

Foresight

Infectious Diseases: preparing for the future

OFFICE OF SCIENCE AND INNOVATION

T5.5: Food-borne pathogens in humans in the UK

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Introduction

This review considers the food-borne bacterial pathogens *Salmonella*, *Campylobacter* and *Escherichia coli* O157:H7. These organisms outscore other food-borne bacterial pathogens in the UK as causes of human infection. Figures for 2004 – a year without notable outbreaks – are shown in Table 1.

Table 1

Food-borne Pathogens, 2004 (England and Wales), Health Protection Agency Data (provisional)

Campylobacter ^(a)	42,146
<i>Salmonella</i> (non enteric) ^(a)	12,725
<i>E. coli</i> O157 ^(b)	701
<i>Salmonella typhi/paratyphi</i> ^(c)	422
<i>Clostridium perfringens</i> ^(d)	475
<i>Staphylococcus aureus</i> ^(c)	18
VCJD ^(e)	9

- a. Faecal and lower gastrointestinal isolates.
- b. Strains examined
- c. Laboratory reports
- d. Total ill
- e. Deaths, UK, CJD Surveillance Unit Data.

Salmonella

The statistical record of cases of disease caused by food-borne organisms in humans throughout the last hundred years shows evidence of massive changes in the incidence of infections caused by particular pathogens, and in their outcomes. *Salmonella* infections illustrate this well. Enteric (typhoid) fever is caused by *S. typhi* and *S. paratyphi*. The only source of *S. typhi* is humans and it causes a septicaemia. Infection is contracted by consuming water or food (including milk) contaminated with faeces or urine from a person with typhoid, or an asymptomatic carrier. Table 2 shows standardised mortality rates (SMR) during the 20th century (figures from 1961 and 1972 Annual Reports of the Chief Medical Officer, Ministry of Health, London).

Table 2

Typhoid fever, England and Wales, Standardised Mortality Rate. Base years 1950 – 52 taken as 100

Year	Ratio
1901 – 10	23,581
1911 – 20	8,926
1921	2,729
1931	1,180
1940	387
1950 – 52	100
1960	17
1971	0

The decline in SMR from 1901 to the 1950s was due to improved sanitation. Antibiotics played a significant additional role thereafter. The last big waterborne outbreak in the UK was in Croydon in 1937¹ with 341 cases and 43 deaths. An enormous typhoid outbreak occurred in Aberdeen in 1964 with 507 cases and no deaths after the organism had been imported in contaminated corned beef from Argentina². Currently, in the overwhelming majority of the small number of cases of typhoid diagnosed in the UK infection was contracted in countries where the infection is still endemic.

There are a large number of non-enteric *Salmonella* serotypes. The Kauffman-White scheme, which defines them, was introduced in 1934. The numbers of isolates sent for typing to the *Salmonella* reference laboratory of the Public Health Laboratory Service (now the HPA) was small in the 1930s and early 1940s. 14 serotypes had been found in England and Wales before 1942. But in that year ten new serotypes appeared, with 18 more being found in 1943 and six in 1944. The number of reports of *Salmonella* food poisoning also increased, rising from 100 in 1942 to more than 450 in 1944. This increase was in large part due to the import of the new serotypes in American spray-dried egg, first distributed on a large scale in the middle of 1942⁽³⁾. The increase was then sustained. Much of it was accounted for by infections with *Salmonella typhimurium*, a serotype present in the UK before the import of dried egg (Table 3).

Table 3***Salmonella* food poisoning incidents, England and Wales⁴**

	1929-40	1941-45	1946-50	1951-55	1956-60	1961-65	1966-70
Number of incidents	567	1,446	5,827	15,983	22,879	15,708	19,592
Percentage due to <i>S.typhimurium</i>	49	49	75	79	69	62	42

With important and significant fluctuations, the number of isolations of *Salmonella* from individuals with gastrointestinal disease has remained high.

***Salmonella* statistics**

The Advisory Committee of the Microbiological Safety of Food's Second Report on *Salmonella* in Eggs⁵ commented (p8) on laboratory statistics as a measure of the incidence of infection. Their comments refer to *Salmonella* but are valid for all food-borne pathogens. 'Concern has been expressed about the validity of laboratory reports in defining the time trends in incidence of *Salmonella* infection in the population. This is because there are several steps between infection and laboratory reporting which are subject to biases which may obscure the true pattern of infection. Patients infected may not become symptomatic and, even if they do, will not usually seek medical advice. General practitioners do not usually request faecal samples for microbiological investigation and, when requested, patients do not always comply. Microbiological investigation is never 100 per cent sensitive, and laboratory reporting of positives to surveillance centres is voluntary and not complete. So long as these steps remain stable, the laboratory reports should give a good indication of trends. However, if a higher proportion of patients consult their GPs for diarrhoeal illness, or if GPs request laboratory investigation more often, an artefact will be a resultant increase in cases. One reassurance that this is not occurring is provided by trends in other enteric infections. An increase in consultations or investigations should artificially increase the reports of all enteric organisms, and this has not happened.

In order to study the stages from infection to reporting, the Department of Health funded the Infectious Intestinal Disease Study in 70 general practices throughout England.⁶ Infectious intestinal disease occurred in one in five people per year, of whom only one in six presented to a general practitioner. For any gastrointestinal illness, one case was reported to national surveillance for every 1.4 laboratory identifications, 6.2 faecal samples sent into laboratories, 23 cases presenting to general practice and 136 community cases. However, for *Salmonella* infection, the ratios were much smaller with an estimated one in every 3.2 cases in the community being reported to national surveillance.'

***Escherichia coli* O157; a new pathogen**

A typing scheme for *Escherichia coli* based on its surface (H and O) antigens was developed in the 1940s.⁷ Serotype *E. coli* O157:H7 appeared abruptly as a pathogen in 1982 in the United States. In February and March that year there were 25 cases of bloody diarrhoea; *E. coli* O157 was isolated from four of these. 18 cases of bloody diarrhoea occurred in Traverse City, Michigan in May and June; *E. coli* O157 was isolated from four.^{8,9} In 1983 Karmali and colleagues reported sporadic cases of the haemorrhagic uraemic syndrome associated with a cytotoxin lethal to African green monkey (Vero) cells in the stools and attributed to *E. coli* of various serotypes including O157:H7.¹⁰ Retrospective analysis of strains in the national *E. coli* collections in the US (over 3,000) the UK (over 15,000) and Canada (over 2,000) found *E. coli* O157:H7 strains isolated from the stools of one patient in the US, one in the UK, and six in Canada before 1982. The earliest was from a patient with bloody diarrhoea in California in 1975.¹¹ In 1983 a verocytotoxin-producing *E. coli* serotype O157 was isolated in the UK from a cluster of cases in Wolverhampton following an outbreak of the haemolytic uraemic syndrome in the West Midlands.¹² *E. coli* O157 infections occurred in Scotland in 1984. In both England and Scotland the annual number of infections increased until the early 1990s, fell, then rose again, with a peak in the number of cases in 1996 in Scotland which has never since been surpassed. It was caused by the central Scotland outbreak, with about 500 cases (*E. coli* O157 was isolated from 279; 17 died directly from the infection).^{13, 14}

***Campylobacter* ; its emergence in the 1970s**

Campylobacter strains were first isolated in 1913¹⁷ but their importance as human pathogens was not established until the 1970s.¹⁸ Most pathogenic strains are microaerobic with an optimal gas environment for growth of 5 per cent oxygen, 10 per cent carbon dioxide and 85 per cent nitrogen. They begin to die on exposure to the atmosphere. They are thermophilic. These characteristics probably explain why *microbiologists overlooked Campylobacter* before the 1970s. The methods they were using then for stool culture of samples from patients with gastrointestinal infections did not grow the organism. In 1981, 12,168 laboratory isolations were reported to the Communicable Disease Surveillance Centre in London. For many years thereafter the number of isolations increased steadily. It is likely that the increased familiarity of medical microbiologists and the staff of diagnostic laboratories with *Campylobacter* and culture methods for it played a role in the increase in the number of laboratory reports. It is not possible to quantify the impact of these developments.

Population genetics of *Salmonella*, *E. coli* O157 and *Campylobacter*

Studies using multilocus enzyme electrophoresis (MLE) have shown that the population structure of *Salmonella* and *Escherichia coli* is clonal, with strong linkage disequilibrium among alleles at enzyme loci.¹⁵ For both *Salmonella* and *E. coli*, clones defined by MLE also map well onto serotypes. Although the antigens used in serotyping are under immunological selection pressure, their association with particular clones is long lived. So are many of the clones. This

means that serotyping and MLE typing define entities which have lifetimes long enough for them to spread over great distances. It also means that typing with these methods is epidemiologically useful. Another epidemiologically useful attribute of *Salmonella* and *E.coli* O157 is their ability to cause outbreaks, sometimes on a large scale. The evidence they provide is as useful to food safety scientists as that provided by earthquakes to seismologists.¹⁶

Most *Campylobacter* infections are sporadic. Table 4 shows that general outbreaks, those affecting members of more than one private residence, or residents of an institution, are rare.

Table 4

***Campylobacter* outbreaks, England and Wales**

Outbreaks	1989	1990	1991
Total	360	328	398
General	9	11	8
Family	351	317	390

The population genetic structure of *Campylobacter* is complex. It has a high genetic and antigenic diversity.¹⁷ There are two species: *C. jejuni*, which accounts for about 90 per cent of UK infections,¹⁸ and *C. coli*. In sharp distinction from *Salmonella*, serotyping has not been epidemiologically useful.⁵⁷ It has lacked discriminatory power and reproducibility between laboratories. A significant number of strains have been untypeable.¹⁹ Multilocus sequence typing has recently been applied to *Campylobacter*.²⁰ This confirms its genetic diversity, but common clonal complexes have been identified. Some, for example, clonal complex 21 occurs in many species including chickens, cattle, sheep, starlings and humans. Complex 45 was most commonly found in turkey and broiler chicks and in humans.³²

The emergence of *Campylobacter*, *Salmonella* and *E.coli* O157; a clonal perspective

As new and emerging pathogens, *Campylobacter*, *Salmonella* and *E.coli* O157 have very different histories. Our awareness for the first time of *Campylobacter* in the 1970s had a technical explanation. It is reasonable to assume that it had caused a significant amount of food-borne disease before then; how much, it is not possible to say. The role of individual clones in the next two decades in the increase in the number of infections reported by laboratories is not clear. For *Salmonella* a big increase in microbiologically confirmed infection rates

occurred in the late 1940s and early 1950s. A common pattern, which continues, is that a serotype appears, persists, and declines even without the application of specific control measures. Some serovars become endemic. Table 5 shows the historical pattern in England and Wales. *S.heidelberg* was common in the UK between 1956 and 1966. At this time it was also common elsewhere in western Europe and in parts of North America.

Table 5

Rank order of *Salmonella* serotypes, food poisoning incidents, England and Wales (from the records of the Salmonella Reference Laboratory, PHLS, London)

	1929-40	1941-45	1946-50	1951-55	1956-60	1961-65	1966-70
1	typhimurium	typhimurium	typhimurium	typhimurium	Typhimurium	typhimurium	typhimurium
2	thompson	enteritidis	thompson	enteritidis	heidelbergHeidelberg	heidelberg	enteritidis
3	enteritidis	newport	enteritidis	thompson	Enteritidis	brandenburg	panama
4	newport	orianenburg	newport	newport	newportnewport	enteritidis	stanley
5	choleraesuis	thompson	dublin	bovismorbificans	thompsonthompson	newport	virchow
6	dublin	montevideo	montevideo	stanley	saintpaul	stanley	heidelberg

In population genetic terms *E.coli* O157 most closely resembles a single *Salmonella* serotype. As a human pathogen with the ability to cause outbreaks, it first appeared in the early 1980s in the UK and in the US. The UK Public Health Laboratory Service investigated 161 outbreaks of diarrhoeal illness that occurred between 1973 and 1983 without finding it, and the Centers for Disease Control in the US had no records of outbreaks of bloody diarrhoea (characteristic of *E.coli* O157 infections) of unknown origin occurring before 1982.

Drivers

What drivers were important in bringing about the increase in numbers of cases of food-borne human infections caused by *Campylobacter* and *Salmonella* in the UK, and the emergency of *E.coli* O157? The overwhelming majority of food-borne infections are due to the contamination of food with animal faeces. Human to human spread via food is rare. None of these organisms (unlike *Salmonella typhi* or many non-pathogenic *E.coli* clones) exist in a human host for long periods or for life. The human infection is a dead end. The drivers of human infection are sources, which affect the burden of infection in the animal hosts, and pathways, which have an influence on food as a vehicle for infection.

The sources and drivers in them of *Salmonella*, *Campylobacter* and *E.coli* O157 will be considered next.

***Salmonella* (non-enteric) sources and drivers in them**

Salmonella serovars can infect a wide range of species. But poultry predominates as the food vehicle in human infections. There were 939 *Salmonella* outbreaks recorded by the PHLS Communicable Disease Surveillance Centre in England and Wales between 1992 and 1999. A food vehicle was identified in 578. It was poultry (meat or eggs) in 477 (83 per cent). A paradigmatic poultry organism is *Salmonella enteritidis* phage type (PT) 4. It has been studied intensively because it became a common cause of human infection in the late 1980s and onwards (Table 6)

Table 6.

Laboratory reports of *Salmonella enteritidis* PT4 infection in humans. England and Wales (source, PHLS, Laboratory for Enteric Pathogens 1981-1991 and the PHLS *Salmonella* dataset 1992 onwards)

Year	Number of infections	per cent of all <i>Salmonella</i> isolates
1981	395	4
1982	413	3
1983	823	5
1984	1,362	9
1985	1,771	13
1986	2,971	18
1987	4,962	24
1988	12,522	46
1989	12,931	43
1990	16,151	54
1991	14,693	53
1992	16,987	54
1993	17,257	56
1994	13,782	45
1995	12,482	42
1996	13,127	46
1997	15,266	47
1998	10,288	43
1999	6,645	39
2004	2,201	17

Why did this organism cause a pandemic? (phage type 4 became common in Austria and Germany, and other phage types in the USA). The conclusions of the Advisory Committee on the Microbial Safety of Food Second Report on *Salmonella* in Eggs⁵ are pertinent.

How did the pandemic begin?

We believe that the pandemic of human salmonellosis due to *S. enteritidis* was a consequence of a panzootic of this serotype affecting both broiler and layer flocks. *S. enteritidis* possesses the unusual, but not unique, property of being able to invade the reproductive tract of a chicken. This led to an increase in the number of *Salmonella*-contaminated eggs being produced, thus increasing the risk of human infection. It has been proposed that the success of *S. enteritidis* in infecting so many hens is due to its similarity to *Salmonella gallinarum* and *Salmonella pullorum*, both chicken-adapted strains. All are Group D *Salmonella* species and they have a number of antigens in common. The virtual elimination of *S. gallinarum* during the 1960s and early 1970s may have provided an ecological niche for the antigenically similar *S. enteritidis*. This has caused widespread environmental contamination which has proved remarkably difficult to eradicate, despite the best efforts of the poultry and egg industries worldwide.

As part of our consideration of the possible origins of the *S. enteritidis* pandemic, we carried out a survey of more than 80 scientists based here and abroad. Unfortunately, this yielded no new information and no consensus emerged.

The propensity of *Salmonella* serotypes (clones) and subclones such as *S. enteritidis* PT4 to expand their population size has been facilitated enormously by the scale and structure of the poultry industry. The timeline of increase in the number of human *Salmonella* infections since the 1940s is similar to that of the expansion of broiler production since the Second World War. This has been an international phenomenon (Table 7).

Table 7

Annual US Broiler Production and Consumption, 1940-1990 (data from reference 23)

Year	Production (million heads)	Per capita consumption (pounds ready to cook)
1940	143	2
1950	631	8.7
1960	1,795	23.6
1970	2,987	36.8
1980	3,963	46.6
1990	5,864	61.0

Poultry consumption in Britain quadrupled between 1956 and 1964, from 0.59oz to 2.82oz (80 grammes) per head per week. It was during this period that chicken became cheaper than beef.²⁵

The structure of the poultry industry may also have been a driver. Commercial sensitivities mean that data is hard to get, but large flocks and the integration of the industry provide opportunities for microbial spread. A survey of English broiler production in 2002²⁶ found that 99.9 per cent were in 1706 flocks larger than 1000 birds, and 97 per cent were in 713 flocks with more than 20,000 birds. Four companies process more than 70 per cent of all UK production and produce almost half themselves in company-owned farms. Farmer-owned holdings are almost invariably contracted to produce for one of these companies, or for one of the 11 other processors prominent in the industry, with chicks, feed and some other inputs either supplied or closely controlled by the company that will process and market the broilers.

The Advisory Committee on the Microbiological Safety of Food's Second Report on *Salmonella* in Eggs⁵ considered breeder birds as a source of infection in the poultry production chain. They said , 'There are currently only three major egg laying breeding companies supplying the world market, claiming approximately 90 per cent of world sales of egg laying birds. Two companies supply 75 per cent of the world market. The breeding chain is as follows:

Stage 1: Elite breeding stock where breeding trials and selection take place.

Stage 2: Great grandparent stock: 8 separate lines, the first multiplication from the elite stock.

Stage 3: Grandparent stock, the second multiplication.

Stage 4: Parent breeders: from which the layers and broilers are hatched.

There are no new egg laying breeders at Stages 1 and 2 in the UK.'

The fact that breeder flocks can be a source of infection is shown by the data in Table 8 from the Report referring to the years 1993-1999, when compensation was available if flocks were slaughtered.

Table 8.

Prevalence of *Salmonella enteritidis* and *S.typhimurium* in British breeder flocks

Year	No. registered breeding flocks	Breeder flocks slaughtered			
		Layers		Broilers	
		<i>S.enteritidis</i>	<i>S.typhimurium</i>	<i>S.enteritidis</i>	<i>S.typhimurium</i>
1993	564	3	0	32	2
1994	591	1	0	11	3
1995	583	1	1	13	2
1996	472	2	0	4	1
1997	540	0	0	7	1
1998	581	1	1	12	2
1999	643	0	0	1	2

The expansion of other *Salmonella* serotypes in the UK in the past also demonstrates the importance of farming practice as a driver. The intensive rearing of veal calves started in the early 1960s and was being done on a large scale by 1964-65. It coincided with the expansion of *Salmonella typhimurium* phage type 29.

Table 9***Salmonella typhimurium* PT29 (data from reference 27)**

Year	1960	1961	1962	1963	1964	1965	1966
Number of isolates of <i>S.typhimurium</i> PT29 from bovines	2	3	2	45	173	1294	347

A high proportion of calves was handled by dealers who dispatched the animals to holding premises and then sent them to buyers, often in crowded and poor-quality transport conditions over long distances. Diarrhoea and systemic infection with high mortality was common. Infected stock was distributed throughout Britain. Antibiotic control was attempted but by 1965 99.7 per cent of isolates were resistant to a range of drugs.²⁷ In contrast, *Salmonella hadar* became common in poultry but only came to attention by causing disease in humans. It appeared in 1971 and persisted until 1981, when the number of cases fell dramatically. It caused outbreaks of food poisoning in humans but was non-pathogenic for turkeys, its reservoir. The distribution of infected turkey poults from a common source spread the infection to many UK poultry farms.²⁸

***Campylobacter* sources and drivers in them**

The Advisory Committee on Microbial Safety of Food's Second Report on *Campylobacter*²¹ succinctly summarises current knowledge about the sources of human *Campylobacter* infection under the heading 'Epidemiological conundrums'. It is reproduced below.

'Despite the multiplicity of risk factors identified for *Campylobacter* infection, in most case-control studies of *Campylobacter* infection the majority of cases remain unexplained. That *Campylobacter* infection, like other food-borne zoonoses, is transmitted through more than one route is not in doubt. What is not known for certain is the relative importance of these transmission routes in the aetiology of infection.

The large proportion of unexplained cases might prove to be due to as yet unidentified risk factors or exposures that are very rare among unaffected individuals in the population. If this is the case, then very high-powered studies will be needed to detect their effects.

It has been suggested that between 20 per cent and 40 per cent of sporadic disease might be due to the consumption of chicken. If this is so, controlling *Campylobacter* carriage in the poultry reservoir might have a measurably beneficial effect on human disease incidence. Nevertheless, the reasons behind the majority of human disease would still not have been tackled.

The paucity of recognised outbreaks has undoubtedly hampered scientific understanding of the epidemiology of *Campylobacter* infection. By contrast, the epidemiology of verocytotoxic-producing *Escherichia coli* O157 is much better defined, and the diligent investigation of recognised outbreaks has made a major contribution to understanding the aetiology of sporadic disease.'

***E. coli* O157 sources and drivers in them**

The two 1982 *E. coli* O157:H7 outbreaks in the US, the first anywhere, mostly affected consumers of beef burgers at McDonalds restaurants. Attention focused on comminuted beef as a vehicle and cattle as the source. Many studies have shown that the organism can be isolated from the lower intestinal tract of healthy cattle. The first positive results came from the US in 1986²⁹ and England in 1989.³⁰ The large central Scotland outbreak in 1996³¹ stimulated further studies on the prevalence of the organism in farm animals. The results and those of earlier studies in the UK have been summarised in the report of the Food Standards Agency/Scottish Executive Health Department Task Force on *E. coli* O157 published in 2001, from which Table 10 is taken.

Table 10

Prevalence of *E. coli* O157

	Scotland on Farm (1998-2000)	England and Wales on Farm (1999)	GB Abattoirs (1999)
Cattle	8 per cent	4.7 per cent	4.7 per cent
Cattle Herds	23 per cent	44 per cent	-
Sheep	-	-	1.8 per cent
Pigs	-	-	0.16 per cent

Note: The age range and type of cattle tested in the Scottish and English/Welsh studies were not identical and the figures cannot be directly compared.

Quantitative studies on the shedding of *E. coli* O157 by sheep were done following an outbreak at a Scout camp in North East Scotland in summer 2000.³² The average number of *E. coli* O157 per gram of ewe faeces was 8400. One lamb was shedding over 10⁶ per gram.

What have been the drivers leading to the carriage of the organism in cattle and sheep, by far the most important sources of infection for humans? Nothing is known about changes in prevalence over time. It is not known

when the organism started to become a member of the *E. coli* clonal population that inhabits the guts of healthy ruminants. Routine veterinary microbiology is concerned with the diagnosis of disease in sick animals, *E. coli* O157 does not usually cause disease in cattle and sheep, and so veterinary investigations have not provided information about animal carriage in the early 1980s and before.

Studies on the evolution of *E. coli* O157 using multilocus enzyme electrophoresis³³ have led to the proposal that it derived from an ancestor genetically related to an enteropathogenic *E. coli* clone associated with infantile diarrhoea of serotype O55:H7. This ancestor then acquired, and lost, functions in a stepwise sequence, including the pathogenicity island designated LEE (locus of enterocyte effacement, coding for proteins mediating the close attachment of bacteria to microvilli and characteristic attaching and effacing lesions) acquired by lateral gene transfer, and the Shiga toxins 1 and 2 (virulence probably acquired by a transduction by a toxin-converting bacteriophage). Comparison of the genome sequences of an *E. coli* O157:H7 strain isolated from Michigan ground beef associated with the 1982 McDonalds outbreaks in the US, with that of *Escherichia coli* K-12, maintained as a laboratory strain since its isolation in 1922 in California from the faeces of a convalescent diphtheria patient, confirmed the importance of lateral gene transfer.^{34, 35} Both strains have a common backbone of 4.1 megabases, co-linear apart from a 422 kilobase inversion. But the homology is punctuated by hundreds of islands of apparently introgressed DNA. *E. coli* O157:H7 has 177 unique islands greater than 50bp in length, its unique islands totalling 1.34 megabases. K12 has 234, its unique islands totalling 0.53 megabases. Nothing is known about the drivers of these evolutionary changes. All that can be said is that it is likely that they have been in progress for a long time. Population genetic studies estimate that *E. coli* O157:H7 and *E. coli* K12 last shared a common ancestor about 4.5 million years ago.³⁶ An outstanding question is why *E. coli* O157:H7 retains the ability to produce virulence factors such as Shiga toxins when in its main ruminant hosts it is non-pathogenic. These toxins play a role in causing diarrhoea in humans which intuitively could be considered to aid faecal-oral spread, so conferring a selective advantage to their production. But humans are an evolutionary dead end for the organism. However, work is in progress to establish whether virulence factors play roles in determining why *E. coli* O157:H7 has a very distinct site of residence in the bovine gut. In experimentally and naturally colonised animals that became persistent carriers, most tissue-associated bacteria were found to be adherent to mucosal epithelium in a defined region extending up to 5cm proximally from the recto-anal junction, on tissue with a high density of lymphoid follicles. Other *E. coli* serotypes were present throughout the large intestine. One consequence of the *E. coli* O157:H7 tropism was that it was present predominantly on the surface of faecal stools. Other serotypes were equally distributed in the stools.³⁷

In the northern hemisphere, the incidence of *E. coli* O157:H7 infections has in general been higher in countries nearer the North Pole. For example, in Scotland, isolation rates have been consistently and significantly higher than in England since 1984.³⁸ A number of intervention studies have been done to

test the effect of different husbandry practices on carriage in cattle. No explanations have been forthcoming of the geographical distribution of *E.coli* O157:H7 human infections. No on-farm interventions or studies of its ecology on farms have produced information that contributes significantly to an understanding of why the organism emerged when it did, although it has been suggested that changes in feeding practices in cattle over the last 40 years may have been connected with its emergence as an acid-resistant organism.³⁹

Pathways of food-borne infection

Even in outbreaks which generate robust epidemiological conclusions regarding food vehicles, it is unusual for direct microbiological evidence of food contamination to be obtained. Thus there were 37 *E. coli* O157:H7 outbreaks recorded in England, Wales and Scotland between 1987 and 1994 in which bacteriological confirmation of the diagnosis in human cases was obtained.³⁸ But the food vehicle was identified bacteriologically in only three. *E. coli* O157:H7 can cause severe infections (47 cases of haemolytic uraemic syndrome and 12 deaths occurred in these outbreaks) and so it is probable that they were investigated with vigour. A detailed study of well-documented outbreaks associated with egg-based food occurring between 1988 and - 1992⁴⁰ found that the causative organism (*Salmonella enteritidis* or *typhimurium*) had been isolated from cases in 60, but from eggs in only three. Microbiologically confirmed *Campylobacter* infections are usually sporadic. This precludes routine epidemiological investigation. The Infectious Intestinal Diseases Study in England done between 1993 and 1996 investigated *Salmonella* and *Campylobacter* infections in 70 general practices.⁴⁰ It found that for every *Campylobacter* case reported to the Communicable Diseases Centre in London, 1.5 cases had been found positive by routine laboratory investigation, 3.6 had presented to a general practitioner, and 7.6 had occurred in the community. The reporting pyramid for *Salmonella* was 1.2 for laboratory positives, 2.3 for presentation to a GP and 3.2 in the community. Food vehicles are therefore not identified in the majority of suspected food-borne infections. A useful discussion on the constraints on and limitations of epidemiological investigations is contained in reference 40.

With the exception of *Salmonella enteritidis* (and some other *Salmonella* serotypes e.g. *typhimurium*) which sometimes occur inside eggs, the pathogens considered in this review transfer to food in faeces.

A very large number of different foods have been identified as vehicles for *Campylobacter*, *Salmonella* and *E. coli* O157:H7 infections. But only a few can be considered important. Milk, for example, has historically been a very important vector of pathogens, their source being the udder, or alternatively, contamination at milking from the cow or the milker, or after milking. It has been estimated that between 1912 and 1937 65,000 people in England died from milk-borne tuberculosis.⁴² But for all three pathogens considered here, milk-borne outbreaks have served as an indicator of the consumption of unpasteurised milk or the incidence of pasteurisation failures rather than anything else. Thus of 45 *Campylobacter* outbreaks associated with milk in England and Wales reported to the Communicable Disease Surveillance

Centre between 1980 and 1992,⁴³ ((a period when most milk sold in England and Wales was pasteurised) the vehicle was identified as unpasteurised milk in 39. In the six associated with heat-treated milk, pasteurisation or other processing failures were identified in all of them.

Quantitatively by far the most important pathway for food-borne pathogens in the UK since *Salmonella* and *Campylobacter* and *E. coli* O157 emerged has been poultry products. The *Salmonella enteritidis* pandemic has been described above as an example. Even if there are big uncertainties about the number of humans infected by *Campylobacter* strains from poultry, it is certain that contamination of chicken meat is very common. A 2001 Food Standards Agency Survey showed that 56 per cent of fresh and 31 per cent of frozen chicken samples tested were positive for *Campylobacter*.⁴⁴ About 60 per cent of housed (broiler) poultry flocks in the UK are *Campylobacter* positive at slaughter age.²¹ The proportion of *Campylobacter* contaminated carcasses is further increased by slaughterhouse practice. The Account given in the 1993 Advisory Committee on the Microbial Safety of Food Interim Report on *Campylobacter* is still pertinent.

'Poultry slaughtering is a multi-stage operation and modern plants with their emphasis on high throughput rates and automation provide ample opportunities for the cross-contamination of carcasses via soiled equipment or water. Studies have shown that campylobacters can survive various processing operations and cross-contamination can occur at a number of points on the slaughter line. These are notably via scalding tanks, plucking machines and automated evisceration equipment where damage to the internal organs may occur resulting in contamination of the carcass with gut contents.

After evisceration and final washing, carcasses are chilled either by immersion in water, blast chilling with cold air or spray chilling. The former is used primarily for birds that are to be frozen and the latter for birds to be sold fresh. Immersion chilling can increase cross-contamination. *C. jejuni* has been shown to remain viable on carcasses stored at -20°C for three months and at 4°C for seven days. Studies of retail broiler chickens have detected contamination rates between 20-100 per cent.'

This means that the slaughterhouse process has been an important amplifier, increasing the risk of infection from pathogens that contaminate poultry products, in addition to the big population of microbes in the broiler gut. Broiler profit margins are low, estimated at 3p per bird²⁶ so that there is strong commercial pressure for high throughput rates and automation.

The relationship between the amount of food consumed and its importance as a vehicle of infection is complex. *E. coli* O157:H7 is still called the 'burger bug'.⁴⁵ But this name derives mainly from a single event, the Jack-in-the-Box burger chain outbreak in the US in 1993. 732 people became ill, 195 were hospitalised, 55 had the haemolytic uraemic syndrome, and four died. The median age of those infected was 8. Cooking practices driven by consumer preference played a role. The Jack-in-the-Box cooking procedure led to a majority of burgers (rare, by customer request) having an internal temperature

below 60°C, low enough to permit the survival of viable organisms.⁴⁶ This presented an opportunity for the organism until cooking temperatures were raised.

There is, however, no evidence that burgers could be considered drivers for *E. coli* O157:H7. The onward march of the burger in the US from its first ever serving at the Louisiana Purchase Exposition at St Louis in 1904, though the first burger chain, White Castle, founded in Wichita, Kansas, in 1916, to Ray Kroc and McDonalds with \$31,812,000,000 sales in 1996⁴⁷ has nothing to do with the emergence of the organism. Human infections caused by it have always been, and remain, rare. Neither has fast food chicken played a role as a driver for *Salmonella* or *Campylobacter*. An early US franchise success was 'Chicken Delight'. It was founded by a scrap dealer who came into the possession of a large number of abandoned cookers. He developed a sealed fryer that franchisers had to use. There were 550 outlets by 1994. Colonel Sanders (Kentucky Fried Chicken) used pressure cookers and fryers. In 1994 KFC sold 1.1 billion meals (274 million chickens).⁴⁷ These cooking processes have always delivered microbiologically safe food for these businesses.

Because *Campylobacter* outbreaks are uncommon and because infections have low mortality and generally cause delayed complications such as Guillain-Barré syndrome, public awareness of the organism is low. It is this reviewer's personal experience that many journalists have not heard of it. So most infections pass under the media radar. But for *Salmonella* and *E. coli* O157 this is clearly not the case. Outbreaks are not only useful to epidemiologists in establishing the sources and pathways of infection but they provide opportunities for investigations into the outcomes of infection. And their impact on public opinion, particularly if fatalities have occurred, drives policy.

Outbreak investigations have illustrated the properties of foods that enhance the likelihood that pathogenic contaminants will cause an infection, and reveal other circumstances that amplify the risk. Human feeding experiments done under circumstances that would be considered unethical today (i.e. on prisoners)⁴⁸ found infective doses of *Salmonella* to range from 125,000 (for *S. bareilly*) to 50 million (*S. anatum*). But epidemiological studies on outbreaks have shown far lower infective doses when the organisms have been associated with particular foods. Results are shown in Table 11.

Table 11

**Estimates of the infective dose of *Salmonella* spp
(Reproduced from Ref 47)**

Foodstuff	Serovar	Infectious dose (CFU)
Cheese	<i>typhimurium</i>	1-10
Chocolate	<i>eastbourne</i>	<100
	<i>napoli</i>	10-100
	<i>typhimurium</i>	10
Maize snack	<i>agona</i>	2-45
Paprika-flavoured potato chips	<i>St Paul, javiana, rubislaw</i>	10-100
Peanut butter	<i>mbandaka</i>	10-100

Amplifiers

For *Salmonella*, even very large outbreaks only contribute a small proportion of human cases in any year. Nevertheless they illustrate amplifiers well. The outbreak at Stanley Royd Hospital in Wakefield in 1984 is paradigmatic. *Salmonella typhimurium* phage type 49 infected 355 of 788 patients and 106 of 980 staff. 19 patients died. Roast beef was contaminated, after cooking, with the juices of defrosting chickens (*S. typhimurium* PT49 is a chicken organism). The beef was then stored at 26°C for 24 hours (the kitchen was constructed in 1865, and had only one very small cold room, and there was a heatwave) before being served. Cross- contamination of ready-to-eat food and the amplification of risk by storage at temperatures suitable for bacterial growth explained the outbreak.

It was the same at Wishaw in central Scotland in 1996, where there were 275 confirmed cases of *E.coli* O157 infections, many contracted by eating meats produced by a butcher that had been contaminated in his premises. Steak pie cooked by him had been also contaminated and after delivery to a church hall, still warm, it was stored overnight unrefrigerated. 29 of those who ate it fell ill and eight died.⁵¹

Bacterial growth on and in food was the amplifier at Stanley Royd and Wishaw. The impact of these outbreaks influenced policy and led to the removal of Crown Immunity from hospitals and the introduction of licensing for butchers. Another amplifier of risk, milk, was the vector of outbreaks that had the same influence. Between 1970 and 1979 there were 29 milk-borne *Salmonella* outbreaks in Scotland.⁵² By the end of 1981 there had been ten more. Some had been very large, such as Brechin/Montrose in 1976, with 700 cases estimated (*Salmonella dublin*) and Keith 1981, 654 cases and two

deaths (*Salmonella typhimurium* PT204). From August 1983 the sale of unpasteurised milk in Scotland was prohibited.

Clinical effects of infection: amplification by secondary spread

For all the pathogens considered here, morbidity and mortality are greater at the extremes of age. Infants and the elderly are less able to withstand the dehydration caused by diarrhoea. The complications of *E. coli* O157 infection, the haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura, are much commoner in the elderly and in young children. Good examples of this are the 1994 West Lothian and the 1996 Wishaw outbreaks in Scotland. In West Lothian the organism was milk-borne. There were 72 cases. One child died. Eight children and adolescents needed kidney dialysis and three required kidney transplants. In Wishaw 17 died. All were over 70 and many were killed by kidney failure. The secondary spread of infection – its communication to other persons by someone infected by food – is also commoner at the extremes of age. Toddlers are learning about personal hygiene while forgetfulness about it is a feature of dementia.

Detection and Identification

Estimating the burden of human disease caused by food-borne pathogens requires their detection and identification. Tracking their sources and routes of spread needs high resolution typing methods which identify clones and subclones accurately. The knowledge that comes from their detection and identification is key in designing systems to deliver safe food. But testing for pathogens is not a universally central feature of such systems. It is far more important in investigating failure than as part of the system for delivering food safely. The system that underpins food safety legislation in the US and in Europe is HACCP – Hazard Analysis and Critical Control Points. It is 'a structured approach to analysing the potential hazards in an operation; identifying the points in the operation where the hazards may occur; and deciding which points are critical to control to ensure consumer safety. These critical control points are then monitored and remedial action, specified in advance, is taken if conditions at any point are not within safe limits. HACCP is both a philosophy and a practical approach to food safety.'³¹

A good example of HACCP at work relates to the pasteurisation of milk. Critical control points are the temperature reached during heating, its duration, and the measures taken to prevent contamination thereafter. Microbiological testing is not necessary to deliver bacteriologically safe milk. HACCP is based on the premise that all uncooked animal products will be contaminated with pathogens. Critical control points are designed in the knowledge of this fact, the heat sensitivity of the pathogen, and the conditions under which they will grow in a food on storage. Critical 'inflection points' in the causation of outbreaks for the pathogens considered in this review were HACCP failures, e.g. for *E. coli* O157 pasteurisation failure in West Lothian or the cross-contamination of ready-to-eat foods at Wishaw.

Without detection and testing, long-term programmes such as the eradication of bovine tuberculosis from cattle would not be possible. But earlier and better

information about the occurrence of human pathogens in food animals through testing would not in itself have acted as a 'critical inflection point' in the prevention of food-borne disease. The stimulus for the development of vaccines and the implementation of better hen house biosecurity came, in this reviewer's opinion, more from publicity about the amount of human disease caused by *Salmonella* and Mrs Edwina Currie's remarks on TV in December 1988 about its source than from information about *S. enteritidis* PT4 carriage in the UK chicken flock. Vaccines are available for *Salmonella* strains. Biosecurity reduces the likelihood that chickens will become infected. There are no vaccines for *Campylobacter* or *E.coli* O157, and no changes in animal husbandry have yet been shown to be particularly effective in reducing carriage rates. This is why their detection and identification in animals has not contributed to finding critical 'inflection points' in their control.

Conclusion

Food-borne bacterial pathogens change rapidly. Clones come and go. Some of the drivers for these changes have been identified. For agriculture in the UK 'the large quantity of her horned stock, and, above all, the enormous facility of communication by railroad, make her peculiarly liable to the ravages of a contagious disorder' is as true now (apart from the reference to 'rail') as when it was written in the First Report on the Cattle Plague in 1865.⁵⁴ But many questions remain unanswered. For example, it is a reasonable assumption that *E.coli* O157 evolved in the Americas. How did it get to the UK and spread there? It is common in cattle, so does it have a selective advantage over other members of the gut flora? Why does it retain virulence factors that only seem to be manifest in a dead-end host, the human? What is its subclonal population structure? Do subclones vary in virulence? (Note that the same subclone caused the West Lothian and Wishaw outbreaks). Why is the incidence of human infections four times greater in Scotland than in England?

In essence, all that sequencing its genome has done is to cause us to say that more needs doing. *E. coli* K12 and O157 turned out to be much more different from each other than anyone expected. The hope that the comparison would lead to the rapid identification of previously unidentified virulence factors was dashed.

For the immediate future it seems most likely that new and emerging food-borne pathogens will continue to be detected and identified through the investigation of human infections. The overwhelming majority of the clones responsible for these infections in the recent past have not been pathogenic for their main hosts, food animals. Humans have been the only reliable indicators of virulence. Exceptions, such as BSE, have been rare.

This review has restricted itself to bacterial pathogens, and their spread to humans by food. Its coverage of gastrointestinal pathogens has been incomplete because for some, other routes of spread are equally important (e.g. from the environment for *E. coli* O157⁽⁵⁵⁾) or more important (e.g. person to person and from the environment for noroviruses.⁽⁵⁶⁾)

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