with respect to travel outside Canada, exposure to cats or cat litter, use of swimming pools, meat consumption (sausage, ground beef, other ground meat, pork, or game meats), raw/rare meat consumption, or handling of raw meat. No cases or controls reported consuming unpasteurised cow's or goat's milk. Infection was associated with eating lamb (OR 4.20, 1.25–14.1); however, only nine (29%) cases and 12 (17%) controls reported eating lamb. Cases were more likely than controls to have resided in the Humpback distribution system between Oct 1, 1994, and April 30, 1995, but the result was not statistically significant (28/31 [90%] vs 52/69 [75%]; OR 3.61, 0.79–16.5). However, cases were five times more likely than controls to have resided in the area served by the Humpback reservoir during two periods of heavy rainfall associated with significant turbidity in the reservoir (OR 5.18, 1.07–25.1; OR 5.42, 1.07–27.5, when adjusted for age and lamb consumption) (figure 2).

Serological results in cats

Cats were trapped around both Sooke reservoir, the major source of water for Greater Victoria, and the Humpback reservoir. Four of seven cats, including cats from both sites, were seropositive (titres 1/256, 1/512, 1/512, and 1/1024) in an indirect latex agglutination test (Toxotest-MI "Eiken", Tanabe, San Diego, CA, USA).

Water quality data

The two peaks in turbidity in Humpback reservoir water (figure 2) followed periods of excess rainfall associated with runoff into the reservoir, and each peak preceded a peak in the epidemic curve (figure 2). Between Oct 1, 1994, and April 30, 1995, results of routine testing for potential pathogens other than *T. gondii* in source and treated water were unremarkable.

Discussion

The sudden onset of cases of toxoplasmosis with acute retinitis and the striking clustering of cases in place and time, support the conclusion that the incident we describe was an outbreak rather than recognition of an ongoing problem. Based on the rate of infection (0.9%) in the screened pregnant women and the rate in individuals selected as potential controls (2.4%), we estimate that between 2894 and 7718 individuals in Greater Victoria were infected. Thus, despite a screening programme in pregnancy, a high level of media attention, and intensive education campaigns and awareness among physicians, at most 3% (100 out of 3000) of infections were diagnosed specifically. Particularly unusual in this outbreak were the high number of cases with apparent acquired retinal toxoplasmosis, and remarkably high titres of IgG antibody in the dye test (data not shown).

Although the chain of events may never be fully elucidated, the weight of evidence suggests that water from the Humpback reservoir was the source of the outbreak. We will probably never prove definitively that water was the source of the outbreak because water specimens were not collected from the Humpback reservoir to attempt parasite isolation in mice until municipal water emerged as a potential source, at least 3 months after the last case was infected. As anticipated, these studies were negative (J. I. Isaac-Renton, J. P. Dubey, W. R. Bowie, unpublished observations).

However, all other data are consistent with a waterborne source of infection and do not suggest an alternative exposure that could account for the size and distribution of the outbreak. Two independent case-control studies and geographical mapping demonstrated significant associations between residing in the area served by the Humpback distribution system and having acute infection with *T. gondii*. These studies also showed a dose-response relation when persons residing in areas receiving high, intermediate, and no water from the Humpback reservoir were compared. The epidemic curve showed clusters of cases occurring during two time periods that were preceded by runoff into the Humpback reservoir, as indicated by peaks in rainfall and turbidity. The runoff may have contaminated the reservoir with oocysts of *T. gondii* because domestic and feral cats, as well as cougars (*Felis concolor*), are known to be present in the watershed. Four of seven cats trapped in the watershed, and all five cougars tested elsewhere on Vancouver Island,¹³ had antibody to *T. gondii*. One infected cat can shed 200 million oocysts,¹ which are hardy and can survive in the environment for a long

time.^{14,15} The temperature of water in the Humpback reservoir (3–18°C over the outbreak period) would support the survival of sporulated oocysts.^{16,17} The relatively small capacity and rapid turnover of water would have decreased the opportunity for oocysts to settle out, and hence would have facilitated entry of oocysts into the Humpback chloramination plant. Since the surface water is chloraminated and not filtered, viable and potentially infective oocysts could be distributed in the water system. Little is known about the susceptibility of oocysts of *T. gondii* to various methods of disinfection; however, infective environmental stages of the similar parasites cryptosporidium and giardia are not reliably killed by chloramination.^{18,19} The inoculum of oocysts needed to infect humans is unknown, but oocysts are believed to be highly infective.^{20,21}

Several factors present in Greater Victoria and the water system facilitated occurrence of the outbreak. These include a surface water supply that was susceptible to direct or indirect contamination, access to the reservoir by domestic, feral, and wild cats because of its proximity to urban and rural habitat, a short retention time in the intake reservoir, use of weak chemicals for primary disinfection, and the lack of filtration for water treatment. Greater Victoria may have the only water system in North America serving 100 000 people or more that has all of these features. Because of the low incidence of symptoms in an affected population, and the inefficiencies of analytical testing and recognition and reporting of disease, contamination of a large water system would be needed for a waterborne outbreak to be detected. As in Snow's famous investigation of cholera in London, if there had not been two discrete distribution systems in one metropolitan area, the association with water would likely not have been identified.²² Many smaller communities may have water systems sharing features of the Greater Victoria system and are thus vulnerable to contamination with toxoplasma. Any resultant outbreaks might well be undetected in the absence of an active surveillance system.

This outbreak demonstrates the importance of having an effective public health system. Without it, this outbreak might not have been recognised and almost certainly its magnitude and source would not have been appreciated. Without the early initiation of the screening programme, with the consequent ability to treat pregnant women and affected infants, the health impact and long-term costs would have been much greater. The water reservoir implicated in the outbreak has been closed.

Contributors

All authors were involved in data analysis and writing the manuscript. W R Bowie and S B Eng were responsible for design and implementation of case-control and mapping studies, and for data management. A S King, D H Werker, and A Bell were responsible for the design and implementation of all studies, for data management, and for ascertainment of cases. J L Isaac-Renton was responsible for design and implementation of studies, and ascertainment and management of cases. S A Marion was responsible for design of case-control studies, and for data management.

Acknowledgements

Members of the BC Toxoplasmosis Investigation Team: Michael Aeberhardt, D Kelly Barnard, Kevin Kirkwood, and Luis Martinez (Epidemiology Services, BC Centre for Disease Control, Vancouver); Brian Berry and Malcolm Parslow (Department of Pathology, Greater Victoria Hospital Society [GVHS], Victoria); *Andrew J Burnett and Stan Shorut (Section of Ophthalmology, GVHS, Victoria); Jenny Cadman and *Patrick MacLeod (Prenatal Assessment Clinic, GVHS, Victoria); J P Dubey (US Department of Agriculture, Beltsville, Maryland, USA); Louise Egan (Public Health Protection, BC Ministry of Health, Victoria); Raj K Gill (Provincial Laboratory, BC Centre for Disease Control, Vancouver); Donna

Guns, *Timothy Johnstone and Myrna Klein (Capital Regional District Health, Victoria); Jamie Hockin (Field Epidemiology Training Program, Laboratory Centre for Disease Control, Health Canada, Ottawa); J A (Jack) Hull and *G Stewart Irwin (Greater Victoria Water District, Victoria); *Frank Jagdis (Pediatric Infectious Diseases, GVHS, Victoria); Kevin Kain (Tropical Disease Unit, University of Toronto, Toronto); John Millar and *Shaun Peck (Office of the Provincial Health Officer, BC Ministry of Health, Victoria); *Jack S Remington (Department of Medicine, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, and Research Institute, Palo Alto Medical Foundation, Palo Alto, California, USA); *Diane Roscoe (Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver); and Craig Stephen (Epidemiology Services, BC Centre for Disease Control, Vancouver, and Department of Health Care and Epidemiology, University of British Columbia, Vancouver)

*Additional members of the writing committee

Financial support was provided by the Ministry of Health, British Columbia, Capital Regional District Health Department, Victoria, and the Laboratory Centre for Disease Control, Health Canada, Ottawa, Ontario

References

- Dubey JP, Beattie CP. Toxoplasmosis of animals and man. Boca Raton: CRC Press, 1988.
- Remington JS, McLeod R, Desmonts G. Toxoplasmosis. In: Remington JS, Klein JO, eds. Infectious diseases of the fetus and newborn, 4th ed. Philadelphia: W B Saunders, 1995: 140–267.
- Beaman MH, McCabe RE, Wong SY, Remington JS. *Toxoplasma gondii*. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and practice of infectious diseases, 4th ed. New York: Churchill Livingstone, 1995: 2455–75.
- Teutsch SM, Juranek DD, Sulzer A, Dubey JP, Sikes RK. Epidemic toxoplasmosis associated with infected cats. *N Engl J Med* 1979; **300**: 695–99.
- Benenson MW, Takafuji ET, Lemon SM, Greenup RL, Sulzer AJ. Oocyst-transmitted toxoplasmosis associated with ingestion of contaminated water. *N Engl J Med* 1982; **307**: 666–69.
- Kean BH, Kimball AC, Christenson WN. An epidemic of acute toxoplasmosis. *JAMA* 1969; **208**: 1002–04.
- Magaldi C, Elkis H, Pattoli D, Coscina AL. Epidemic of toxoplasmosis at a university in São-José-dos-Campos, S P Brazil. *Rev Latinoam Microbiol Parasitol* 1969; **11**: 5–13.
- Wong S-Y, Remington JS. State of the art clinical article: toxoplasmosis in pregnancy. *Clin Infect Dis* 1994; **18**: 853–62.
- Montoya JG, Remington JS. Studies on the serodiagnosis of toxoplasmic lymphadenitis. *Clin Infect Dis* 1995; **20**: 781–89.
- Dannemann BR, Vaughan WC, Thulliez P, Remington JS. Differential agglutination test for diagnosis of recently acquired infection with *Toxoplasma gondii*. *J Clin Microbiol* 1990; **28**: 1928–33.
- MapInfo for Windows 3.0 Users Guide and Reference, Troy, NY: MapInfo Corp, 1992–94.
- Mantel N. Chi-square tests with one degree of freedom; extensions of the Mantel-Haenszel procedure. *J Am Statistical Assoc* 1963; **58**: 690–700.
- Stephen C, Haines D, Atkinson K, Schwantje H, Bollinger T. Serologic evidence of toxoplasma infection in cougars (*Felis concolor*) on Vancouver Island, British Columbia. *Can Veterinary J* 1996; **37**: 241.
- Frenkel JK, Ruiz A, Chinchilla M. Soil survival of *Toxoplasma* oocysts in Kansas and Costa Rica. *Am J Trop Med Hyg* 1975; **24**: 439–43.
- Yilmaz SM, Hopkins SH. Effects of different conditions on duration of infectivity of *Toxoplasma gondii* oocysts. *J Parasitol* 1972; **58**: 938–39.
- Dubey JP, Miller NL, Frenkel JK. The *Toxoplasma gondii* oocyst from cat feces. *J Exp Med* 1970; **132**: 636–62.
- Frenkel JK, Dubey JP. Toxoplasmosis and its prevention in cats and man. *J Infect Dis* 1972; **126**: 664–73.
- Finch GR, Black EK, Labatiuk CW, Gyurek L, Belosevic M. Comparison of *Giardia lamblia* and *Giardia muris* cyst inactivation by ozone. *Appl Environ Microbiol* 1993; **59**: 3674–80.
- Korich DG, Mead JR, Madore MS, Sinclair NA, Sterling CR. Effects of ozone, chlorine dioxide, chlorine, and monochloramine on *Cryptosporidium parvum* oocyst viability. *Appl Environ Microbiol* 1990; **56**: 1423–28.
- Miller NL, Frenkel JK, Dubey JP. Oral infections with *Toxoplasma* cysts and oocysts in felines, other mammals, and in birds. *J Parasitol* 1972; **58**: 928–37.
- Dubey JP, Lunney JK, Shen SK, Kwok OCH, Ashford DA, Thulliez P. Infectivity of low numbers of *Toxoplasma gondii* oocysts to pigs. *J Parasitol* 1996; **82**: 438–43.
- Snow J. On the mode of communication of cholera, 2nd ed. London: Churchill, 1855. Reproduced in: Snow on Cholera. New York: Hafner, 1965.

CIRC DESK THE LANCET

Volume 350, Number 9072 • Founded 1823 • Published weekly • Saturday 19 July 1997

EDITORIAL

- 155 **A curious stopping rule from Hoechst Marion Roussel**

COMMENTARY

- 156 **CHART for non-small-cell lung cancer—promises and limitations**
E E Vokes
- 157 **Making DOTS succeed** J M Grange A Zumla
- 157 **NIDDM and breastfeeding** D Simmons
- 158 **Prevention of hearing loss from meningitis** S L Kaplan
- 159 **Genes, familial enuresis, and clinical management**
M Super, R J Postlethwaite
- 160 **Wakley Prize, 1997** R Horton
- 160 **Diabetes and the heart** K Hopkins

ARTICLES

- 161 **Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial**
M Saunders and others
- 166 **Breastfeeding and incidence of non-insulin-dependent diabetes mellitus in Pima Indians**
D J Pettitt and others
- 169 **Control of tuberculosis by community health workers in Bangladesh**
A M R Chowdhury and others
- 173 **Outbreak of toxoplasmosis associated with municipal drinking water**
W R Bowle and others

EARLY REPORT

- 178 **Nerve ingrowth into diseased intervertebral disc in chronic back pain** A J Freemont and others

CASE REPORT

- 182 **A blinding headache** J M Embil and others

RESEARCH LETTERS

- 183 **Ambiguous genitalia in infant exposed to tamoxifen in utero** K Tewari and others
- 184 **Efficacy of troglitazone measured by insulin resistance index** S Nagasaka and others
- 185 **Adult night terrors and paroxetine** S J Wilson and others
- 185 **Does blinding of readers affect the results of meta-analyses?** J A Berlin
- 186 **Birth of infant after transfer of anucleate donor oocyte cytoplasm into recipient eggs** J Cohen and others
- 187 **Multidisciplinary breath-odour clinic** G Delanghe and others
- 187 **Is the neuropathology of new variant Creutzfeldt-Jakob disease and kuru similar?** P L Lantos and others
- 188 **Type of prion protein in UK farmers with Creutzfeldt-Jakob disease** A F Hill and others

NEWS

Science & medicine

- 189 FDA warning on diet drugs
Diabetic diagnosis in children
- 190 Tolerating immunology
Back-sleeping for babies is best
Smoking, costs and conduct
- 191 Antibiotic cuts heart risk
The iceman's adipocere
Nasal 'flu vaccine

Feature

- 192 Beating the malaria parasite at its own game

Dispatches

- 193 US academic health faces strain and UK strains academic staff

Policy & people

- 194 UNICEF reports poor sanitation
Disagreement over stents
Drugs in brief
- 195 AIDS drug assistance in USA
UK smoking initiative
Roadblock for US tobacco deal
- 196 Rationing debate in UK
Danish breast-cancer screening
Indian polio-eradication programme

See contents list inside

REVIEW AND OPINION

Seminar:
Diabetic eye disease
Literature and medicine:
W H R Rivers
Public health:
Syphilis in Russia

CORRESPONDENCE

DISSECTING ROOM

Poetry, Books, Art
Lifeline, Jabs & jibes