# E. coli O157 phage type 21/28 outbreak in North Cumbria associated with pasteurized milk

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#### **SUMMARY**

In March 1999, a large community outbreak of *Escherichia coli* O157 infection occurred in North Cumbria. A total of 114 individuals were reported to the Outbreak Control Team (OCT); 88 had laboratory confirmed *E. coli* O157. Twenty-eight (32%) of the confirmed cases were admitted to hospital, including three children (3·4%) with haemolytic uraemic syndrome. There were no deaths. A case-control study found that illness was strongly associated with drinking pasteurized milk from a local farm (P = < 0.0001) on single variable analysis. Microbiological investigations at the farm revealed *E. coli* O157 phage type (PT) 21/28 VT 2 which was indistinguishable from the human isolates by pulsed field gel electrophoresis. At the time of occurrence this was the largest *E. coli* O157 outbreak in England and Wales and the first *E. coli* O157 PT 21/28 VT 2 outbreak associated with pasteurized milk. This outbreak highlights lessons to be learnt regarding on-farm pasteurization.

## INTRODUCTION

Verocytotoxin producing *Escherichia coli* (VTEC) O157 is a serious pathogen with the potential to inflict life-threatening complications such as haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura. Between 2% and 7% of infections with *E. coli* O157 develop HUS which is considered a major cause of acute kidney failure in children in the United Kingdom [1].

The detection of *E. coli* O157 in England and Wales has increased in the last decade. The Laboratory of Enteric Pathogens at Central Public Health Labora-

tory, London, reported 411 isolates in 1994, 1087 isolates in 1997 and 890 isolates in 1998 respectively. Between 1992 and 1994, 18 outbreaks involving a total of 173 people were recorded, compared with 7 outbreaks and 76 people affected between 1989 and 1991 [2]. Since 1994 there have been: 11 outbreaks in 1995; 14 in 1996; 25 in 1997; 17 in 1998 [3]. Investigations of outbreaks showed links to contaminated food, direct contact with cattle and person to person spread. Unpasteurized and pasteurized milk have been implicated in a few outbreaks in the United Kingdom [4–7]. The Advisory Committee on Microbiological Safety of Food recommended careful control of pasteurization of milk and dairy products [8]. In 1996 the

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largest outbreak in the United Kingdom occurred in central Scotland related to contamination of meat within a butcher's shop. The ensuing enquiry and report made further wide-ranging recommendations to safeguard the public [9].

We report a large outbreak of E. coli O157 infection, which occurred in North Cumbria in March 1999.

#### THE OUTBREAK

On 1 March 1999 a general practitioner (GP) in a town in North Cumbria, notified the Consultant in Communicable Disease Control (CCDC) of four cases of 'bloody diarrhoea'. He mentioned that a colleague had also seen several cases of diarrhoea in the same area. This prompted enquiries to the hospital laboratory, wards regarding admissions, the GP deputizing service manager, other GPs, and the Environmental Health Department.

The next day, the local laboratory reported four cases of E. coli O157 infection, the organism isolated from faecal specimens. These cases were interviewed using a detailed structured questionnaire. By late afternoon preliminary analysis of data raised suspicion of a possible association with pasteurized milk from a local farm. The same evening Environmental Health Officers (EHOs) visited the farm and served a detention of food notice [10], on the milk produced.

On 3 March, eight further cases of E. coli O157 were reported. An Outbreak Control Team (OCT) convened on the same day, agreed on immediate control measures which included an emergency prohibition notice [10], heat treatment notice [11], and a press release to warn the public not to drink the suspect milk. A telephone helpline was established to coincide with the press release. All GPs and hospital doctors were requested to report suspect cases to the CCDC and to obtain faecal specimens. The two local laboratories reported positive cases on a daily basis. EHOs questioned all household contacts and also requested faecal specimens from these contacts, other high risk groups, such as food handlers, children and staff at a nursery. An electronic message was sent to alert all CsCDC and laboratories. Television, radio and newspapers reported the outbreak and requested those living locally, who had diarrhoea to consult their GPs.

## **Epidemiological investigations**

An initial review of exposures was conducted on 22 out of 25 individuals on whom more detailed information was available and who either had diarrhoea only (possible cases) or diarrhoea with blood (probable cases). Three individuals who did not have diarrhoea were excluded.

## Case control study

A case control study was carried out to test the hypothesis that illness was associated with drinking pasteurized milk from the local farm. Cases were defined as persons suffering from diarrhoea with date of onset after 21 February and with laboratory confirmation of E. coli O157. Controls were selected systematically from North Cumbria's primary care patient registration database, matched for post-code of residence (four characters) and broad age bands (<1, 1-4, 5-9, 10-14, 15-19, 20+). Controls reporting a diarrhoeal illness in the 3 weeks prior to interview were excluded. Interviews were conducted face to face (for cases) and by telephone (for controls) by EHOs and staff of North Cumbria Health Authority, using a specially designed questionnaire.

#### Data analysis

Inferential analysis was designed to assess exposure to various risk factors in the 7 days prior to illness (cases) or prior to interviews (controls). Single variable analysis was performed using Epi-Info statistical package. Multivariable logistic regression was also performed. Age and sex together with all other variables that had a positive association with risk and a P value less than 0.1 were included in the multivariable model, together with those variables necessary to test the hypothesis.

#### Microbiological investigations

The two local laboratories analysed human faecal samples submitted by EHOs and GPs. Faecal specimens were examined by direct culture onto Cefixime Tellurite Sorbitol MacConkey agar. Isolates were sent to the Laboratory of Enteric Pathogens (LEP) at the Central Public Health Laboratory (CPHL) Colindale, in London, for confirmation, phage typing and tests for verocytotoxin genes [3]. Further sub-typing was performed by pulsed field gel electrophoresis (PFGE) analysis [12]. A small number of sera was tested at the LEP for antibodies to E. coli O157 lipopolysaccharide.

Detailed enquiries were made concerning milk production and distribution, the pasteurizer, and the farm

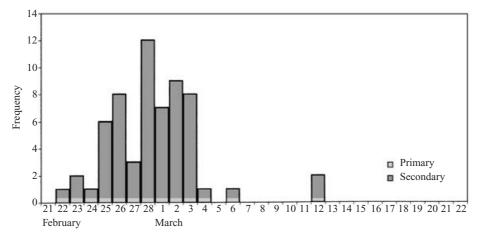


Fig. 1. Epidemic curve: symptomatic cases (61).

animals. Samples taken for microbiological testing included bottled pasteurized milk and cream, raw and bulk milk, filter rinses, rectal swabs from livestock, slurry, cow faeces from the floor of the milking parlour and other parts of the farm. In addition, EHOs sampled tap water from homes of the 20 confirmed cases included in the case control study. These were examined by the local public health laboratory using standard operating procedures for coliforms and *E. coli* [13].

## RESULTS

# **Epidemiological investigations**

The outbreak affected a total of 114 individuals of which 88 had E. coli O157 confirmed by laboratory tests. Onset dates of the 61 symptomatic cases indicated a point source outbreak, rising to a peak on 28 February and then declining after 3 March (Fig. 1). All the cases up to and including 4 March were primary cases, whereas the three cases after 4 March were probably secondary cases. Of the 114 individuals in the outbreak the majority (99%) were local Cumbrian residents with ages ranging from 3 months to 85 years. Forty-four (39%) were children under 10 years, and 16 (14%) were over 60 years (Table 1). There were 28 hospital admissions (12 adults, 16 children) including 3 nursery school age children (mean = 3.3 years) who developed HUS. There were no deaths and the three children with HUS recovered after receiving haemodialysis at the regional centre.

The descriptive study did not suggest any relationship with specific restaurants or fast food outlets; the majority having not eaten out or purchased food from

Table 1. *All reported individuals (age and location)* 

Age	Local town	Cumbria (other)		Unknown	Total
<1	1	1	0	0	2
1-4	24	2	0	0	26
5–9	14	2	0	0	16
10-14	8	1	0	0	9
15-19	5	0	0	0	5
20-59	38	0	1	0	39
60+	16	0	0	0	16
Unknown	0	0	0	1	1
Total	106	6	1	1	114

take-away food shops. Most cases reported drinking cold tap water from the mains. However, the comparison of post-code information with water supply zones, showed that cases did not live within one particular water treatment supply area. Although contact with pets and other animals was regularly reported, there was nothing to suggest a single animal or species. Various cheeses, meats and other food items were reported as being bought. Where there was a single shop involved, there were a number of product lines with no consistent pattern of a particular food item emerging or a particular food source. In contrast to other food items and exposures examined, 68 % (15/22) had consumed milk from a single farm. A further individual not being supplied with the farm milk at home, ate at a restaurant, which was supplied with milk from the farm. These results together with information from the GP deputizing service and the water supply data, suggested that illness was likely to be associated with drinking pasteurized milk from the local farm.

Table 2. Single analysis of case control study (selected variables)

	Case		Control		0.11		
Variable	Yes	No Y	Yes	No	Odds ratio	95% CI	<i>P</i> -value
Sex*	9	11	27	25	0.76	0.24; 2.43	0.79
Other person in household with diarrhoea	5	14	5	47	3.36	0.70; 16.43	0.12‡
Contact with farm animals	0	20	9	43	0	0; 1.45	0.05†
Visited farm	2	17	10	42	0.49	0.07; 2.87	0.49†
Ate at restaurant or hotel	3	16	22	30	0.26	0.05; 1.12	0.07
Ate at burger restaurant	3	16	19	33	0.33	0.06; 1.44	0.17
Ate at other fast food outlet	5	14	16	36	0.80	0.21; 3.00	0.94
Ate burger	2	10	13	25	0.38	0.05; 2.39	0.30
Ate beef	3	9	1	33	11	0.82; 318.64	0.05†
Ate other beef products	17	2	50	2	0.34	0.03; 3.79	0.29†
Ate bacon	6	11	33	17	0.28	0.07; 1.03	0.05
Doorstep delivery of milk	18	2	24	26	9.75	1.83; 69.07	0.003
Purchase of milk	10	10	36	13	0.36	0.11; 1.22	0.11
Other milk supplier	1	16	6	33	0.34	0.01; 0.34	0.42
Drank milk	20	0	48	4	35948.25	$0.64; \infty$	0.57†
Drank cold milk	10	9	27	21	0.86	0.26; 2.88	1.00
Milk on cereal	19	1	42	6	2.71	0.28; 65.15	0.66
Drank milk warmed	6	13	7	41	2.70	0.64; 11.43	0.17†
Unpasteurized milk	0	19	2	44	0	0; 10.58	1.00†
Ate yogurt	12	8	39	13	0.50	0.14; 1.72	0.33
Mains water supply	20	0	49	3	286634.4	$0.43; \infty$	0.55†
Drank tap water	17	3	45	7	0.88	0.17; 4.98	1.00
Drank the farm milk‡	17	2	10	39	33.15	5.77; 250.5	< 0.0001

<sup>\*</sup> Sex: Yes, Male; No, Female.

## Case control study

This study was conducted over the week-end of 6 and 7 March. Twenty cases and 52 controls were recruited to the study. The onset date of illness of the 20 cases ranged from 22 February to 3 March with a peak on 26 February. The median age for the cases was 8.5 years, ranging from 1 to 69 years. Of the 20 cases with a diarrhoeal illness, abdominal pain (19) and blood in the stools (18) were the most common features. The duration of illness ranged from 3 to 7 days.

Single variable analysis showed a strong association between illness and the consumption of milk from the farm (P = < 0.0001) (Table 2). Multivariable analysis showed that of the single variables with positive association, only drinking milk from the farm (OR = 33.15, 95% CI (5.77, 250.5)) was independently significantly associated with illness in the case (P = 0.0000008). There were no other significant positive

associations when this factor had been taken into account.

## Investigations at the farm

The farm located in a rural area had a herd of 88 cows, of which 65 were in milk. In addition, there were more than 50 young cattle over 1 year old and 28 calves under 1 year old. The cattle and calves were housed in sheds and pens in adjacent buildings to the milking parlour or across the farmyard. The farmer did not sell unpasteurized milk and any excess milk was collected on a daily basis by a large national milk processor.

The farmer pasteurized milk at 2.00 p.m. on each Sunday, Tuesday and Thursday. Raw milk was stored in the bulk raw milk tank with a maximum storage time of 15–18 h. The farmer produced around 540–640 pints of pasteurized milk on each of the 3 days and supplied 321 premises including 11 commercial

<sup>†</sup> Fisher's Exact Test.

<sup>‡</sup> The possible presence of the farm milk in the house was determined by looking at whether they bought milk or had milk to their door and its source. This information was then combined with whether or not the individual drinks milk (which included drinking it in tea or coffee) to produce a variable which indicated any exposure to the farm milk.

establishments. The weekly production was 120 pints of skimmed milk, 960 pints of semi-skimmed milk, and 840 pints of whole milk. In addition, 2–3 gallons of pasteurized cream were produced on a daily basis. All bottled milk was then stored in a refrigerated store, prior to distribution.

Enquiries at the farm revealed that a fault had occurred in the heat exchanger plates of the pasteurization unit 9 days before the first cases were notified. Some new heat exchanger plates had been fitted by the farmer. However, there was no evidence or record of tests having been undertaken after the repair. Other identified faults included the failure of automatic recording of flow diversion activity and the absence of adequate temperature monitoring. This type of pasteurizer was the subject of a food hazard warning to food authorities in the summer of 1998. The farmer had been informed by the authority at the time, but was unsure of his need to act.

# Microbiological results

Of 400 human faecal specimens tested for *E. coli* O157, 87 were identified by culture and confirmed as *E. coli* O157 verocytotoxin 2, phage type (PT) 21/28 by LEP, one case was detected by serology only. Isolates from clinical cases had identical profiles by PFGE. Six sera were positive for antibodies to *E. coli* O157 lipopoly-saccharide; five of these were from patients from whom a culture had also been received. Altogether there were 88 microbiologically and or serologically confirmed cases. Samples of tap water from homes of cases in the control study did not have coliforms or *E. coli*.

Examination of faecal samples of 12 staff and 46 children at the nursery supplied with milk from the farm, revealed that the faecal specimens from all the staff were negative but two children were positive for *E. coli* O157. At this same nursery, four additional children had previously been identified as harbouring *E. coli* O157.

*E. coli* O157 were recovered, on the farm, from 66 environmental and animal faeces samples: straw bedding of 2 calf pens, the calf shed (1), slurry samples (2), floor samples in various pens housing existing animals (>50). The bottled pasteurized milk, cream, milk filter, heat exchanger plates samples, rectal swabs from livestock were all negative. Of 31 isolates examined further, 29 were confirmed to be *E. coli* O157 PT 21/28 VT 2. PFGE analysis of 30 human, 4 environmental and 11 animal faeces isolates showed that

the human isolates were indistinguishable from the 4 environmental isolates and from 6 of the animal isolates. The other 5 animal isolates showed minor differences.

The excretion period (from the first symptoms or date of collection of first positive specimens in asymptomatic cases to the date of collection of the second negative sample) had a mean of 20 days (median, 18 days; range, 7–28 days) in adults and 40 days (median, 45 days; range, 13–61 days) in children. Two children had excretion periods of 57 days and 61 days respectively.

## **DISCUSSION**

This North Cumbria *E. coli* O157 phage type (PT) 21/28 community outbreak in early March 1999 was the largest reported in England and Wales at that time. It is notable that although 114 persons were involved there were no deaths. Three children who developed HUS, recovered after undergoing haemodialysis, and were discharged home.

Early control measures were crucial in this outbreak. In addition to statutory controls placed on the farm and exclusions, hygiene measures were widely publicized. In line with PHLS guidelines (1995), high risk individuals harbouring the infection were excluded until they demonstrated two consecutive negative faecal samples 48 h apart [14]. This was especially pertinent to nursery schools as outbreaks have been well documented [15-17]. In this outbreak long excretion periods were recorded in nursery children, (median 45 days) similar to those in Minnesota, USA [15] and Wales [17]. PHLS guidelines published in 2000 reinforced recommendations that nursery school children who were household contacts of cases of E. coli O157 should not attend until the case was asymptomatic [18]. Those who were infected were required to have two negative faecal samples before reattendance. The exclusions of household contacts, and cases had marked social implications. This was especially notable in working parents, and should be taken into consideration in other large outbreaks, as compliance with exclusion advice could be a problem. The prompt and sustained advice on hygiene measures from all health professionals and the press coverage probably contributed to the low secondary spread.

Reducing morbidity and mortality was also a major concern. Doctors were alerted early and advised on several occasions not to prescribe anti-motility drugs and antibiotics. Anti-motility drugs can increase the likelihood of HUS [1, 19, 20]. In June 2000, an American study [22] found that antibiotic treatment of children with *E. coli* O157:H7 infection also added to the risk of HUS. As a result, the Chief Medical Officer's Newsletter [22] to all doctors cautioned against the use of antibiotics in infected children. The review of the *E. coli* O157 outbreaks between 1992 and 1994 in England and Wales [2] showed that 38% were admitted to hospital, 21% developed HUS and 3% died. This outbreak recorded 28 admissions (32% of all laboratory positive cases), 3 HUS cases (3·4%) and no deaths.

The results of investigations showed strong association between illness in E. coli O157 cases and drinking milk from a local farm. The case control study was carried out within 5 days of the first reported case. Despite widespread publicity, recall bias would have been unlikely. Cases were identified by the laboratories and controls randomly selected from GPs patient register. Microbiological studies confirmed that the isolates of E. coli O157 PT 21/28 VT 2, in human cases and in the environmental and slurry samples from the farm, were indistinguishable by pulsed field gel electrophoresis (PFGE). Although no positive microbiological results were obtained from the milk at the time of the outbreak, many calf pen samples housing existing calves and slurry were positive. Studies have shown that excretion of E. coli O157 in cattle is intermittent and maximum at calving [23, 24]. E. coli O157 can also survive long periods in the farm environment [25]. Enquiries at the farm revealed that a fault had occurred in the heat exchanger plates of the pasteurization unit 9 days before the first cases were notified. Although it could not be proved conclusively, the most likely explanation is that at some stage raw and treated milk mixed at the heat exchanger unit of the in-house pasteurizer.

E. coli O157 PT 21/28 accounted for approximately 15–29% of all VTEC O157 isolates confirmed in England and Wales by the Laboratory of Enteric Pathogens (LEP) in 1998 and 1999 respectively. In reported outbreaks between 1996 and 1998, 12 were caused by VTEC O157 PT 21/28:1996 (4); 1997 (6); 1998 (2). None of these was associated with milk; in two, animal contact was the likely route of transmission of infection [26, 27]. In March 1999, a small outbreak of VTEC O157 PT 21/28 VT 2 occurred in North Yorkshire, England [28] associated with consumption of cheese made from unpasteurized cows' milk. The PFGE profile of the strain from the North Cumbria outbreak differed from that of the strain from the cheese-associated Yorkshire cases and from other

VTEC O157 PT 21/28 isolates in the country at that time.

Legislation with regard to production of milk and milk-based products is set out in the Dairy Products (Hygiene) Regulations 1995 [29] and the associated Code of Practice of the Food Safety Act 1990 [30]. Operators of pasteurizers should have an adequate system of controls in place. The Local Authority successfully prosecuted the farmer for the sale of milk unfit for consumption and for breaches of the Regulations.

Recommendations were made to the Department of Health which included: review of the advice given in food hazard warnings on milk pasteurizers issued in summer 1998; the need for annual certification of pasteurization units to defined standards; the benefits of using flurometric phosphatase tests. There should be basic training and guidance for farm operatives on the routine use of in-house pastuerizers, with particular emphasis on temperature monitoring and cleaning regimens and amendment of British Standard BS7771 1994 to ensure that certain aspects of maintenance are only carried out by approved engineers.

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