Escherichia coli O157

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Lancet 2010; 376: 1428–35

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***Escherichia coli* O157 is an uncommon but serious cause of gastroenteritis. This bacterium is noteworthy because a few, but significant, number of infected people develop the haemolytic uraemic syndrome, which is the most frequent cause of acute renal failure in children in the Americas and Europe. Many infections of *E coli* O157 could be prevented by the more effective application of evidence-based methods, which is especially important because once an infection has been established, no therapeutic interventions are available to lessen the risk of the development of the haemolytic uraemic syndrome. This Review takes into account the evolution and geographical distibution of *E coli* O157 (and its close pathogenic relatives); the many and varied routes of transmission from its major natural hosts, ruminant farm animals; and other aspects of its epidemiology, its virulence factors, the diagnosis and management of infection and their complications, the repercussions of infection including costs, and prevention.**

Introduction

Escherichia coli O157 (figure 1) is the most common member of a group of pathogenic *E coli* strains known variously as enterohaemorrhagic, verocytotoxin-producing, or Shiga-toxin-producing organisms. The first outbreaks caused by *E coli* O157 occurred in Oregon and Michigan, USA, in 1982, when it was isolated from individuals who developed bloody diarrhoea and severe abdominal cramps[1] after eating hamburgers in a restaurant chain. An outbreak of this type is unlikely to have gone unrecorded previously. Searches of culture collections in the USA dating from 1973, and in Canada and the UK dating from 1978, found only eight *E coli* O157 isolates deposited before 1982—one in the USA, one in the UK, and six in Canada.[2] *E coli* O157 is a new pathogen; the first outbreak in the UK happened in 1983;[3] the first isolation in continental Europe was in Belgium in 1987,[4] the first in Africa in 1990,[5] and the first in New Zealand in 1993.[6]

An essential virulence factor is the production of at least one Shiga toxin. A very useful marker for bacterial identification is the inability of most strains to ferment sorbitol. Genome analyses have generated an evolutionary model in which *E coli* O157 has evolved stepwise from a non-toxigenic sorbitol-fermenting precursor related to *E coli* O55:H7, a pathogenic clone associated with infant diarrhoea.[7] The ancestor had the locus of enterocyte effacement genes, which mediate the intimate attachment of bacteria to the intestinal epithelium. The first evolutionary step was the acquisition of the Shiga toxin 2 (Stx2). The next steps were the switching of the somatic antigen from O55 to O157 and the acquisition of a large virulence plasmid, p O157. Then, the ability to ferment sorbitol was lost and another toxin, Shiga toxin 1 (Stx1), was gained.

Bacteriophages have a dominant role in genome change, with phage genes being rapidly gained and lost. The acquisition of genes by horizontal transfer or duplication and the loss by deletion happen at a rate 140 times greater than that for point mutations in housekeeping genes.[8] Analysis of single nucleotide polymorphisms in stable genome regions—backbone open reading frames—of ancestral and present O157 strains collected from three continents during three decades from man, food, and cattle[9] has shown that the backbone genomes of present strains are almost identical. This evidence of evolutionary constraint points to a recent origin and to the occurrence of one of two types of mutations: mutations that confer a strong selective advantage in cattle (the natural host), thus making them more available for spillover to man; or those of the type proposed by the so-called source-sink evolutionary dynamic that has been used to describe uropathogenicity in *E coli*. In this model, the occurrence of particular mutations in a subset of strains in their usual environment—in this case the human bowel—in which they are not pathogenic (the source), confers on them a phenotype that can cause incidental injury elsewhere (the sink).[10]

The source of *E coli* O157

Generally, the source-sink model describes the natural history of human infections with *E coli* O157 well. Man is the sink (a dead end in terms of the long-term survival of the organism) and ruminants, particularly cattle and sheep in which the organism is not pathogenic, the source. By contrast with *Salmonella typhi*, very long-term carriage of the organism after infection in man has not been recorded. The median duration of shedding in a group of German children (median age 3·6 years) was 13 days (range 2–62) in those with diarrhoea or haemorrhagic colitis, and 21 days (range 5–124) in those who had developed haemolytic uraemic syndrome and had thus been intensively studied with a sensitive detection method.[11] Secondary spread in man is common. A review of 90 outbreaks in Britain, Ireland, Scandinavia, Canada, USA, and Japan indicated that about 20% of outbreak cases resulted from secondary spread.[12] However, the

Search strategy and selection criteria

PubMed, Medline, CAB Abstracts, and ISI Web of Knowledge were searched for all article types in all languages from 1990 to 2010. Search terms included "*E coli* O157","verocytotoxin-producing *E coli*", "Shiga toxin-producing *E coli*", and "HUS". References were selected on the basis of importance, novelty, and relevance. Priority was given to those published in the past 5 years in peer-reviewed journals.

duration of outbreaks shows that continued transmission thereafter in the affected communities is very rare.

Many studies have measured the prevalence of *E coli* O157 in cattle. Comparisons of reported data[13–15] have shown big differences between studies. For dairy cattle, the prevalence estimated by testing faeces ranged from 0·2% to 48·8%. In the USA (prevalence in calves 0·4–40%) and Canada, Italy, Japan, and the UK (prevalence in calves 1·7–48·8%) the highest figure was for carriage by calves with a functioning rumen rather than cows or heifers. Prevalence was higher in warmer months than in cooler months. *E coli* O157 can also be present in sheep and pigs; in a study done in Great Britain in 2003,[16] intestinal contents of 4·7% of cattle, 0·7% of sheep, and 0·3% of pigs tested positive for *E coli* O157 at slaughter. Cattle carriage is dynamic;[17] at individual farms, prevalence is highly variable, with occasional high prevalences and periods of apparent absence. The distribution of prevalences is highly skewed; at any one time most herds of cattle are not shedding the organism whereas others contain many animals with positive faeces.[18] Results from a study of 474 Scottish cattle farms showed that fitting dynamic epidemiological models to the recorded prevalences, including the substantial heterogeneity of shedding from individual animals (most excrete small numbers of bacteria whereas a few, so-called supershedders,[19] excrete far more), identified a robust pattern in which about 80% of transmission arises from the 20% of animals that are most infectious. Bovine supershedding is associated with the colonisation of a lymphoid follicle-dense mucosal region at a short distance proximal to the recto-anal junction.[20,21] Cattle colonised at this site shed higher numbers of organisms for a longer period than do those colonised at other sites. The presence of these animals on a farm is associated with a high prevalence of low-level shedders, and they are likely to infect another animal in the same pen. Risk factors for the presence of supershedders on farms have been studied in Scotland.[22] The *E coli* O157 type (phage type 21/28, the most common human type at the time of the study, was more common than was expected by chance in supershedders), and the individual host were important. The type of cattle (female breeding cattle) and cattle stress (movement and weaning) were identified as risk factors; environmental factors including water supply and feed were not.

Transmission of *E coli* O157

Results from a study of 90 outbreaks confirmed microbiologically in the UK, Ireland, Denmark, Norway, Finland, USA, Canada, and Japan, occurring between 1982, and 2006,[12] showed that the source of transmission was food in 42·2% of the outbreaks, dairy products in 12·2%, animal contact in 7·8%, water in 6·7%, environmental in 2·2%, and unknown in 28·9%. Many foods and dairy products have acted as vectors[23] (figure 2)—ground beef hamburgers; steak tenderised by injection; steak tartare; kebabs; ready-to-eat cold meats including poultry, pork, and beef products; salami and other fermented meat products; venison jerky; cheese; milk; butter; yoghurt; ice cream; apple juice; grapes; coleslaw; lettuce; spinach; radishes; alfalfa sprouts; and melons. The list continues to expand—eg, consumption of prepackaged raw cookie dough was strongly associated with a multistate outbreak in the USA in 2009, with 72 cases of *E coli* O157 infection, ten with haemolytic uraemic syndrome.[24] Waterborne outbreaks have been associated with recreational waters (lakes, ponds, and paddling and swimming pools), drinking water (municipal and local, from springs and wells), and ice. Outbreaks attributable to direct and indirect contact with ruminant animals have occurred on farms, agricultural shows (UK), county fairs (USA), open farms, and camps. The largest such outbreak recorded so far happened in England in August and September, 2009, with 93 infections. 78 patients had symptoms and 17 developed haemolytic uraemic syndrome.[25] Various occupational infections have been recorded in laboratory workers.[26]

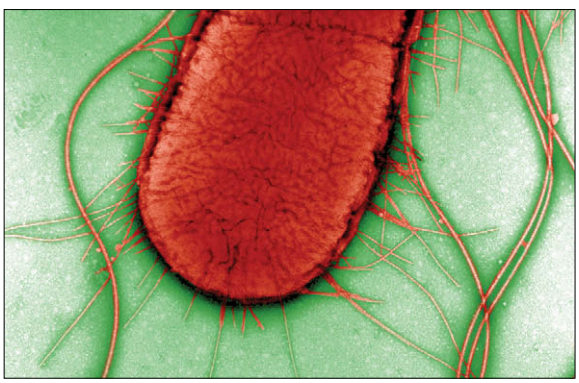

Figure 1: **Electron micrograph of an *E coli* O157 isolate from the 1996 Central Scotland outbreak**
Magnification ×50 000.

The types of food associated with outbreaks and the geographical distribution of cases differ between countries. These differences are an indicator of local food preferences, culinary customs, and patterns of food distribution. The largest outbreak recorded so far happened in Sakai City, Japan, in 1996, with 7966 cases (2764 microbiologically confirmed, 106 with haemolytic uraemic syndrome) associated with white radish sprouts served at school meals. The dominance of ground beef as a vector in the USA has been striking; it was the transmission route in 41% of foodborne outbreaks[23] between 1982 and 2002. Such outbreaks are rare in the UK, where butcher-associated outbreaks have occurred much more often than in any other country; 30 outbreaks were recorded between 1995 and 2004.[27] About 40% of outbreaks in Scotland between 1994 and 2003 were foodborne[28] (accounting for 83% of cases), 54% were environmental, and 6% had both transmission routes. Quantitative microbial risk assessment showed that the risk was 100 times greater for visits to pastures than for consumption of burgers in the northeast of Scotland. In the USA, 24 multistate outbreaks were recorded between 1992 and 2002, with at least one occurring every year. All

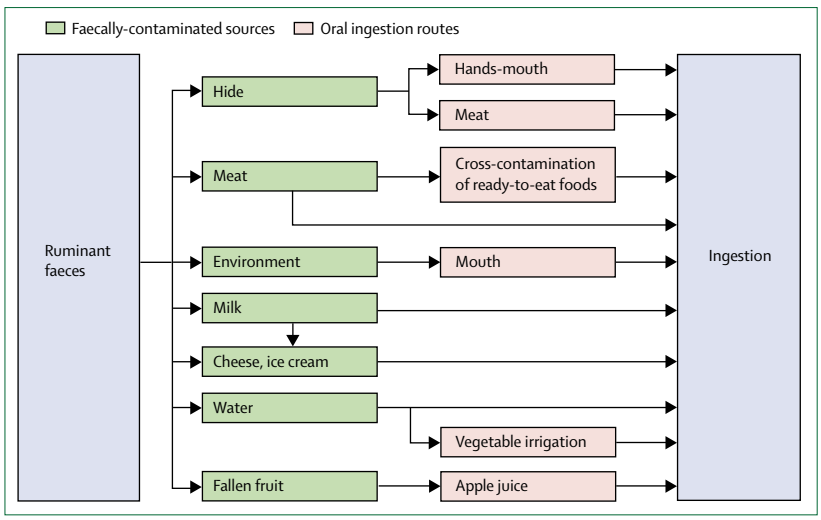

Figure 2: **Transmission of *E coli* O157**

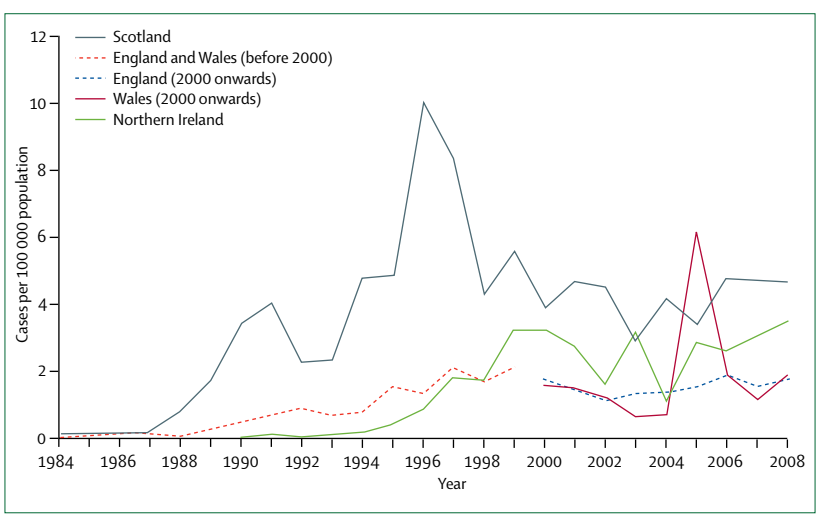

***Figure 3*: Isolation rates of *E coli* O157, UK, 1984–2008**
The spike in the Scottish number in 1996 and in the Welsh number in 2005 were attributable to the outbreaks in central Scotland and south Wales in those years. Reproduced from reference 36 with permission.

were foodborne; 16 (67%) were associated with ground beef and six (25%) with produce. International outbreaks are rarely recorded in Europe; lettuce caused an outbreak in Iceland and the Netherlands in 2007.[29]

Heavy rain is frequently associated with *E coli* O157 outbreaks; notable examples are the first outbreak recorded in Africa (a large one in Swaziland and South Africa in 1990);[5] the large outbreak at Walkerton, ON, Canada, in 2000;[30] and the smaller outbreak at the Glastonbury festival in England, in 1997.[31] Heavy rain has been repeatedly associated with the occurrence of outbreaks linked to the consumption of water from private wells and springs.[32]

Laboratory-based surveillance data show that the incidence of infection with *E coli* O157 differs greatly between countries, but these data are biased.[33,34] The extent to which stool samples are sent for testing and provided by patients varies, as do the laboratory tests that are used and the extent to which laboratory-confirmed cases are followed up. The national statistics do not include all the data that are generated; national notification schemes vary and administrations change them periodically. Asymptomatic cases are not routinely ascertained. In 2006, the incidence of infection per 100 000 in European countries[35] was 2·1 in England and Wales, 2·87 in Ireland, 4·7 in Scotland (from 1998 to 2007 the mean yearly rate was 4·28) (figure 3), 0·43 in Germany, and 0·08 in France. In the USA in 2006,[37] this incidence was about 1·3 and in Canada, in 2004,[38] it was about 4. The incidence of all Shiga-toxin-producing organisms (including *E coli* O157) in Japan from April, 1999, to October, 2004, was 2·74.[39] Major national differences exist also in the proportion of isolates of verocytotoxin-producing organisms accounted for by *E coli* O157,[35] ranging from 99·6% in the UK, to 93·7% in Canada (2004), 74·27% in the USA (2005), to 30·5% in Germany, where serogroups O103, O26, O91, O145, and a sorbitol-fermenting strain of serogroup O157 are common. Such strains of *E coli* O157 have also been found in the Czech Republic, Austria, Finland, Scotland, and Australia. The serogroup O111 has had an important public health effect in Australia, whereas O157 has predominated in New Zealand.[40]

Substantial regional variations exist within countries. In a study by Innocent and colleagues[41] in Scotland, case rates increase from west to east and from north to south, with a high rate of sporadic cases in the northeast. In this study, residence in an area with a high human population seemed to be protective, and high risk of infection seemed to be correlated with residence in areas with a high number of cattle per person.[41] The big regional difference in incidence in Scotland has been maintained for many years; in 2009, the incidence per 100 000 was 11·1 in the northeast (Grampian) and 2·4 in Greater Glasgow and Clyde.[42] Studies in Sweden[43] and Canada[44] using geographical information systems have shown that the incidence of human disease is greater in rural areas, which have high densities of cattle and sheep, than in urban areas. Residence close to farms in Sweden significantly correlates to infection with enterohaemorrhagic *E coli*.[45] Studies done in Europe, the USA, Argentina, and Australia between 1998 and 2008[33] were reviewed to elucidate risk factors for verocytotoxin-producing *E coli* (mostly *E coli* O157). The only studies that did not identify farm, manure, or ruminant contact as main risk factors were small studies done in Australia and Belgium, and a case-control study in the USA that identified eating undercooked hamburgers as the main factor. In northeast Scotland (Grampian) $1{\cdot}01\times10^{13}$ *E coli* O157 are estimated to be shed per day by cattle and $1{\cdot}96\times10^{13}$ by sheep.[46]

Transmission from person to person has been recorded many times in children's day care facilities or nurseries, and in institutions providing care for those with physical disabilities, learning difficulties, and dementia. Domestic transmission is most common to contacts aged 1–4 years and 15–34 years.[47] The review of secondary spread in the

90 outbreaks that arose between 1982 and 2006[12] ranked the route of secondary transmission as person to person in the home (45·6%); person to person in nurseries (11·1%); recreational water (ie, swimming and paddling pools, 10%); person to person in institutions (4·5%); and others and unknown (5·5%). The highest mean proportion of secondary cases was recorded in outbreaks in which patients had a median age of less than 6 years. The lowest was in outbreaks in which median age of patients was 17–59 years.

That a very small number of organisms is thought to be necessary for infection and disease comes from observations made during outbreaks.[48,49] However, because experimental studies in man are out of the question, quantitative risk assessments to determine this number of organisms are difficult to do.

A risk assessment[50] done with data from a Japanese outbreak related to salad and seafood[51] predicted a probability of infection per bacterium of 0·93% and a probability of illness of 0·5% (55% of those infected fell ill). The quantitative data were very comprehensive; information from outbreaks is very rarely completely available, even from those that are thoroughly investigated. Faecal samples had been taken from all the people who had consumed the food (at a primary school) and, as mandatory in Japan after the Sakai City outbreak, samples of the food served had been retained, which allowed the presence and concentration of the pathogen to be estimated. A risk assessment of infection associated with the recreational use of animal pasture[52] concluded that the probability of infection was 0·1% after an 8 h visit or a 24 h overnight camp immediately after cattle had been on the field for 28 days, with the proportion of them shedding the organism ranging from 4% to 6%. This study assumed that animal faeces became homogeneously mixed in the top 1 cm of soil and used estimates based on scarce evidence—eg, how much soil was ingested by visitors and campers (for children on a camp site an evidence-based figure of 30–200 mg/24 h was used), and the rate of decay of infectivity after deposition of organisms on the field.

Disease caused by *E coli* O157

The effects of an *E coli* O157 infection range from asymptomatic to lethal. Most information comes from outbreak reports. These data are biased because many reports are not publically available, outbreak investigations vary in thoroughness and in denominator (population at risk) information, and different routes of spread in outbreaks cause different populations to be over-represented or under-represented. Outbreaks vary in the severity of illness and the frequency of the most serious complication, the haemolytic uraemic syndrome,[53] because of differences in the virulence of the causative *E coli* O157 strains. The strains that caused the Sakai City outbreak[54] and the 2006 outbreak related to spinach in the USA (>50% people admitted to hospital[55]) have been chosen for detailed study in this regard.[53]

Asymptomatic infections have been recorded in outbreaks with robust denominator data, but the rarity of these data and the absence of large population surveys of healthy individuals mean that their frequency cannot be estimated accurately. In the 1996 outbreak in central Scotland,[56] which was associated with meat from a butcher, 279 individuals had the outbreak strain isolated from their stools and 35 of them (12%) were asymptomatic. In an Irish outbreak,[57] possibly from water-borne spread with subsequent person-to-person spread, nine of the 18 individuals with positive culture from their stool were asymptomatic and six were children 4 years and younger. Finally, in the 2010 English outbreak[25] on an open farm, 15 (16%) asymptomatic infections arose. None of these outbreaks was mild; in the Scottish outbreak 17 people died from the direct effects of infection, in the Irish outbreak two children developed haemolytic uraemic syndrome, and in the English outbreak 17 (22%) developed haemolytic uraemic syndrome, eight of them receiving dialysis. The typical features of *E coli* O157 gastroenteritis are abdominal pain, non-bloody diarrhoea becoming bloody after 1–4 days, five or more bowel movements in the day before presentation, and no fever.[58,59] Data gathered in 2007 and 2008 from Europe,[60–62] where non-O157 strains are common, show that a clinical presentation with bloody diarrhoea was much more common with *E coli* O157 (39% of cases) than with other strains (7% of cases).

About 10–15% of patients infected with *E coli* O157 develop haemolytic uraemic syndrome[58,63] 5–13 days after the onset of diarrhoea. The initial infection is asymptomatic in a few people. The case definition of haemolytic uraemic syndrome[64] is an acute onset of renal impairment with oliguria or anuria and high concentrations of serum urea and creatinine, platelet count less than 15×10^9 cells per L, and microangiopathic haemolytic anaemia with haemoglobin <10 g/dL and with fragmented red cells in a peripheral blood smear. Haemolytic uraemic syndrome is most common in children younger than 5 years. In England and Scotland between 1997 and 2001, 226 (65%) of the 350 cases occurred in this age group.[65] Outcomes[36] of the 180 cases of haemolytic uraemic syndrome in Scotland reported between January, 2003, and December, 2009, are typical: 53% received peritoneal dialysis, haemodialysis, or haemofiltration; 48% initially recovered and were released home; 13% had renal impairment; 7% became dependent on dialysis; 4% had neurological impairment; and 4% died. Extrarenal effects include an increase in pancreatic enzymes and oedema; necrosis of the colon wall; rhabdomyolysis; myocardial damage with high concentrations of troponin 1; and, in about 25% of cases, CNS damage[66] with seizures, paralysis, and coma. Deaths are usually associated with severe extra-renal complications.

Diagnosis and management of *E coli* O157 infections

Rapid diagnosis is essential.[67] Early separation of infected individuals from their siblings will substantially reduce

	Number of cases and deaths	Vector	Costs
Jack in the Box fast food chain, US, 1993	>700 cases, 4 deaths	Hamburgers	Individual and class action 1992, settlements >US$50 million
Odwalla, USA, 1996	>65 cases, >12 people with haemolytic uraemic syndrome, 1 death	Unpasteurised apple juice	Federal fine $1·5 million, recall $6·5 million, victim claim settlements about $12 million
One person, UK, 1997	1 case, haemolytic uraemic syndrome with severe neurological sequelae	Visit to open farm	Out of court settlement £2·6 million
South Wales, UK, 2005[71]	157 cases, 31 admitted to hospital	Cross-contamination	Prosecution costs from public funds £596 000. Public inquiry, £2·4 million

Table: **Non-health-care costs of *E coli* O157 outbreaks**

secondary transmission,[68] and the development of oligoanuric renal failure is associated with delays in the start of intravenous volume expansion.[69] The earlier epidemiological investigations of outbreaks start, the sooner control measures can be implemented.

E coli O157 is identified[70,71] by culture on selective indicator media (sorbitol MacConkey or the same agar containing cefixime and tellurite). Overnight colonies are colourless and have a diameter of 2–3 mm. Their identity is confirmed by agglutination with specific antiserum. Enrichment broth culture and immunomagnetic separation with antibody-coated beads are used to increase the sensitivity of culture methods in outbreak investigations and food testing. Retrospective diagnoses are sometimes made by measurement of antibodies to lipopolysaccharide.[72] In the UK, strain differentiation by phage typing and pulsed-field gel electrophoresis is done at reference laboratories in London and Edinburgh. A few phage types dominate; pulsed-field gel electrophoresis is much more discriminatory than is phage typing and has been widely used in outbreak investigations. Neither method points to evolutionary associations,[73] and tests based on DNA sequences such as multilocus variable number tandem repeat analysis are beginning to replace them.[74] This type of analysis of German clinical isolates done between 1987 and 2008 has shown not only much diversity but also the persistence of some genotypes for many years; the two most common profiles were strongly associated with haemolytic uraemic syndrome.[75] In patients with postdiarrhoeal haemolytic uraemic syndrome, no intervention has proved to be better than supportive therapies (control of fluid and electrolyte imbalance, dialysis, control of hypertension, or blood transfusion).[64]

Virulence factors

The production of Shiga toxin is central to the pathogenesis of bloody diarrhoea and haemolytic uraemic syndrome.[76] *E coli* O157 strains have the locus of enterocyte effacement genes but other serogroup strains without these genes have also caused haemolytic uraemic syndrome.[77]

E coli O157 can produce two different Shiga toxins encoded by bacteriophage. Stx1 is very similar to the type 1 toxin of *Shigella dysenteriae*; Stx2 is genetically and immunologically distinct with 55–60% similarity in genetic and aminoacid sequences. The possession and expression of the Stx2 gene and the variant Stx2c (which often occurs with Stx2) correlate strongly with the causation of bloody diarrhoea and haemolytic uraemic syndrome.[76,78,79] Shiga toxins bind to glycosphingolipid globotriaosylceramide (Gb3), a cell surface receptor. They are then internalised by clathrin-dependent endocytosis, and go on to specifically depurinate 28S eukaryotic rRNA, inhibiting protein synthesis. This step induces a ribotoxic-stress response that can lead to cytokine release and apoptotic cell death. In the human kidney, Gb3 is present on glomerular endothelial cells, podocytes, and various tubular epithelial cell types. Shiga toxin binds to these cells in renal sections from patients with haemolytic uraemic syndrome, and damage markers from these cells can be detected in their urine; biopsy samples from these patients show apoptosis of glomerular and tubular cell types and fibrin-rich glomerular microangiopathy.[58,80] Results from experimental studies in vitro on human blood showed that an interaction between shiga toxin and *E coli* lipopolysaccharide (particularly the O157 serotype) triggers the release of microparticles bearing tissue factor. Blood from patients with haemolytic uraemic syndrome showed an increase in microparticles with surface-bound tissue factor and in functional tissue factor. Tissue factor can contribute to a prothrombotic state.[81]

The locus of enterocyte effacement[82,83] genes encode a system of type III secretions that mediates intimate attachment of the organism to enterocytes, giving rise to attachment and effacement lesions in which the microvilli's brush border surrounding the point of attachment is destroyed. This step is controlled by distal regulators carried by chromosomes and plasmids. The bacterial protein translocated intimin receptor translocates into the host cell by the type III secretion system. Part of the protein remains exposed on the cell surface and binds to another bacterial protein, intimin. This binding results in the clustering of translocated intimin receptor molecules, starting a signalling cascade that triggers the formation of actin-filled pseudopods, actin pedestals, at the site of bacterial attachment.

Analysis of single nucleotide polymorphisms at 96 loci in more than 500 clinical isolates of *E coli* O157 identified eight clades (specific genetic lineages).[53] The strains from the US outbreaks associated with spinach and lettuce in 2006 (275 cases, 157 admitted to hospital) fell into clade 8. Clades 1, 2, and 3 contained strains from the Sakai City outbreak in 1996 and US outbreak in 1982 and 1993 from hamburgers. Infections with clade 8 strain resulted in much higher rates of admissions to hospital than the average, and significantly higher rates of haemolytic uraemic syndrome. Infections with clade 1, 2, and 3 strains were much less severe than with clade 8. All clade 8 strains were positive for Stx2. Gene expression by the strains of the Sakai City and of outbreak associated with spinach were compared before and after exposure to epithelial cells

with whole-genome microarrays and RT-PCR.[84] Most locus-of-enterocyte-effacement genes, the Stx2 genes, and several plasmid-encoded genes promoting adherence were upregulated in the strain from the outbreak associated with spinach. By contrast, in the Sakai City strain, flagellar and chemotaxis genes were upregulated. Evidence from Germany and Scotland shows that infection with sorbitol-fermenting O157 strains is associated with an increased incidence of progression to haemolytic uraemic syndrome. Scottish strains adhere to human colonic cell lines at significantly higher levels than do non-sorbitol-fermenting O157 strains, and expression of curli (thin aggregative fimbriae) is the main factor controlling adhesion.[85]

Effect and prevention of *E coli* O157 infections

The severity and long-term sequelae of infection with *E coli* O157 and other verocytotoxin-producing *E coli* result in high costs. The medical, productivity loss, and outbreak control costs of the 1994 West Lothian outbreak in Scotland (milk pasteurisation failure, 71 cases, 11 with haemolytic uraemic syndrome, one death) were estimated to be £3·2 million for the first year. Over 30 years the costs were projected to be £11·9 million.[86] The medical and productivity loss costs of the 1995 outbreak of *E coli* O111 in South Australia (contaminated mettwurst, about 200 cases, 23 with haemolytic uraemic syndrome, one death) were estimated at AUS$5·6 million.[87] In both outbreaks haemolytic uraemic syndrome and premature death accounted for much of the costs. The directly measurable costs of the Walkerton outbreak (excluding costs attributable to premature deaths) was CAD$64·5 million.[88] Non-health-care costs can also be great (table) as is media interest.[89]

Outbreak investigations underline the importance of preventive measures by showing their failure. Failures during or after milk pasteurisation caused the third (Cumbria, England, 1999, 117 cases)[90] and fourth (West Lothian, Scotland, 1994) biggest UK outbreaks. Rare and light cooking of hamburger patties caused the Jack in the Box outbreak in 1993. A failure in municipal water chlorination caused the Walkerton outbreak in Canada.[31] Failure to prevent cross-contamination of ready-to-eat foods by direct or indirect contact with raw meat brought about the largest outbreak in the UK (Central Scotland,[56] 1996), and the largest in Wales (2005, 157 cases, one death).[74] In the outbreak in Aberdeenshire in 2000 that occurred in campers (environmental exposure, camp ground contaminated with sheep droppings, 20 cases), those who did not wash their hands before meals were nearly nine times more likely to be infected than were those who did.[91] Despite this figure, handwashing is often done poorly, or not at all.[25]

Hazard analysis critical control points (HACCP) is the universally accepted management system for delivering microbiologically safe food.[92] It was driven forward for US slaughterhouses by the outbreak at Jack in the Box restaurants and for British butchers by the 1996 outbreak in central Scotland.[93] The system was developed by NASA (National Aeronautics and Space Administration) and others in the 1960s to deliver safe food for astronauts and since then, it has worked best in large enterprises. US outbreaks from fast-food chain restaurants serving ground beef are now prevented by the critical control point of raised cooking temperatures. But failures of HACCP implementation were found in the slaughter house and the butcher associated with the 2005 outbreak in south Wales.[74] Much work remains to be done before universal effective implementation of this system in businesses of small and medium size can be assured, despite its ability to deliver food that is free from microbiological and other contaminants. The implementation of critical control points in the domestic environment is entirely dependent on education and exhortation; ground beef outbreaks still occur in the USA but are now associated with home-made burgers.

No methods that substantially and consistently reduce shedding and carriage rates in ruminants exist. A vaccine that shows promise has been developed.[94] If this vaccine proves efficacious, the likelihood of its use in the USA might be increased by commercial considerations; the US Department of Agriculture declared *E coli* O157 to be an adulterant in ground beef in 1994. This zero tolerance policy has led to many high-publicity recalls of large batches of meat.

Conclusion

E coli O157 is a virulent pathogen that is carried undetected by a few ruminants. Once an infection is established, the development of haemolytic uraemic syndrome cannot be prevented. Faecal to oral transmission occurs by many routes, so many barriers are needed to prevent infection (figure 2). Some of these barriers, such as milk pasteurisation and water chlorination, protect the bulk of the population effectively. But handwashing and the working practices that prevent cross-contamination rely heavily on human behaviour. The organism can escape detection by the traditional visual inspection systems still in use in European and North American slaughter houses. Therefore, risk reduction and mitigation strategies—available after transmission to human beings, such as outbreak control and rapid diagnosis with timely supportive treatment—are all that can be expected. Substantial reduction of the present magnitude of disease will only come about if the extent of ruminant carriage is similarly reduced. In this regard, the South Wales Public Inquiry report from 2005 recommended investigation of so-called supershedders.[74]

Conflicts of interest

I declare that I have no conflicts of interest.

Acknowledgments

I thank Debbie Marshall for supplying figure 3.

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