Drinking water and diarrhoeal disease due to *Escherichia coli*

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ABSTRACT

Escherichia coli has had a central place in water microbiology for decades as an indicator of faecal pollution. It is only relatively recently that the role of *E. coli* as pathogen, rather than indicator, in drinking water has begun to be stressed. Interest in the role of *E. coli* as a cause of diarrhoeal disease has increased because of the emergence of *E. coli* O157:H7 and other enterohaemorrhagic *E. coli*, due to the severity of the related disease. There are enterotoxigenic, enteropathogenic, enterohaemorrhagic, enteroinvasive, enteroaggregative and diffusely adherent strains of *E. coli*. Each type of *E. coli* causes diarrhoeal disease through different mechanisms and each causes a different clinical presentation. Several of the types cause diarrhoea by the elaboration of one or more toxins, others by some other form of direct damage to epithelial cells. This paper discusses each of these types in turn and also describes their epidemiology, with particular reference to whether they are waterborne or not.

Key words | diarrhoea, *Escherichia coli*, virulence, waterborne disease

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INTRODUCTION

Of all the bacterial species, *Escherichia coli*, though more usually known along with some other species as faecal coliforms or thermotolerant coliforms, has had a central and long role in water bacteriology. The species was introduced into water bacteriology, not because of its intrinsic pathogenicity, but because it was a useful marker of faecal pollution. The theory was that if *E. coli* was present then so could pathogenic enteric bacteria such as *Shigella* and *Salmonella* spp. Despite recent concerns about the reliability of the organism as a marker of water safety, it is still the only species that almost all routine samples are tested for (Gleeson & Gray 1997).

Although it has long been known that *E. coli* can cause disease in humans, its role as an enteric pathogen in its own right has been recently reinforced with the appearance of *E. coli* O157:H7 and its association with a haemorrhagic enteritis and haemolytic uraemic syndrome.

Escherichia coli are motile, non-spore-forming, gram-negative bacilli. Typically they ferment lactose or give a positive o-nitrophenyl-betab-d-galactopyranoside

(ONPG) reaction. The reservoir for *E. coli* is the intestines of man and other warm-blooded animals, both mammals and birds. Although it will survive in the environment, it does not appear to reproduce itself and ultimately dies out (Feachem *et al.* 1983). Consequently, when *E. coli* is detected in the environment, it is still taken as an indication of faecal pollution. There has been some evidence that *E. coli* can survive and multiply in tropical environments and so its value as a marker of faecal pollution in the tropics is now uncertain (Rivera *et al.* 1988).

Escherichia coli can cause a variety of infections in humans. Most of the time this is due to spread from the intestinal flora when the patient has some other deficit or problem. However, certain strains of *E. coli* can also cause diarrhoea. In all of these cases infection follows direct or indirect faecal–oral spread from other humans or from animals. This paper considers diarrhoeal infections due to the various pathogenic types of *E. coli*. The virulence mechanisms of the diarrhoeal *E. coli* and the genetic mechanisms underlying them are complex, and our

understanding of them is changing rapidly (Nataro & Kaper 1998). This paper will describe outbreaks of waterborne disease linked to *E. coli*.

There are six main virulence types of *E. coli* and each one will be discussed in turn. In general each type combines some initial attachment of the bacterium to the cell with subsequent production of an adverse effect, either by the elaboration of a toxin, or some direct action. Although not absolute, there is a strong correlation between virulence and certain serotypes. Those serotypes that have been linked to the various virulence mechanisms are shown in Table 1.

THE ENTEROVIRULENT *E. COLI*

Enterotoxigenic *E. coli* (ETEC)

ETEC strains are those strains that produce a heat-stable (ST) and/or a heat-labile (LT) enterotoxin (Sears & Kaper 1996). There are two antigenic types of both ST (Sta and STb) and LT (LT-I and LT-II). LTs are large oligomeric toxins whilst STs are short polypeptides. LT-I is closely related to cholera toxin (CT). By a chain of intracellular reactions, which includes an increase in intracellular cAMP, there is a marked net excretion of chloride from the enterocyte into the gut lumen. There is also a reduction in absorption of sodium. The net result of these reactions is that the intraluminal osmolality increases and water is drawn into the gut. STa, an 18 amino-acid peptide, binds to guanylate cyclase C (GC-C), an enzyme present in the luminal membrane of enterocytes. The binding of STa to GC-C causes an increase in intracellular cGMP. The end result is increased chloride excretion in the same way as for LT. STb differs from STa in being larger, 48 amino-acids, and not causing an increase in cAMP or cGMP. Also chloride transport is not directly affected, instead there is a net increase in bicarbonate excretion.

ETEC strains cause watery diarrhoea with no mucus, pus or blood present. Patients only occasionally have vomiting or fever. The severity of illness can vary substantially from being relatively mild and short-lived, to a severe life-threatening illness. The infectious dose, ID_{50}, is high (the number of organisms needed to infect 50% of individuals is approximately 10^8 to 10^{10} organisms; Kothary & Babu 2001).

There are two groups of patients who typically suffer from ETEC infection. The first group is young children in tropical countries soon after weaning, most commonly less than 2 years old. Indeed in this age group up to 30% of sporadic infant diarrhoea may be due to ETEC. Even though older adults and children in tropical countries frequently excrete large numbers of ETEC in their stools they are rarely symptomatic due to the prior development of mucosal immunity. It is only non-immune adults who develop symptomatic infection. The largest group of adults that comes within this description is travellers to tropical countries. Travellers' diarrhoea can affect up to 60% of people going to tropical countries and of these some 20 to 40% are due to ETEC infection. In Ecuadorian children aged 7 to 10 months, there was a statistical association between consumption of low quality drinking water and antibodies to ETEC (RR 1.9, 95% CI 1.11–3.25; Brussow *et al.* 1992).

Person to person transmission of ETEC appears uncommon. Most transmission of sporadic disease is via food and water sources. There have been several waterborne outbreaks due to ETEC described in the literature. One particularly large outbreak affected more than 2000 staff and visitors to an American National Park in Oregon in the summer of 1975 (Rosenberg *et al.* 1977). Enterotoxigenic *E. coli* were isolated from 20 (16.7%) of 120 rectal swabs examined. There was a strong correlation between illness and drinking park water in park staff and visitors ($p < 0.00001$). The only group in which there was no association with drinking water were visitors on 7–9 July when chlorination of the water supply was being more closely monitored. Water came from a shallow spring that was found to be contaminated by a sewage overflow some 650 m uphill from the spring. The supply was supposed to be chlorinated, but there was no systematic monitoring of chlorine levels throughout the distribution system.

Another outbreak affected 251 passengers and 51 crew members on a Mediterranean cruise (O'Mahony *et al.* 1986). Enterotoxigenic *E. coli* was isolated from 13 of 22 passengers and 6 of 13 crew members sampled. Faecal coliforms were isolated from tap water, and drinking tap water was the only risk factor associated with

Table 1 │ Serogroups and associated H antigens of *E. coli* associated with each of the types of diarrhoeal disease (Nataro & Kaper 1998)

ETEC		EPEC		EHEC		EAEC		EIEC	
O6	H16	O55	H6, NM	O26	H11, H32, NM	O3	H2	O28ac	NM
O8	H9	O86	H34, NM	O55	H7	O15	H18	O29	NM
O11	H27	O111	H2, H12, NM	O111ab	H8, NM	O44	H18	O112ac	NM
O15	H11	O119	H6, NM	O113	H21	086	NM	O124	H30, NM
O20	NM	0125ac	H21	O117	H14	O77	H18	O136	NM
O25	H42, NM	O126	H27, NM	O157	H7	O111	H21	O143	NM
O27	H7	O128	H2, H12			O127	H2	O144	NM
O78	H11, H12	O142	H6			O?	H10	O152	NM
O128	H7							O159	H2, NM
O148	H28							O164	NM
O149	H10							O167	H4, H5, NM
O159	H20								
O173	NM								

illness in a case-control study ($p = 0.01$). There were several defects in the ship's water system including potentially faulty chlorination, and defective covers possibly allowing bilge water into the water tanks.

A more recent outbreak affected 175 Israeli military personnel and at least 54 civilians in the Golan Heights (Huerta *et al.* 2000). All affected military posts and civilian communities were supplied by a common water pipeline. Samples of water from several points along the distribution system showed inadequate chlorination and high concentrations of *E. coli*.

Daniels and colleagues reported three outbreaks of ETEC infection associated with cruise ships (Daniels *et al.* 2000). All three outbreaks were associated with consuming drinks containing ice cubes on board the ship, and two were also associated with drinking unbottled water. The authors suggested that water bunkered in overseas ports was the likely source of the infection and that such water should be treated before use.

Enteropathogenic *E. coli* (EPEC)

EPEC are characterised by infections that produce a characteristic histological picture in the intestinal tract known as attaching and effacing lesions. These lesions show the intimate adherence of the bacteria to the epithelial cell membrane with affacement of the microvilli. Diarrhoea is probably related to poor absorption secondary to the loss of absorptive area due to the dissolution of the microvilli.

Clinically EPEC presents with watery diarrhoea which can vary in its severity and duration. Indeed in several outbreaks there has been a high mortality of up to 30% or more. The infectious dose is very high, the ID_{50} being about 10^8 to 10^{10} organisms (Kothary & Babu 2001).

EPEC primarily causes disease in children under 2 years old and especially in those less than 6 months. EPEC is a major cause of infant diarrhoea in the developing world. The evidence suggests that transmission of infection is primarily directly from person to person. This author is not aware of any reported waterborne outbreaks. However, in a study of children admitted to hospital with diarrhoea in Rio de Janeiro, children with EPEC were less likely to have a water supply (RR 0.62, 95% CI 0.37–1.02; Regua *et al.* 1990). However, it is not clear whether this was due to waterborne infection or a lack of water for hygiene.

Enterohaemorrhagic *E. coli* (EHEC)

EHEC are probably the most important emerging diarrhoeal pathogens of the past decade. Recognised in the early 1980s, their importance derives largely from the severity of disease caused especially in the very young and the elderly (Riley *et al.* 1983). There have been several outbreaks in the UK and US in recent years, several of which have generated considerable press and public interest.

EHEC combine the virulence mechanism of the EPEC with the production of a toxin, the Shiga toxin. Stx 1 is identical to the Shiga toxin of *S. dysenteriae* type 1. Stx 2 is immunologically distinct and is only some 55–57% homologous. Within the cytoplasm the toxin disrupts protein synthesis and leads to cell death. Diarrhoea is probably caused by the death of the intestinal absorptive cells whilst leaving the secretary cells intact. The development of haemolytic uraemic syndrome (HUS) is thought to follow transport of this toxin to the kidneys through the blood.

Of all the infections discussed in this article, the clinical features of EHEC infection are most striking. Initial symptoms are of colicky abdominal pain followed by diarrhoea and, in about half of cases, vomiting. After a couple of days abdominal pain increases and the diarrhoea becomes bloody. The blood loss can be severe. Fatality rates in the elderly and the very young can be high. Approximately 10% of children less than 10 years old will develop HUS. HUS is the combination of haemolytic anaemia, thrombocytopaenic purpura and acute renal failure. In the UK HUS is now the commonest cause of acute renal failure in children. The infectious dose is low compared with the other virulence types. Depending on what dose-response model is used, the ID_{50} is estimated to be in the range 10^2 to 10^6 though it is known that outbreaks have occurred with doses of around 102 organisms (Haas *et al.* 2000; Strachan *et al.* 2001).

EHEC are found in the intestines of several animal species, especially cattle. Infection of humans can follow direct faecal–oral spread from infected animals or other humans, or be related to contamination of food or water. Many outbreaks have followed the consumption of beef products, particularly undercooked beef-burgers or salad products. There have been several outbreaks of EHEC reported associated with recreational water contact and drinking potable water. Serotype O157:H7 is the most frequently reported EHEC strain in Europe and North America by a large margin. During the years 1995 to 1998 there were 3429 strains of enterohaemorrhagic *E. coli* O157 in England and Wales compared with only 11 non-O157 strains (Willshaw *et al.* 2001). Of these 11 non-O157 strains, five were due to O26:H11, and the remaining types were only identified once. However, EHEC strains other than O157 are increasingly being recognised as causes of outbreaks due to foodborne and person-to-person transmission. There has been one outbreak of O26 associated with drinking water (Hoshina *et al.* 2001) and one outbreak of O121:H19 with recreational water contact (McCarthy *et al.* 2001).

The first outbreak of infection due to *E. coli* O157:H7 strongly linked to the consumption of drinking water occurred in Burdine Township, Missouri between 15 December 1989 and 20 January 1990 (Swerdlow *et al.* 1992). Of a population of 3126, 243 people developed illness, and of these 86 developed bloody diarrhoea, 36 were hospitalised and four died. In a case-control study based on 53 cases, the only significant factor was that cases drank more cups of municipal water per day (7.9) than did controls (6.1) ($p = 0.04$). The water supply to the city came from two deep-ground water sources. It was noted that two mains water breaks had occurred on the 23 and 26 December, after the start of the outbreak but before

its main peak. The sewage system was inadequate and sewage overflow, which could cross drinking water mains, often resulted.

An outbreak of *E. coli* O157:H7 in Grampian, Scotland affected four people during the hot summer of 1990 (Dev *et al.* 1991). All four (three boys aged 4, 8 and 9, and one woman aged 20) developed haemorrhagic colitis. The village normally took its water from a reservoir situated on a hillock in the village. However, because of the hot weather, this supply was low and so water from two subsidiary reservoirs was also used. One of these was fed from a source that resembled a field-drain system that may have been contaminated by cattle slurry.

During October 1992 a large outbreak of bloody diarrhoea affected thousands of individuals in South Africa and Swaziland (Isaacson *et al.* 1993). There were fatalities and cases of renal failure. *E. coli* O157 was isolated from 22.5% of 89 stools. In some areas cases were mainly men who drank surface water in the fields while women and children who drank borehole water were spared. *E. coli* O157:H7 was isolated from 14.3% of 42 samples of cattle dung and 18.4% of 76 randomly collected water samples. The underlying problem seems to have been cattle carcasses and dung washed into rivers and dams by heavy rains after a period of drought.

An international outbreak affected holidaymakers returning from Fuerteventura, Canary Islands, in March 1977 (Pebody *et al.* 1999). Fourteen confirmed cases and one probable case were identified, from five different countries and staying in four hotels. Three of the four hotels were supplied with water from a private well. When investigating small outbreaks of travellers' diarrhoea international collaboration may be essential to identify the cause.

An outbreak in the Highland region of Scotland illustrated a number of important lessons (Licence *et al.* 2001). The source of the outbreak was an untreated and unprotected private water supply that came from an area where animals were allowed to graze. Six people were affected, all of whom were visitors to the area. No cases occurred in permanent residents. This outbreak illustrates that immunity to EHEC can develop. It also illustrates the risk of allowing visitors to drink from private waters supplies where those supplies come from areas where animals graze and where there is no effective water treatment.

An outbreak of *E. coli* O157:H7 infections occurred in Alpine, Wyoming, during 1998 (Olsen *et al.* 2002). A total of 71 out of 157 ill people were stool positive. Illness was significantly associated with drinking municipal water (town residents: adjusted odds ratio = 10.1, 95% confidence intervals [CI] = 1.8–56.4; visitors attending family reunion: relative risk = 9.0, 95% CI = 1.3–63.3). Interestingly, the attack rate was significantly higher in visitors who drank water compared with residents who drank the water, suggesting a degree of immunity from prior exposure in residents. The water supply was from an unconfined aquifer and the water was not chlorinated. Investigations showed high levels of coliforms, and a sanitary survey highlighted the risk of contamination of the aquifer from the faeces of deer or elk.

However, the largest and most notorious outbreak of EHEC associated with drinking water occurred during May and June 2000 amongst residents of Walkerton, Ontario (Anon 2000). There were about 1,346 cases of illness identified, though many people were infected with *Campylobacter* rather than EHEC. In addition, 65 people were admitted to the hospital of which 27 developed haemolytic uraemic syndrome and there were six fatalities. Illness was strongly associated with drinking water consumption. The drinking water came from a number of wells and there was strong evidence suggesting that one of the wells had become contaminated with cattle faeces following heavy rains and flooding.

In addition to causing outbreaks associated with contaminated drinking water, enterohaemorrhagic *E. coli* have caused outbreaks linked to recreational water contact. There have been a number of outbreaks associated with swimming pools (Friedman *et al.* 1999; Paunio *et al.* 1999), a paddling pool (Brewster *et al.* 1994; Hildebrand *et al.* 1996) and natural lakes or other surface water (Keene *et al.* 1994; Anon. 1996; Cransberg *et al.* 1996; McCarthy *et al.* 2001). The general assumption is that outbreaks have generally followed faecal accidents from other bathers. Swimming pool outbreaks have occurred in pools with inadequate chlorination. McCarthy and colleagues (2001) described an outbreak of haemolytic uraemic syndrome in children due to *E. coli* O121: H19, a

non-O157 strain. In addition to three cases of HUS, there were eight cases of diarrhoea.

Enteroinvasive *E. coli* (EIEC)

The precise pathogenic mechanisms of EIEC are, as yet, poorly understood, although they are thought to mirror those of *Shigella* spp. Indeed, biochemically, EIEC are very closely related to *Shigella*. As the name suggests, there is invasion of the epithelial cell itself with subsequent intracellular multiplication and lateral movement through the cell to allow subsequent penetration of adjacent cells. This can cause a significant inflammatory response. Although not yet fully understood, there also seems to be production of an enterotoxin which is though to be responsible for the initial watery diarrhoea.

Most cases of EIEC present with watery diarrhoea indistinguishable from ETEC. A small proportion develops the bloody diarrhoea associated with the dysenteric syndrome. The infectious dose (ID_{50}) is high, between 10^6 and 10^{10} organisms.

Most illness is thought to be food- or waterborne, although person-to-person spread also occurs. However, only one outbreak of invasive EIEC due to water has been reported in the literature and this was some 40 years ago (Lanyi *et al.* 1959). EIEC has also been isolated from recreational water in at least one study in South America (Falcao *et al.* 1993).

Enteroaggregative *E. coli* (EAEC)

EAEC are named after their characteristic aggregative adherence to Hep-2 cells in tissue culture. The mechanism of pathogenicity is still poorly understood. Clinically, the infection presents with watery mucoid diarrhoea with no fever or marked blood. In a small proportion of patients the diarrhoea may become chronic. The infectious dose is thought to be high.

EAEC is primarily a disease of developing countries. There is one outbreak in the literature linked to drinking water. In an outbreak in a village in India, people who drank water from a borehole were much less likely to have diarrhoea than people drinking from shallow wells. Fur-

thermore, *E. coli* were isolated from the shallow wells but not the borehole (Pai *et al.* 1997).

Diffusely adherent *E. coli* (DAEC)

The typical feature of this group is adherence to Hep-2 cells, but in a more diffuse pattern than seen in EAEC. The pathogenic mechanisms for DAEC are not known at this stage. The infection causes watery diarrhoea, predominantly in older children. The infectious dose is thought to be high.

CONCLUSIONS

On a global scale diarrhoeal illness due to *E. coli* is a major cause of morbidity and mortality, especially in children. The recent emergence of EHEC has also reawakened concern in the West about the importance of *E. coli* in food and drinking water. As already has been indicated, all enterovirulent *E. coli* are acquired directly or indirectly from a human or animal carrier. Risk from drinking water, therefore, only follows from faecal contamination of the supply. Given the sensitivity of *E. coli* to chlorine and other disinfectants, even if the organisms did contaminate the supply adequate chlorination would effectively remove any risk. There is some concern about the potential role of biofilm in protecting enterovirulent *E. coli* and so posing some subsequent threat. Given the very high infectious doses required for all enterovirulent *E. coli*, other than EHEC, this risk can be discounted. Although the lower infectious dose of EHEC does potentially increase the risk of infection from this source, there have been no outbreaks or studies of sporadic cases of EHEC implicating an adequately disinfected water supply. Prevention of waterborne outbreaks of diarrhoeagenic *E. coli* rests on adequate disinfection of drinking water supplies.

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