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Food and Waterborne Illnesses

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Defining Statement

Introduction

Current Foodborne Illnesses Epidemiology

Specific Foodborne Microorganisms

Foodborne Illness due to Preformed Toxins

Natural Toxins

Scombroid

Ciguatera

Shellfish Poisoning

Tetrodotoxin

Aflatoxins

Foodborne Microbes that Produce Toxins following Ingestion

Infant Botulism

Foodborne Infections that Cause Disease by Mechanisms other than Toxin Production

Actions to Prevent Foodborne Illness

Further Reading

Abbreviations

AIDS	acquired immunodeficiency syndrome
Ail	attachment-invasion proteins
BIG-IV	Botulism Immune Globulin Intravenous
cAMP	cyclic adenosine monophosphate
CAST	Council for Agricultural Science and Technology
CDC	Centers for Disease Control and Prevention
CFA	colonization factor antigens
DNA	deoxyribonucleic acid
EAEC	enteroaggregative <i>E. coli</i>
EHEC	enterohemorrhagic <i>E. coli</i>
EIEC	enteroinvasive <i>E. coli</i>
EIP	Emerging Infections Program
EPEC	enteropathogenic <i>E. coli</i>
ETEC	enterotoxigenic <i>E. coli</i>

FDA	Food and Drug Administration
FoodNet	Foodborne Diseases Active Surveillance Network
GBS	Guillain–Barré syndrome
GMP	guanosine monophosphate
HPLC	high-performance liquid chromatography
HUS	hemolytic uremic syndrome
Inv	Invasin
NLV	Norwalk-like virus
STEC	Shiga toxin-producing <i>E. coli</i>
Stx	Shiga toxins
TDH	thermostable direct hemolysin
USDA	US Department of Agriculture
Yop	<i>Yersinia</i> outer protein
Yst	<i>Yersinia</i> enterotoxin

Defining Statement

The topic under discussion is foodborne illness. While there are many causes of foodborne illness the focus of this text is on microbes. The text approaches the issues by discussing illness due to toxins preformed in foods and toxins made once the microbes have been ingested, illness due to other mechanisms that affect the gastrointestinal tract, and finally foodborne illness that has manifestations other than purely gastrointestinal. A wide variety of the common foodborne pathogens is discussed, with a brief description of what they are, the types of illness they cause, and the kinds of food

most frequently associated with them along with some commentary with regard to treatment.

Introduction

Food- and waterborne illness typically brings to mind the image of an individual who develops an acute gastrointestinal illness following exposure to contaminated food or water. However, the definition of illness that may be attributed to food or water is broad and encompasses exposure to toxins, carcinogens, metals, prions, allergens,

Table 1 Bacterial, viral, protozoal, and toxic agents that are associated with food- and waterborne illness in humans**Bacterial pathogens****Bacteria causing disease primarily mediated by a preformed toxin**

Clostridium botulinum
Staphylococcus aureus
Bacillus cereus

Bacteria causing disease by production of toxins within the intestine

Vibrio species
Clostridium perfringens
 STEC
 ETEC

Bacteria causing disease primarily by invading the intestinal epithelial cells

Salmonella spp.
Campylobacter spp.
Yersinia spp.
Listeria monocytogenes
Shigella spp.
 EIEC

Other bacterial causes of foodborne illness

Aeromonas spp.
Plesiomonas shigelloides
 EPEC
 EAEC
Enterobacter sakazakii

Viral pathogens

Hepatitis A virus
 Hepatitis E virus
 Rotavirus
 Noroviruses
 Enteric adenovirus
 Coronaviruses
 Toroviruses
 Reoviruses
 Saporo-like viruses
 Astroviruses
 Parvoviruses
 Picobirnaviruses

Protozoal pathogens

Toxoplasma gondii
Cryptosporidium parvum
Giardia lamblia
Entamoeba histolytica
Cyclospora cayetanensis
Microsporidium (Enterocytozon bieneusi, Septata intestinalis)
Isospora belli
Dientamoeba fragilis
Blastocystis hominis

Cestodes and worms

Taenia saginata
Taenia solium
Diphyllobothrium latum
Hymenolepis nana
 Ascariasis
 Trichuriasis
Trichinella spiralis

Natural toxins

Ciguatera
 Scrombroid

Shellfish poisoning (neurotoxic, diarrheic, and toxic-encephalopathic)

Tetrodotoxin
 Mushroom toxins
 Aflatoxins

and other factors, in addition to the classic infective pathogens. As reviewing each of these agents in detail is beyond the scope of this article, our focus will be on food- and waterborne infections only; an extensive list of foodborne pathogens is given in **Table 1**. This article discusses the current epidemiology of foodborne illness, provides an overview of the various toxins and organisms considered to be the more important foodborne agents, and discusses some preventative approaches that can be used to help ensure consumers stay safe with regard to the food they prepare and eat at home. The clinical symptoms, treatment, and long-term consequences of various foodborne infections are also briefly reviewed.

Foodborne illness typically consists of acute gastrointestinal upset with nausea, vomiting, diarrhea, and abdominal cramps. Typically, symptoms resolve without the need for significant medical intervention and without long-term consequence. However, on occasion foodborne infection causes severe illness or death. Unfortunately, in the early stages of illness, differentiating between a patient with an inconsequential infection and the patient who may develop life-threatening sequelae can be difficult. Some systemic consequences of infection occur several days or weeks after the initial exposure. Examples include the hemolytic uremic syndrome (HUS) secondary to Shiga toxin-producing *Escherichia coli* (STEC), the development of Guillain-Barré syndrome (GBS) after *Campylobacter* infection, and the association of a number of enteric bacterial pathogens with reactive arthritis and postinfectious irritable bowel syndrome.

Current Foodborne Illnesses Epidemiology

The true burden of foodborne illnesses in the United States and in other parts of the world is largely unknown; however, the number of suspected deaths worldwide from foodborne pathogen exposure is staggering. Several million children die each year worldwide from acute diarrheal disease and resulting dehydration, the majority of which is likely due to contaminated food or water. In the United States, until recently, we had very little data on the numbers and outcomes of foodborne infection. The development of the Foodborne Diseases Active Surveillance Network (FoodNet) in 1996 by the Centers for Disease Control and Prevention (CDC) has provided, for the first time, the opportunity to determine the epidemiology of foodborne disease in the US population. FoodNet is the

main foodborne disease component of the CDC's Emerging Infections Program (EIP), and is a collaborative venture with EIP program sites, the US Department of Agriculture (USDA), and the Food and Drug Administration (FDA). FoodNet performs population-based active surveillance for confirmed cases of *Campylobacter*, *E. coli* O157:H7, *Listeria*, *Salmonella*, *Shigella*, *Vibrio*, *Yersinia*, and HUS, as well as *Cryptosporidium* and *Cyclospora* infections. In 2006, surveillance occurred within a defined population of 44.9 million Americans using information from clinical microbiology laboratories in ten states. FoodNet monitors only confirmed cases of diarrheal infection, missing cases that never present to medical attention. However, through additional surveys, FoodNet has the capacity to determine the frequency of diarrhea and the number of physician visits within the study population. Utilizing FoodNet and other data, the CDC provides our current best estimate of the true burden of foodborne infections in the United States.

Mead and his colleagues from the CDC estimate that there are 76 million illnesses, 325 000 hospitalizations, and 5000 deaths annually due to foodborne infections. This means that, on average, somewhere between one in three and one in four Americans will have a foodborne infection each year. While these data provide an excellent estimate of disease prevalence in the United States, they also illustrate some major gaps in our knowledge of foodborne infections. Specifically, determining attribution can be very difficult. For example, in the context of sporadic infections, the precise food that has caused the illness and the point at which the food was contaminated are usually unknown. Or indeed whether the infection was acquired through person-to-person spread or by some other route is difficult to ascertain. Also, in 62 million cases, or 82% of the estimated 76 million infections each year, no specific pathogen is identified. Disease due to unidentified agents results in 265 000 hospitalizations and 3200 deaths, which begs the question as to whether these are due to known pathogens or foodborne infections yet to be discovered.

Our ignorance as to the cause of more than 80% of the estimated foodborne illness is a daunting problem. However, many new agents have been discovered and linked to foodborne disease in the last 30 years. Table 2 offers a list of some recently described food- and waterborne pathogens, some are new pathogens and others are agents previously recognised but infrequently linked to illness or considered nonpathogenic. For example, *Campylobacter jejuni* was once thought to be an unusual cause of bacteremia but is now known to be one of the most frequent bacterial causes of enteritis in the United States.

In 2006, the most recent year for which preliminary FoodNet data are available, the CDC confirmed 17 252 laboratory-confirmed cases of infections from the FoodNet sites. Incidence varied dramatically between the FoodNet sites. For example, *Campylobacter* affected 6.27 per 100 000

people in Georgia and 26.82 per 100 000 in California. *Salmonella* infections varied from 11.01 per 100 000 in Oregon to 20.04 per 100 000 in Georgia. Though the explanation for these geographic differences is unknown, they seem to suggest true regional variation of foodborne pathogens.

Another trend observed in FoodNet data was the preponderance of cases in the young and elderly. In 2006, FoodNet identified 71 cases of HUS in children aged below 18 years (rate: 0.68 per 100 000 children); 47 (66%) of these cases occurred in children aged below 5 years (rate: 1.63). Across all age groups, clinical outcomes differed by pathogen. While the total number of *Listeria monocytogenes* and *E. coli* O157:H7 infections were less than for some of the other pathogens, they were associated with much higher hospitalization rates and death rates than any of the other bacterial pathogens monitored (Table 3). Table 3 reflects the lack of correlation between the propensity for an organism to cause disease and its propensity to result in the death of the patient.

Since FoodNet began to operate in 1996, the accumulated data have also revealed a seasonal trend, with a spike in infection with the three major pathogens (*Salmonella*, *C. jejuni*, and *E. coli* O157:H7) during the summer months (Figure 1). The summer predominance of bacterial

Table 2 Examples of foodborne pathogens described since 1977

<i>Campylobacter jejuni</i>
<i>Campylobacter fetus</i> spp. <i>fetus</i>
<i>Cryptosporidium parvum</i>
<i>Cyclospora cayentanesis</i>
<i>Enterobacter sakazakii</i>
STEC (e.g., O157:H7, O111:H8)
<i>Listeria monocytogenes</i>
Noroviruses
<i>Salmonella enteritidis</i>
<i>Salmonella typhimurium</i> DT104
Spongiform encephalopathy prions
<i>Vibrio cholerae</i> O139
<i>Vibrio vulnificus</i>
<i>Vibrio parahaemolyticus</i>
<i>Yersinia enterocolitica</i>

Table 3 Death rates of the common foodborne bacteria

Organism	Number of deaths/infections	% of deaths per infection
<i>Listeria</i>	19/119	16.0
<i>E. coli</i> O157:H7	4/402	1.0
<i>Salmonella</i>	38/6498	0.58
<i>Shigella</i>	3/2248	0.001
<i>Campylobacter</i>	9/5684	0.002
<i>Vibrio</i>	5/123	4.07
<i>Yersinia</i>	1/176	0.57

From FoodNet 2004 Surveillance Results, Centers for Disease Control and Prevention.

foodborne infections is likely multifactorial. Clearly, warmer weather allows for more rapid bacterial growth on food that is improperly refrigerated. Consumer habits also change in the warmer months, with more picnics and barbecues, contributing to problems with keeping food refrigerated, increased risk of cross contamination, and so on. FoodNet surveillance effectively monitors trends in the rates of infection over time and there have been a number of changes since FoodNet surveillance began, with the estimated annual incidence of several infections

changing significantly from baseline to 2006 (Figure 2). The estimated incidence of infection with *Yersinia* decreased 50% (CI = 37–60%), *Shigella* decreased 35% (CI = 8–54%), *Listeria* decreased 34% (CI = 17–47%), *Campylobacter* decreased 30% (CI = 24–35%), and *Vibrio* increased 78% (CI = 34–138%). The estimated incidence of *Cryptosporidium*, *Salmonella*, and STEC O157 did not change significantly compared with the baseline. Although *Salmonella* incidence did not decrease significantly overall, the incidence of *Salmonella typhimurium*

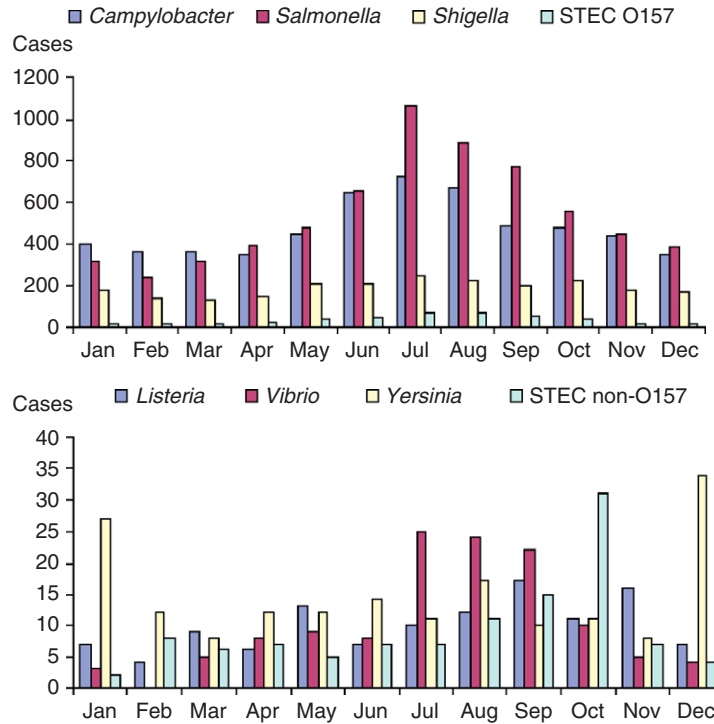


Figure 1 Cases of foodborne disease caused by specific pathogens, by month, FoodNet sites, 2004. From FoodNet Surveillance Report for 2004 (Final Report).

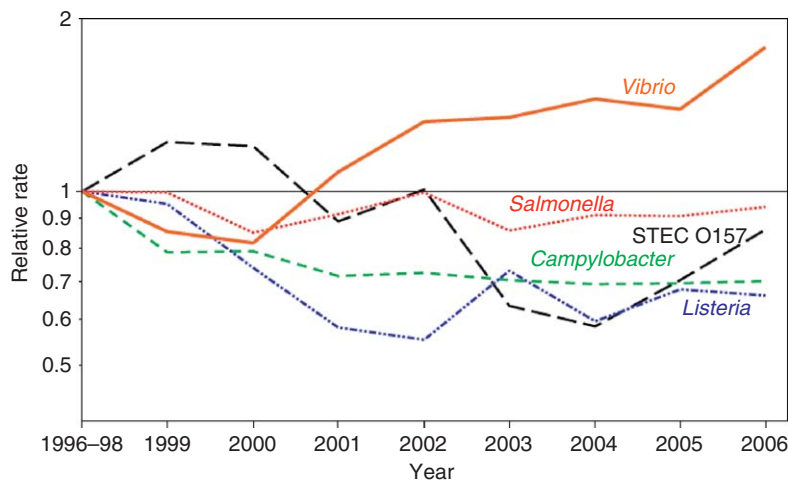


Figure 2 Relative rates compared with the 1996–98 baseline period of laboratory-diagnosed cases of infection with *Campylobacter*, STEC O157, *Listeria*, *Salmonella*, and *Vibrio* by year.

decreased significantly (41% CI = 34–48%). In contrast, significant increases in incidence compared with baseline occurred for *Salmonella enteritidis* (28%, CI = 4–57%), *Salmonella newport* (42%, CI = 7–87%), and *Salmonella javiana* (92%, CI = 22–202%). The estimated incidence of *Salmonella heidelberg* and *Salmonella montevideo* did not change significantly compared with baseline.

While FoodNet produces excellent data on the epidemiology of foodborne illness overall, it has several important areas of weakness. It does not survey for many of the common foodborne pathogens, including viruses, which are thought to cause the vast majority of foodborne illness. Similarly, it does not address the cause of illness in patients who do not have a stool sample sent for analysis: those who either do not seek medical care or do seek care but do not have a stool sample analyzed. In an adjunctive study reported by the CDC, 11% of 10 000 residents interviewed through random phone consultations reported an episode of diarrhea during the previous month. This translates to 1.4 episodes of diarrhea per person per year, which if multiplied roughly by the population of the United States, represents ~375 million diarrheal cases per year. In this study, merely 8% of those with a diarrheal episode sought medical care, and of those, only 20% reported submitting a stool sample for culture. Thus, our best data on the causes of acute gastrointestinal disturbance from FoodNet surveillance are based on cultures of less than 2% of diarrheal episodes. Nonetheless, despite the current limitations of our evaluation of foodborne illness, the endeavors of state, local, and federal authorities have been critical to improving our knowledge of disease frequency, pathogen epidemiology, and the establishment of control systems to limit food contamination. The knowledge gained from FoodNet surveillance allows for targeted efforts to improve food safety and education.

Specific Foodborne Microorganisms

As noted previously, the diversity of foodborne pathogens listed in **Table 1** is far too extensive to be discussed completely within the scope of this article. In the following sections therefore, many of these microbial agents will be discussed briefly with a focus on typical modes of transmission, the foods they frequently contaminate, and the specific serious consequences that may ensue from infection. Although foodborne agents cause disease by a wide variety of mechanisms, the mode of infection often falls into one of the following three categories: (1) ingestion of preformed toxins produced by bacteria in food prior to consumption; (2) infection with pathogens present in food which, following ingestion, produce toxins in the gastrointestinal tract; and (3) infection with organisms having various virulence factors that permit the microbes

to be invasive, cause local damage, or create physiologic perturbations that result in clinical disease.

Foodborne Illness due to Preformed Toxins

Of the three mechanisms, the preformed toxin is the most consistently transmitted via food. As each toxigenic organism requires a specific environment to stimulate toxin production, each has a predilection for certain types of food. As a result, different types of foods confer different risks for toxin ingestion. The major toxins of the common foodborne pathogens are discussed in detail in the next few sections and were reviewed by Sears and Kaper in 1996.

Clostridium botulinum Toxins

C. botulinum produces one of the best-known and deadly preformed toxins. The organism's natural habitat is soil, and therefore, its spores frequently contaminate fresh fruits and vegetables. Commercial food sources have been occasionally implicated, but the majority of outbreaks have been traced to home-canned foods, especially vegetables, fruits, fish, and condiments. Recent outbreaks have been attributed to chili, carrot juice, and home-prepared fermented tofu. Generally the disease is rare, and in the United Kingdom, only 62 cases have been recognized between 1922 and 2005. A recent report from the United Kingdom provides a brief review of *C. botulinum* and foodborne botulism as well as descriptions of the six episodes (33 cases with three deaths) of this disease that occurred in the United Kingdom between 1989 and 2005.

To prevent botulism, the *Clostridium* spores must be destroyed by heating food to a temperature of 120 °C for 30 min, usually with the aid of a pressure cooker. In an anaerobic environment with a pH above 4.6, any surviving spores will germinate and produce their deadly toxins.

There are seven antigenically distinct types of botulinum toxin, each of which is designated by a letter, A–G. Types A, B, E, F, and G are associated with human disease, with type A accounting for about 25% of outbreaks and type B 8%. Once ingested, the toxin is absorbed through the proximal small intestine and spreads via the bloodstream to the peripheral cholinergic nerve synapses where it irreversibly blocks acetylcholine release. A flaccid paralysis results, with cranial nerves affected first, followed by respiratory muscle paralysis and death if left untreated.

The diagnosis of botulism is clinical and treatment should be initiated prior to confirmation with laboratory data, as the traditional mouse bioassay for toxin detection requires ~4 days for final results. Samples such as food, vomitus, serum, gastrointestinal washings, and feces are all reasonable specimens to test. Newer PCR- and enzyme

immunoassay-based detection methods are now being used. Early in the course of disease, treatment may include emetics or gastric lavage to remove unabsorbed toxin. A trivalent (A, B, E) horse serum antitoxin decreases the progression and duration of paralysis, but it does not reverse existing paralysis. Pentavalent and heptavalent antitoxins are also being investigated. Human Botulism Immune Globulin Intravenous (BIG-IV) may also be beneficial. Botulism carries a significant mortality rate, of up to 25%, with type A toxin. Of those who survive the acute phase of illness, most recover completely. See later in the article for a discussion of infant botulism, which is a similar condition but not due to preformed toxin.

***Staphylococcus aureus* Toxin**

A second well-known group of preformed toxins are those produced by *S. aureus*. *S. aureus* produces a variety of enterotoxins, defined by their antigenicity as enterotoxins A–H. Staphylococcal enterotoxins A through G are responsible for 95% of staphylococcal food poisoning outbreaks. On rare occasions, other staphylococcal species, including coagulase negative staphylococci, have been found to produce similar enterotoxins. The toxins are small proteins with similar tertiary structures and biologic activity, including superantigen properties. Ingestion of as little of 100–200 ng of toxin is considered sufficient to cause disease in humans. Compared with botulinum toxin, staphylococcal toxins are not inactivated by heating or boiling; nor are they susceptible to pH extremes, proteases, or radiation. As a result, once formed in food, these toxins are almost impossible to remove.

The mechanism through which the toxin acts is not fully understood, but is suspected to be via stimulation of the autonomic nervous system and gut inflammation. As the toxin is not absorbed systemically, protective immunity is not induced following exposure. Typically, patients become symptomatic between 1 and 7 h after ingestion of the food containing staphylococcal enterotoxin, with nausea (73–90%), vomiting (82%), and abdominal cramps (64–74%). Diarrhea occurs in a large proportion of patients (41–88%), but fever is rare. Treatment of affected individuals is supportive and symptoms usually abate within 2 days. There is no need to treat with antibiotics directed toward *S. aureus*.

S. aureus is present in the mucous membranes and skin of most warm-blooded animals. Food is most often contaminated with *S. aureus* through the fingers or nose of a food worker. The toxin is produced when contaminated food is stored at room temperature for a sufficient length of time to allow the organism to grow and produce toxin. The bacterial population must be greater than 10^5 organisms per gram of contaminated food before appreciable amounts of toxin will be produced to elicit illness. A number of different foods have been associated with

staphylococcal food poisoning, including egg products, cooked meat products, poultry, tuna, mayonnaise, and particularly cream-filled desserts and cakes. This disease is more frequently associated with food from the home or a service establishment rather than commercially prepared food. It has also occasionally occurred in large outbreaks with thousands of affected individuals.

***Bacillus cereus* Toxin**

A third example of preformed toxins are those of *B. cereus*, a Gram-positive, spore forming aerobe that causes two distinct clinical syndromes: a short-incubation period emetic syndrome and a long-incubation period diarrheal syndrome. The organism is known to produce up to three enterotoxins. Cereulide and the tripartite hemolysin BL have been identified specifically as emetic and diarrheal toxins, respectively. Nonhemolytic enterotoxin, a homologue of hemolysin BL, has also been associated with the diarrheal syndrome. The toxins associated with the diarrheal illness are not preformed but produced by the organism during the vegetative growth phase in the small intestine. The emetic toxin, named cereulide, is thought to be an enzymatically synthesized peptide produced as the organism grows in food, especially starchy foods such as rice and pasta. Like staphylococcal toxin, cereulide is resistant to heat, pH variation, and proteolysis, and is therefore rarely destroyed during food preparation. Its exact pathogenic mechanism remains unknown, but it has been shown to stimulate the vagus afferent by binding to the 5-HT₃ receptor. The emetic syndrome presents much like *S. aureus*-related foodborne disease, occurring 1–6 h after exposure and causing nausea and vomiting. Fever is not characteristic of the illness and full recovery usually occurs. Diagnosis can be made by finding the organism in the food or vomitus of the patient, or through detection of the emetic toxin through bioassays or the enterotoxins by commercial immunoassays. New approaches include the use of real-time PCR to detect Cereulide-producing *B. cereus* genes in potentially contaminated food.

Natural Toxins

Derived from various types of food, a number of naturally occurring toxins may cause human foodborne illness. Many are associated with consumption of seafood contaminated by algae. Others are due to fungal contamination of food or inherent to certain fruits and vegetables.

Scombroid

Scombroid poisoning typically occurs after the ingestion of spoiled, dark-fleshed fish, especially tuna and mackerel.

The clinical symptoms of poisoning, including flushing, headache, palpitations, dizziness, nausea, vomiting, and diarrhea, are attributable to excess levels of histamine present in temperature-abused fish. Histamine is produced by bacterial metabolism of the amino acid histidine in fish muscle. Bacterial replication and histamine production occur when fish is not frozen promptly after being caught or is stored at room temperature for several hours. Symptoms of intoxication begin within minutes to several hours following ingestion. Most resolve fully within hours, but, occasionally, bronchospasm or circulatory collapse may occur. The diagnosis is clinical, and treatment consists of antihistamines. Elevated histamine levels in the contaminated fish or the patient's serum may be diagnostic, but few laboratories, other than regulatory laboratories, are equipped to undertake this analysis.

Ciguatera

Ciguatera poisoning is due to the ingestion of neurotoxins from tropical and subtropical marine fin fish, including mackerel, groupers, barracudas, snappers, amberjack, and triggerfish. It affects 50 000 individuals yearly, mainly in the Caribbean and South Pacific islands. The toxin is produced in reef algae, the dinoflagellates (e.g., *Gambierdiscus toxicus*). It spreads through the food chain via consumption of smaller organisms and fish by larger predators, accumulating at dangerous levels in the flesh of large fish. Two groups of compounds are implicated in ciguatera fish poisoning: the lipid-soluble ciguatoxins, which activate nerve synapse sodium channels, and the water-soluble maitotoxin, which induces neurotransmitter release by binding to calcium channels. In humans, these toxins cause gastrointestinal symptoms 3–6 h after ingestion, including nausea, vomiting, and watery diarrhea. Neurologic symptoms follow, with weakness, heat–cold temperature reversal, vertigo, ataxia, paresthesias, and dysaesthesias of the perioral region, palms, and soles. Death and serious cardiovascular complications are uncommon. Most symptoms resolve within a week, but neurologic symptoms can persist for months. The diagnosis of ciguatera is clinical; however, the toxin can be detected in fish using a mouse bioassay or newer enzyme immunoassays.

Shellfish Poisoning

Five main types of shellfish poisoning have been described: paralytic, neurotoxic, diarrhetic, amnesic, and azaspiracid. Like ciguatera, illness is due to toxins generated by algae, usually dinoflagellates, which accumulate in the shellfish. The paralytic variant of shellfish poisoning is due to saxitoxin, an agent that blocks neuronal sodium channels and prevents propagation of the action potential.

Clinically, this results in a rapid-onset, life-threatening paralysis. Brevetoxin, the agent responsible for neurotoxic shellfish poisoning, also binds sodium channels but does not cause paralysis; instead, it produces a clinical syndrome similar to but less severe than ciguatera. Symptoms of nausea, vomiting, and paresthesias occur within hours of exposure and resolve completely within 3 days. Diarrhetic shellfish poisoning causes gastrointestinal disturbance with nausea, vomiting, and diarrhea. The toxin acts by increasing protein phosphorylation.

Amnesic shellfish poisoning, also known as toxic encephalopathic poisoning, causes outbreaks of disease in association with consumption of mussels. Manifestations include nausea, vomiting, diarrhea, severe headache, and, occasionally, memory loss. The toxin domoic acid is a glutamate receptor agonist that causes excitatory cell death.

Diagnosis of human illness due to shellfish toxins is clinical based on symptom profile and prompt onset of symptoms after shellfish consumption. The exception to this is amnesic poisoning, which may not cause symptoms until 24–48 h after exposure. The toxins can be detected using either mouse bioassays or high-performance liquid chromatography (HPLC), but this is done primarily for research purposes or in monitoring. Owing to the serious consequence of shellfish poisoning, large-scale surveillance systems for contamination of shellfish populations have been implemented.

Tetrodotoxin

Tetrodotoxin is present in certain organs of the puffer fish and if ingested can cause rapid paralysis and death. Symptoms may occur in as little as 20 min or after several hours. The illness progresses from gastrointestinal disturbance to almost total paralysis, cardiac arrhythmias, and death within 4–6 h after ingestion of the toxin. The diagnosis is clinical and based on history of exposure. Mouse bioassays and HPLC have been used to detect tetrodotoxin in food.

Aflatoxins

Aflatoxins are produced by certain strains of fungi (e.g., *Aspergillus flavus* and *Aspergillus parasiticus*) that grow in various types of food. Most human exposure occurs through mold-contaminated corn or nuts, especially tree nuts (Brazil nuts, pecans, pistachio nuts, and walnuts), peanuts, and other oilseeds. Because mycotoxins can be produced prior to or after harvest, eliminating them from food is nearly impossible. Aflatoxin B1 is the most common and toxic, but there are several types of toxins (B2, G1, and G2). They are potent mutagens and carcinogens, with B1 causing deoxyribonucleic acid (DNA) damage in

the P53 tumor suppressor gene. Exposure to the aflatoxin predisposes the patient to hepatocellular carcinoma, especially in conjunction with chronic hepatitis B infection. With a high ingested dose of aflatoxin, a condition known as aflatoxicosis may occur, characterized by fever, jaundice, abdominal pain, and vomiting. Aflatoxin exposure is common in Asia and parts of Africa but uncommon in the United States. The diagnosis is clinical, but assays to detect the toxins in food exist. Serum and urine markers have also been developed to quantify exposure.

Foodborne Microbes that Produce Toxins following Ingestion

Vibrios

Currently, there are over 40 *Vibrio* species, a group of Gram-negative marine organisms, most of which are not human pathogens. The most common and severe human illness is caused by *Vibrio cholerae* O1, the species responsible for seven cholera pandemics. The previous six were caused by the 'classic' biotype and the seventh pandemic, which began in 1961, was caused by the 'El Tor' biotype. In the United States, cholera is mainly acquired through consumption of Gulf Coast seafood or through foreign travel. A clean water supply is critical to cholera prevention, as the organism is resistant to washing, refrigeration, and freezing of a wide variety of seafood and fresh produce.

Because stomach acidity does kill many of the organisms, more than 10^6 *V. cholerae* are usually required for infection; those with decreased gastric acidity may be infected with lower doses. The incubation period is usually 1–3 days, but may be as short as a few hours or as long as 5 days. Infection causes voluminous watery diarrhea. Hypotension and shock may result within the first 12 h of infection. The primary virulence factor is the cholera toxin, which targets an intestinal G-protein, producing cyclic adenosine monophosphate (cAMP). The increase in cAMP produces watery diarrhea by inhibiting intestinal sodium absorption and increasing chloride and bicarbonate secretion. The toxin is transmitted to the organism via a bacteriophage. Indeed, in recent years a new pathogen, *V. cholerae* O139, evolved in the Indian subcontinent. Non-O1 strains were not previously associated with human epidemics, but this pathogen appears to have acquired the cholera toxin and other virulence factors through horizontal transmission and bacteriophage infection.

Vibrio parahaemolyticus also inhabits marine environments and is acquired principally through the ingestion of raw shellfish. This *Vibrio* has been a major foodborne pathogen in Japan, but is less common in the United States. In recent years there has been global dissemination of *V. parahaemolyticus* serotype O3-K6.

Infection is characterized by diarrhea, abdominal cramps, nausea, and vomiting, with fever and chills present

in about 25% of cases. Dysentery occurs in a minority of patients, more often in children than in adults. Occasionally, wound infections and septicemia occur. Symptoms may appear in as little as 4 h, but are typically present 12–24 h after exposure. Disease is attributed to a 23 kDa protein called thermostable direct hemolysin (TDH). The gastroenteritis is usually self-limiting. Patients require fluids, and antibiotics may be useful if intestinal symptoms persist.

Vibrio vulnificus is another free-living estuarine organism that is frequently isolated from shellfish, most often acquired through raw oyster or clam consumption. It is the most common life-threatening *Vibrio* infection in the United States. Individuals with diabetes, immunosuppressive disorders, and liver disease including hemochromatosis and alcoholic liver disease are especially susceptible to infection. In these groups the case fatality ratio may exceed 50%. Infection presents with fevers, chills, nausea, vomiting, and diarrhea. Hypotension and sepsis ensue. Large hemorrhagic bullae erupt and progress to necrotic ulcers. *V. vulnificus* is an encapsulated organism, thereby resistant to the bactericidal activity of normal human serum. The pathogenesis of *V. vulnificus* is not well understood but has been summarized recently by Gulig and colleagues.

The organisms are sensitive to the amount of transferrin-bound iron in the host, which may explain the increased susceptibility in patients with hemochromatosis. Definitive diagnosis may be made from blood, stool, or wound cultures. Due to the severity of infection, antibiotics should be initiated promptly. *V. vulnificus* is susceptible to many antimicrobials, including tetracycline, ciprofloxacin, trimethoprim–sulfamethoxazole, ampicillin, and chloramphenicol.

Clostridia

Clostridium perfringens is an anaerobic, spore-forming, Gram-positive rod associated with two distinct types of foodborne disease. The species has been divided into five distinct types, A–E. Type A causes the majority of human infections and is usually linked to the consumption of meat or poultry (typically high-protein foods) that have been stored between 15 and 60 °C for more than 2 h. At this temperature, clostridial spores germinate and begin vegetative growth. At an infective dose of 10^5 vegetative cells, ingested clostridial spores transiently colonize portions of the intestine and produce enterotoxin. Ingestion of preformed toxin or nongerminated spores will not usually result in disease. The enterotoxin (CPE) is a heat-labile 35 kDa protein encoded by the *cpe* gene. *C. perfringens* types A, C, and D all carry this gene, but for unclear reasons only type A is frequently associated with foodborne disease. CPE functions by a complex mechanism, inserting itself into the host cell membrane and altering membrane permeability.

Clinically, diarrhea and severe abdominal cramps develop 6–14 h after exposure; vomiting and fever are less common. Diagnosis is complicated by the presence of *C. perfringens* in the bowel microflora of many asymptomatic individuals. However, a number of tests are able to detect the enterotoxins in stool, including enzyme immunoassays or latex agglutination.

C. perfringens type C causes the second distinct foodborne illness, mainly in developing countries. It causes a necrotizing enterocolitis seen in the context of malnutrition. The type C strains produce enterotoxin and type ‘a’ and ‘b’ toxins. The b toxin appears to be responsible for the cell necrosis associated with infection. As the b toxin is inactivated by intestinal proteases, illness occurs in patients in whom these enzymes are inadequate (e.g., in malnutrition) or in the presence of trypsin inhibitors found in undercooked pork or sweet potatoes.

Infant Botulism

Infant botulism results from the germination of ingested spores of botulinum toxin-producing clostridia that colonize the large intestine. The spores germinate within the intestine and produce botulinum toxin. Of the various potential environment sources such as soil, dust, and foods, honey is the one dietary reservoir of *C. botulinum* spores that has definitively been linked to infant botulism by both laboratory and epidemiological studies. Children aged ≤12 months are very susceptible to developing infant botulism. Honey continues to be an important exposure source in young infants and cases continue to occur. Jars of honey bear a label advising parents to not feed honey to children less than 12 months old.

E. coli

The two main *E. coli* species associated with foodborne illness are STEC and enterotoxigenic *E. coli* (ETEC). The former are relative newcomers to the scene of foodborne pathogens. The first STEC to be associated with disease in humans was *E. coli* O157:H7 following two outbreaks of hemorrhagic colitis in 1982. Since then, at least 60 different serotypes of STEC have been associated with clinical disease and have become recognized as the most common cause of HUS. Not all STEC have been associated with human illness and the more virulent forms are often referred to as enterohemorrhagic *E. coli* (EHEC) that are characterized by having the ability to attach and efface intestinal epithelium, produce Shiga toxins (Stx), and carry a specific plasmid. STEC bacteria colonize the intestinal tracts of many mammalian species, particularly ruminants (cattle, sheep, and goats). Most human illness is due to the ingestion of contaminated bovine products, but an increasing number of reports associate infection with

fecally contaminated fresh produce (lettuce, alfalfa sprouts, unpasteurized apple cider, spinach) and water.

One of the key virulence factors of STEC is bacteriophage-encoded Stx. The two main types are Stx1 and Stx2, but there are at least five subtypes of Stx2 (Stx2, 2c, 2d, 2e, and 2f). The infectious dose of some STEC (e.g., O157:H7) is known to be very low, in the region of 10–100 organisms. Symptoms typically develop 2–4 days after ingestion, but may occur in as little as 1 day or as long as 8 days. Nonbloody or bloody diarrhea is the primary acute manifestation.

Treatment of STEC and its major complications is currently largely supportive. Controversy exists as to the role of antibiotics, with concern that treatment of pediatric patients with certain antimicrobials (e.g., fluoroquinolones and trimethoprim–sulfamethoxazole) may actually increase the likelihood of serious complications such as HUS. Several recent reviews relating to foodborne *E. coli* infections have been written, and the reader is referred to them for more details.

A well-described example of a long-term consequence following infection with a foodborne and waterborne pathogen is the HUS resulting from STEC infection. In the United States, 1.5% of patients will require a renal transplant following HUS. In up to 20% of patients with HUS, the pancreas is also damaged, causing some patients to develop permanent diabetes mellitus.

ETEC infection is a common cause of disease in developing countries, and is frequently associated with travelers’ diarrhea. ETEC are transmitted through contaminated water and food and have caused a number of large outbreaks in the United States; however, their importance in sporadic disease is not known. Incubation periods range from 12 h to 2 days, and typical symptoms are abdominal discomfort and watery, nonbloody diarrhea without fever. ETEC have two significant virulence characteristics: the ability to colonize the intestine and the capacity to produce enterotoxins. A variety of colonization factor antigens (CFA) and two different types of toxins, known as heat-stable (ST) and heat-labile (LT) toxins, have been found in ETEC. The ST group consists of small peptides that effect intracellular concentrations of cyclic guanosine monophosphate (GMP). The LT toxins are structurally and functionally much like the cholera toxin. Oral rehydration is the mainstay of treatment and is often life saving for infants. Antibiotic therapy is not routinely required.

Foodborne Infections that Cause Disease by Mechanisms other than Toxin Production

Salmonella

Salmonella are one of the most common causes of foodborne illness in humans. They can be divided into two

broad categories: those that cause typhoid and those that do not. The typhoidal *Salmonella*, such as *S. typhi* and *S. paratyphi*, colonize humans and are acquired through the consumption of food or water contaminated with human fecal material. The much larger group of nontyphoidal *Salmonella* are found in the intestines of other mammals and, therefore, are transmitted through food or water that has been contaminated with fecal material from a wide variety of animals and poultry. More than 2300 serovars of *Salmonella* are differentiated by their somatic (O) antigens and flagellar (H) antigens.

In the United States, most typhoid is the result of food contamination by an asymptomatic chronic carrier, or from foreign travel. Typhoid fever continues to be a global health problem, but is uncommon in the United States; only 60 outbreaks occurred between 1960 and 1999. In contrast, the number of cases of nontyphoidal *Salmonella* increased steadily over the last four decades. *S. enteritidis* infection due to contamination of hen eggs is a particular problem, with an estimated contamination rate of 1 in 10 000 eggs. The bacteria penetrate intact eggs lying in fecal material or infect them transovarially before the shell is formed. Other common sources of nontyphoidal salmonellosis are inadequately pasteurized milk, foods prepared with raw eggs, meat, poultry, and fecally contaminated fresh produce.

The infectious dose of *S. typhi* is thought to be around 10^5 organisms. Typhoid infection is characterized by high fevers, abdominal discomfort, and a rose-colored macular rash. The infective dose of nontyphoidal *Salmonella* may vary from <100 to 10^6 depending on the host, the food vehicle, and the type of *Salmonella*. These species tend to cause bloody or nonbloody diarrhea, fever, nausea, vomiting, and abdominal discomfort. In all types of *Salmonella* the most critical virulence determinant is their ability to cross the intestinal epithelium and cause invasive disease. The most pressing problem regarding *Salmonella* is the emergence of multidrug-resistant strains. For example, *S. typhimurium* phage type DT104 is resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. In Europe quinolone-resistant strains of *Salmonella* have been detected.

Campylobacter

Campylobacter, which was not recognized as a foodborne pathogen until the mid 1970s, is now one of the most common bacterial foodborne infections diagnosed in the United States. *Campylobacter* are Gram-negative, spiral, microaerophilic organisms. Two species of *Campylobacter*, *C. jejuni* and *C. coli*, are responsible for the vast majority of human disease, with *C. jejuni* causing 90% of infections and *C. coli* near 10%. *Campylobacter fetus*, *Campylobacter upsaliensis*, *Campylobacter hyointestinalis*, and *Campylobacter lari* have occasionally been associated with gastroenteritis.

In human studies, infectious doses as low as 100 organisms may result in disease, and one drop of chicken juice may contain 500 infectious organisms. *Campylobacter* are more frequently associated with sporadic disease than with outbreaks, and person-to-person spread does not appear to be common. *C. jejuni* and *C. coli* are intestinal commensals in many animals and birds, including domestic pets. The main vehicle for human infection is poultry, but other raw meats, milk, and water have also been implicated. Surface water can be contaminated with *Campylobacter* and waterborne outbreaks have been reported.

The pathogenicity of *Campylobacter* depends on its motility; *in vitro*, nonmotile strains are not capable of invading intestinal epithelial cells. Typical infection causes diffuse colonic inflammation with marked inflammatory cell infiltration of the lamina propria, which may be mistaken for inflammatory bowel disease. Symptoms usually occur within 2–3 days after exposure, but may occur as quickly as 10 h or as late as 7 days. High fevers, headache, and myalgias may precede the onset of nausea, vomiting, and diarrhea. The diarrhea may be loose and watery or grossly bloody. Abdominal cramps and pain may predominate. Interestingly, the disease is sometimes biphasic, with an apparent settling of symptoms after 4–5 days followed by a recrudescence. Local complications resulting from direct spread of the organisms from the gastrointestinal tract are rare and include cholecystitis, hepatitis, acute appendicitis, and pancreatitis. The case fatality rate is low, approximately 0.5 per 1000 infections. However, long-term complications may occur including GBS. GBS affects 1–2 persons per 100 000 in the United States each year, or less than 1 person per 1000 infected.

A recent article by Hughes and Cornblath address this issue and they point out that about a quarter of patients with GBS have had a recent *C. jejuni* infection, and that axonal forms of the disease are especially common in these people. The pathogenesis of injury is molecular mimicry, in which the immunologic response to the core oligosaccharides of *Campylobacter* lipopolysaccharide cross-react with a variety of neuronal glycosphingolipids. Up to 20% of individuals affected by GBS require mechanical ventilation, and another 20% will have permanent neurologic deficits. The overall risk of developing GBS following *Campylobacter* infection is considered to be ~1 in 1000. The percent of cases of GBS linked to prior infection with *Campylobacter* is estimated to be 30–40%.

At least 11 *Campylobacter* serotypes have been associated with GBS, but serotype O:19 is thought to be the most common association. The interval between infection and the development of GBS may be as short as 1 week or as long as 6. Those with a rapid onset of GBS are suspected to have had prior exposure to the critical *Campylobacter* serotypes and therefore primed for a rapid immune response.

Diagnosis of *Campylobacter* is confirmed by stool culture. PCR and enzyme immunoassays are now available and may become useful for species-specific antigen detection. As with *Salmonella*, a growing number of *Campylobacter* are developing antimicrobial resistance. Fluoroquinolones are generally very active against *Campylobacter* when they are susceptible, and there was a period when it appeared that these would be the drugs of choice. However, the increasing problems with fluoroquinolone resistance now makes fluoroquinolones much less desirable and not a drug of choice in first-line therapy. In Sweden, quinolone resistance in clinical isolates of *C. jejuni* increased more than 20-fold in the early 1990s; macrolide resistance is also increasing.

Yersinia

Of the three members of the genus *Yersinia*, *Y. enterocolitica* and *Y. pseudotuberculosis* are considered to be foodborne pathogens, whereas *Y. pestis* is typically not. Overall, *Yersinia* cause less foodborne illness than *Salmonella* or *Campylobacter*, and the majority of isolates in food, environmental samples, and human stool are non-pathogenic species. *Y. enterocolitica* is divided into biogroups, with more than 50 'O' antigens used to designate strains. Most human disease is associated with serotypes O3, O5, O8, or O9. *Y. enterocolitica* is an invasive organism. All pathogenic strains carry a plasmid pYV, coding for the virulence proteins *Yersinia* outer proteins (Yops) and adhesin A (YadA), which block phagocytosis, opsonization, and complement activation; and *Yersinia* enterotoxin (Yst), invasin (Inv), and attachment-invasion proteins (Ail), which mediate invasion and serum resistance. A variety of tests, including PCR and DNA hybridization, Congo red absorption, salicin fermentation, and esculin hydrolysis, can be used to determine if a strain is pathogenic.

Y. enterocolitica infection results in mesenteric lymphadenitis, enteritis, and diarrhea. Most infections are self-limited, but symptoms can be prolonged, lasting several weeks or longer. Complications such as ulceration and intestinal perforation may occur. The classic long-term complication following yersiniosis is the development of reactive arthritis, occurring most commonly in patients who are HLA-B27-positive. Although antibiotic therapy is not routinely required, many antimicrobials are effective; ceftriaxone or fluoroquinolones are recommended for serious infection. *Yersinia* infection is most frequently associated with raw or undercooked pork consumption. Swine are the major reservoir of these organisms, though pathogenic human strains have been found in sheep, dogs, cats, and wild rodents. Milk is a frequently reported source, and since *Y. enterocolitica* can survive and indeed multiply in milk at 4 °C, small numbers of organisms can

become a significant health threat, even if the milk is refrigerated.

Six serotypes and four subtypes of *Y. pseudotuberculosis* have been described, but serotype O1 is associated with about 80% of human disease. The clinical picture is similar to that of *Y. enterocolitica*.

Listeria

L. monocytogenes is a pathogen of great concern because of the high mortality rate associated with infection. Listeriosis is the major concern from exposure to *L. monocytogenes* and although rare and usually occurring only in high-risk populations (1800 cases per year estimated to occur in the United States) is associated with high morbidity and mortality rates, with a case fatality rate of over 20%. Of the seven *Listeria* species, only *L. monocytogenes* is a significant human pathogen. It is common in the environment, present in soil, water, on plants, and in the intestinal tracts of many animals. Thirty-seven different types of mammals, at least 17 species of birds, and between 1 and 10% of humans are carriers of *Listeria*. Although the organism is readily killed by heat and cooking, the fact that it is ubiquitous makes recontamination a real risk. Of particular concern is that the organism is able to grow and multiply at refrigerator temperatures in certain foods, so even minor contamination of a product may result in high levels of bacteria after extended storage. The infectious dose is not known, with some studies suggesting it may be as high as 10⁹ organisms, and others suggesting that it may be as low as several hundred. The more critical determinant of *Listeria* infection is likely individual susceptibility, with the elderly, pregnant women, the immunocompromised, and newborns having higher rates of infection and higher mortality rates.

Foods associated with listeriosis include unpasteurized milk, soft cheeses (e.g., feta, camembert, and brie), coleslaw, smoked seafood, luncheon meats, and hot dogs. Human infection occurs sporadically and in outbreaks. Infected individuals suffer a mild, transient gastroenteritis 2–3 days after contaminated food is consumed. Most immunocompetent adults have no further symptoms. Susceptible individuals may suffer, after a period of days, fevers and myalgias, septicemia, meningitis, or encephalitis. Pregnant women have a 12-fold increased risk of infection, and transplacental transmission may cause spontaneous abortion, premature birth, neonatal sepsis, and meningitis. Once the diagnosis is established, *L. monocytogenes* is readily treated by penicillins or aminoglycosides.

L. monocytogenes has also been associated with febrile gastroenteritis and is linked with a variety of food items. Generally, such episodes are self-limiting and do not lead to listeriosis. It is unclear how frequently *L. monocytogenes*

causes enteritis since it is not an organism that is routinely looked for in this context.

***Shigella* spp.**

Shigellae are unusual in that they are not present in fecal material from animals such as poultry, beef, and pork, and are therefore not transmitted in the same manner as nontyphoid *Salmonella*, *Campylobacter*, or *E. coli*. Instead, these bacteria are highly host adapted, infecting only humans and some nonhuman primates. Transmission occurs when a food product is contaminated by human fecal material. There are four different species of *Shigella* (*S. dysenteriae*, *S. flexneri*, *S. sonnei*, and *S. boydii*) and all cause human disease. In the United States and other developed countries, most infection is due to *S. sonnei*, though *S. flexneri* is also common. One of the most striking features of shigellosis is the very small inoculum of organisms required to cause disease: as few as 10–100 of the most virulent genus, *S. dysenteriae*, are sufficient to cause dysentery in healthy adult volunteers. This low infectious dose permits person-to-person spread, with ~20% of persons in a household becoming infected when an index case is identified in a family. Given that these organisms are not typically present in food other than through human contamination – either directly during food preparation or indirectly from contamination with human fecal material – all shigellosis could be considered to be due to person-to-person spread. A variety of foods have been implicated in shigellosis including salads (potato, tuna, shrimp, macaroni, and chicken), raw vegetables, dairy products, poultry, and common-source water supplies. *Shigella* often cause bloody diarrhea. Some species carry Stx and may cause HUS like *E. coli* O157:H7. Treatment with antibiotics shortens the duration of fever, diarrhea, and bacteremia, and reduces the risk of lethal complications. It also shortens the duration of pathogen excretion in stool, thereby limiting the spread of infection. A recent concern, however, is the increasing antibiotic resistance of *Shigella* species. Antibiotic resistance occurs quickly in *Shigella*, attributed to horizontal transfer of resistance genes on integrons. Multidrug-resistant isolates have been discovered in several developing countries.

Enterobacter sakazakii

E. sakazakii is a motile, peritrichous, Gram-negative rod that was previously referred to as a ‘yellow-pigmented *Enterobacter cloacae*’. *E. sakazakii* is a recently identified foodborne pathogen that has been implicated most frequently in causing illness in neonates and children from 3 days to 4 years of age. A recent review by Bowen and Braden of 46 cases indicated that *E. sakazakii* has a mortality rate of 40–80%. Twelve infants had bacteremia, thirty-three had meningitis, and one had urinary tract

infection. Most newborns with *E. sakazakii* infections die within days of infection. Death is usually attributed to sepsis, meningitis, or necrotizing enterocolitis. The case fatality rates vary from 40 to 80%. Sources of *E. sakazakii* associated with infant infections have not been identified in many cases; however, epidemiological investigations have implicated rehydrated powdered infant formula as well as equipment and utensils used to prepare rehydrated formula in hospital settings.

Other Bacterial Agents that May Be Foodborne

Enteroinvasive *E. coli* (EIEC) is not frequently recognized as a foodborne pathogen, but infection has been linked to water and other foods such as cheese. EIEC causes morbidity and mortality in young children in developed countries, but is a more important pathogen in developing countries due to poor hygiene and sanitation. A number of prominent serogroups found to be EIEC have been described, including O28, O112, O124, O136, O143, O144, O147, and O164. Clinically, EIEC produces disease similar to shigellosis, with watery diarrhea or dysentery. EIEC should be considered in those subjects with dysentery and substantial fecal leukocytes, in whom other invasive organisms have been ruled out.

Enteropathogenic *E. coli* (EPEC), like *Shigella* species, is transmitted mainly by the fecal–oral route from one infected individual to another. EPEC has no known animal reservoir and is transmitted via food and water once contaminated by an infected person. EPEC is a major cause of infantile diarrhea worldwide, but mostly affects the developing world. The organisms have caused major outbreaks in various developed countries, but their role in sporadic disease is unknown because we lack routine diagnostic testing for these bacteria. Clinically, EPEC infection presents with a watery, nonbloody diarrhea. Low-grade fever and vomiting are common. In the developing world, mortality rates may be high, especially among infants.

Enteroaggregative *E. coli* (EAEC) get their name from the way in which they adhere to epithelial cells in culture, in a ‘stacked brick’ pattern. These bacteria have been associated with acute or persistent diarrhea among immunocompromised patients and in developing countries. Currently, there is no known animal reservoir for EAEC, and fecal–oral spread from one person to another is considered to be the usual route of transmission. As with EPEC, contamination of food and water from infected individuals is probably important. In HIV patients with persistent EAEC-associated diarrhea, antibiotic treatment has resulted in clearing of the organisms and in improvement in symptoms, suggesting that these bacteria are true pathogens, but they may be more opportunistic than other foodborne bacteria.

Aeromonads are Gram-negative, facultatively anaerobic, motile, oxidase-positive bacilli that have been associated with foodborne illness. They are present in soil, freshwater, and sewage, and can contaminate fresh produce, meat, and dairy products. The infection rate tends to peak during the summer months. Of the various species, *Aeromonas hydrophila*, *Aeromonas caviae*, *Aeromonas veronii*, and *Aeromonas jandaei* are most frequently associated with acute enteritis and foodborne infections. All typically cause persistent watery diarrhea. Patients often have abdominal pain and dysenteric-like symptoms can occur, but fecal leukocytes and red cells are usually absent from stool. Nausea, vomiting, and fever may occur in up to 50% of patients. Infection is usually self-limiting and full recovery occurs in most healthy individuals without antimicrobial therapy, often making the diagnosis of academic interest only. The exception may be the patient with persistent diarrhea in whom no other cause has been identified.

Protozoal Foodborne Pathogens

A number of protozoa have been associated with consumption of contaminated food and water. According to a review by Karanis and colleagues, at least 325 water-associated outbreaks of parasitic protozoan disease have been reported. *Giardia lamblia* and *Cryptosporidium parvum* account for the majority of outbreaks (132, 40.6 and 165, 50.8%, respectively), *Entamoeba histolytica* and *Cyclospora cayentanensis* were the etiological agents in nine (2.8%) and six (1.8%) outbreaks, respectively, while *Toxoplasma gondii* and *Isoospora belli* were responsible for three outbreaks each (0.9%) and *Blastocystis hominis* for two outbreaks (0.6%). *Balantidium coli*, the microsporidia, *Acanthamoeba*, and *Naegleria fowleri* were responsible for one outbreak each (0.3%). However, questions remain in the literature as to whether some of these less frequently seen agents are truly the cause of illness or simply 'detected at the time'.

C. parvum is an apicomplexan protozoan parasite that causes diarrhea in both immunocompetent and immunocompromised individuals. Its pathogenic potential in immunocompromised patients first became evident during the early acquired immunodeficiency syndrome (AIDS) epidemic. Its ability to affect healthy individuals was confirmed in 1993, when more than 400 000 people in Milwaukee developed cryptosporidiosis as a result of contaminated municipal drinking water. Cryptosporidia are typically waterborne, but foodborne and person-to-person spread have occurred. The primary reservoirs are bovine and human. Symptoms tend to occur 5 days after ingestion of the oocysts. Once ingested, the oocysts release four sporozoites, which then attach to and invade intestinal epithelial cells, especially in the jejunum and ileum. As a result, infection may be missed by diagnostic evaluation such as endoscopy. The diagnosis is made by a modified

acid-fast or Kinyoun stain for oocysts in the stool, or using commercially available immunofluorescence assays.

Typically, cryptosporidiosis causes watery diarrhea, abdominal cramping, nausea, and vomiting. Fever is infrequent. In the immunocompetent, infection is self-limiting and recovery is the rule after a week or two. Immunocompromised hosts do not clear the infection, and malabsorption may become a significant and life-threatening problem. Unfortunately, there is no known treatment for *C. parvum* infection, and current methods of water purification are ineffective for removal of the organism from the public water supply.

G. lamblia is probably the most common enteric protozoan worldwide. Though it may not cause dramatic enteric disease and has few systemic complications, giardiasis can lead to profound malabsorption and misery. Only *G. lamblia* is known to infect humans. Like other enteric protozoa, it is transmitted via the fecal-oral route and is most commonly spread through contaminated water. Disease is caused by ingestion of cysts, which excyst in the proximal small intestine and release trophozoites. The trophozoites divide by binary fission and attach intimately to the intestinal epithelium via a ventral disk. The infectious dose is as low 10–100 cysts. Clinical symptoms vary greatly; infection may be asymptomatic, or at the other extreme, may result in substantial abdominal discomfort, chronic diarrhea, protein-losing enteropathy, and intestinal malabsorption. *G. lamblia* can be diagnosed by fecal microscopy looking for either cysts or trophozoites. Currently, many laboratories use commercially available kits utilizing either fluorescence microscopy with specific antibodies or enzyme immunoassays. Metronidazole is the drug of choice for treatment.

E. histolytica is the second leading cause of parasitic death in the world, with more than 40 000 deaths annually. It is spread through fecal contamination of food and water or by person-to-person contact. Amebic cysts are the infectious agent. They may survive for weeks in an appropriate environment. Following ingestion, they pass unharmed through the stomach, travel to the small intestine, and excyst to form trophozoites. The trophozoites then colonize the large bowel and either multiply or encyst, depending on local conditions. The trophozoites invade the colonic epithelium, resulting in ulceration of the mucosa and amebic dysentery. They may also spread hematogenously to the portal circulation, causing parenchymal liver damage and amebic abscesses. The onset of symptoms in amebic dysentery may be gradual, initially presenting with mucoid stools and constitutional symptoms before progressing to bloody stools, abdominal pain, and fever. Amebic abscesses may develop months to years after exposure.

There are two types of *Entamoeba*: *E. histolytica* is pathogenic while *E. dispar* is a commensal. Microscopic examination of the stool has been the standard technique

used to diagnose amebic dysentery, but this technique cannot distinguish between the two species. In the patient with classic symptoms of amebic dysentery, this distinction may not be important. However, ELISA and stool PCR techniques are now commercially available and allow specific identification of *E. histolytica*. Once the diagnosis is made, in the United States, metronidazole is the only drug available for treatment. In invasive amebic infections metronidazole should be followed by a luminal agent such as paromomycin or iodoquinol to eliminate bowel colonization by cysts.

C. cayetanensis has caused a number of outbreaks in North America associated with consumption of imported raspberries in 1996–99. *Cyclospora* has also been associated with basil and snow peas, undercooked meat and poultry, and contaminated drinking and swimming water. In immunocompetent patients, *Cyclospora* infection results in self-limiting diarrhea with nausea, vomiting, and abdominal pain. In immunocompromised patients there can be a chronic cycle of diarrhea with anorexia, malaise, nausea, and abdominal discomfort followed by transient remissions. Infection is diagnosed through detection of oocysts in stool by direct stool microscopy and oocyst autofluorescence. The infection can be treated successfully with trimethoprim–sulfamethoxazole.

T. gondii is an intracellular pathogen that invades the human host from the gastrointestinal tract and causes symptomatic or asymptomatic toxoplasmosis. The vast majority of persons infected with *T. gondii* are asymptomatic. However, there is a risk of reactivating infection at a later time should the individual become immunocompromised. This is especially a concern in patients with AIDS. There is a greater risk of this when the CD4 lymphocyte count falls below 100 cells/ μ l. Primary maternal infection during pregnancy can be transmitted to the fetus and can result in serious sequelae and there are an estimated 400–4000 cases of congenital toxoplasmosis in the United States each year.

Felines of all types are the only animals in which *T. gondii* can complete its reproductive cycle; thus cats are a major source of infection. With regard to foods, humans may become infected from consuming undercooked contaminated meat from an infected animal or from consuming food that has been contaminated in the environment with oocysts in the soil and then not cooked (e.g., fresh produce).

Viral Foodborne Infections

According to CDC, viruses account for many more cases of foodborne infection than bacterial causes. Viral syndromes range from simple gastroenteritis to life-threatening hepatitis. Viruses contaminate both food and water, but they do not reproduce in these media; nor do they produce toxins. Several viruses, such as the Noroviruses, cause large outbreaks, while others are only associated with sporadic

disease. The difficulty in diagnosing viral illness has precluded the acquisition of large amounts of epidemiologic data. However, the advent of rapid tests such as enzyme immunoassays is beginning to change this and will eventually lead to a better understanding of the epidemiology and disease burden caused by the various foodborne viral pathogens.

Noroviruses

Noroviruses (genus *Norovirus*, family Calciviridae) are a group of related, single-stranded RNA, nonenveloped viruses that cause acute gastroenteritis in humans. Norovirus is the official genus name for the group of viruses provisionally described as ‘Norwalk-like viruses’ (NLV). Noroviruses are the principal cause of epidemic, nonbacterial gastroenteritis in the United States. Mead and colleagues estimate these viruses cause 23 million infections, 50 000 hospitalizations, and 300 deaths annually. Norwalk virus (now called norovirus) was first described after a large outbreak in 1972. Noroviruses have been associated with many large outbreaks in cruise ships, nursing homes, banquet halls, and other institutional settings. The primary source of infection is feces-contaminated drinking water, but the virus may also be spread through food that has been stored or washed in contaminated water or handled by an infected food service worker. Noroviruses are highly contagious, with fewer than 100 viral particles sufficient to cause disease, and are resistant to freezing, heating, pH extremes, and disinfection. Symptoms tend to occur 48 h after exposure and consist of vomiting and diarrhea. The diarrhea is watery without red cells, leukocytes, or mucus. The disease is usually self-limiting, resolving in 1–3 days without long-term sequelae. Diagnosis can be made using transmission electron microscopy to find Norovirus particles in stool, vomitus, or food. Serologic testing, enzyme immunoassays, and PCR techniques also establish the diagnosis. The only treatment required is to prevent dehydration. Handwashing will have a significant impact on the spread of the infection.

A number of other viruses have also been associated with outbreaks of acute enteritis and are suspected to be spread through the fecal–oral route. **Table 1** includes a list of potential foodborne viruses: rotavirus, enteric adenovirus, saporo-like viruses, coronaviruses, toroviruses, reoviruses, and the smaller-sized viruses such as caliciviruses, astroviruses, parvoviruses, and picobirnaviruses. All cause a similar acute illness with a self-limiting non-inflammatory, watery diarrhea.

Hepatitis A Virus

Hepatitis A is an RNA virus, belonging to the family Picornaviridae, with a worldwide distribution. It is spread via the fecal–oral route through contaminated food and

water, and person-to-person spread. In sporadic infections, up to 50–75% of susceptible household contacts of the affected individual are infected with hepatitis A. Large outbreaks have been traced to a variety of foods including contaminated water, shellfish, milk, potato salad, and fresh fruits. One of the largest outbreaks in the United States was in 2003 from green onions.

Symptoms develop 30 days after exposure on average, with a range of 15–50 days. The lengthy incubation period complicates tracing the source of infection. During the incubation period and the first week of acute illness, hepatitis A virus can usually be detected in stool. Therefore, there is a prolonged phase when an individual is asymptomatic, but may transmit the disease to others, a significant concern in relation to food workers and foodborne transmission. An inactivated viral vaccine was licensed in 1995 and the CDC and the American Academy of Pediatrics have been implementing an incremental hepatitis A immunization strategy for children since then. In endemic countries, childhood infection and immunity are almost universal; childhood disease tends to be asymptomatic. In the United States, disease typically occurs after foreign travel to an endemic region. It may present with fever, jaundice, fatigue, abdominal pain, nausea, and diarrhea. Diagnosis of the acute infection may be established serologically and treatment is supportive. An immune globulin may also be used for pre- or postexposure prophylaxis.

Hepatitis E Virus

Hepatitis E virus was first described in 1978 after an epidemic affecting 52 000 individuals occurred in Kashmir, causing 1650 cases of fulminant hepatic failure and 1560 deaths. It is a small RNA virus from the Caliciviridae family usually transmitted through contaminated drinking water. Hepatitis E is responsible for most of the epidemics of hepatitis in the developing world and is transmitted through contaminated water. It is the major etiological agent for acute hepatitis and acute liver failure in endemic regions. It causes severe liver disease among pregnant females and patients with chronic liver disease.

Person-to-person spread occurs rarely, with secondary attack rates of 0.7–2.2% in household contacts of infected individuals. Foodborne spread has not yet been documented. Hepatitis E is endemic to India, Southeast and Central Asia, parts of Africa, and Mexico. It has an incubation period of 2–9 weeks, although most people develop symptoms around 40 days postexposure. Clinically, the disease is similar to hepatitis A, with constitutional symptoms followed by jaundice. Most patients recover, but mortality rates of up to 3% have been reported, with pregnant women at higher risk. The

diagnosis is made serologically. Hepatitis E vaccines remain experimental.

Actions to Prevent Foodborne Illness

Preventing illness in the first place is clearly the most desirable approach when dealing with food safety and foodborne illness and there are many approaches to take with regard to prevention. Prevention is particularly important when it comes to individuals who are young, elderly, or have compromised immune systems, and there are a number of steps that can be undertaken to minimize the potential risk. At the outset, it is important to recognize that certain groups are at much greater risk than others. This is well illustrated in the context of listeriosis in which the likelihood of developing illness varies in relation to a variety of underlying conditions (Table 4). For example, there is a 2584 times greater risk of a transplant patient becoming sick from listeriosis as compared to an individual under the age of 65 with no underlying medical conditions.

According to the Council for Agricultural Science and Technology (CAST), a majority of foodborne illnesses can be attributed to improper food-handling behaviors (Tables 5 and 6). Leading causal behaviors are failure to (1) hold and cool foods appropriately, (2) practice proper personal hygiene, (3) prevent cross-contamination, (4) cook to proper internal temperatures, and (5) procure food from safe sources. Information related to the proper handling of food can be found at www.foodsafety.gov.

Table 4 Estimates of the risk of serious illness from *Listeria monocytogenes* in different susceptible populations relative to the general population

Condition	Relative susceptibility
Transplant	2584
Cancer-blood	1384
AIDS	865
Dialysis	476
Cancer-pulmonary	229
Cancer-gastrointestinal/liver	211
Noncancer liver disease	143
Cancer-bladder and prostate	112
Cancer – gynecological	66
Diabetes – insulin-dependent	30
Diabetes – non-insulin-dependent	25
Alcoholism	18
Perinatals	14
Over 65 years of age	7.5
Over 60 years of age	2.6

Risk assessment of *Listeria monocytogenes* in ready-to-eat foods. Technical report (Microbiological risk assessment series; no. 5), Food and Agriculture Organization of the United Nations and the World Health Organization, 2004.

Table 5 Consumer food-handling behaviors of special importance to pregnant women, infants, and young children

<i>Behavior^a</i>	<i>Pathogen</i>
<i>Pregnant women, infants, and young children</i>	
Avoid soft cheeses, cold smoked fish, and cold deli salads	<i>Listeria monocytogenes</i>
Avoid hot dogs and lunchmeats that have not been reheated to steaming hot or 165 °F	<i>L. monocytogenes</i>
Use cheese and yogurt made from pasteurized milk	<i>Salmonella</i> species
Avoid eating foods containing raw eggs/cook eggs until both the yolk and white are firm	<i>Salmonella enteritidis</i>
<i>Pregnant women only</i>	
Do not clean cat litter boxes if pregnant	<i>Toxoplasma gondii</i>
Use plastic gloves when cleaning cat litter boxes	<i>T. gondii</i>
Do not handle pets when preparing foods	<i>T. gondii</i>
Keep pets out of food preparation areas	<i>T. gondii</i>
<i>Infants and young children only</i>	
Drink only pasteurized milk and fruit juices	<i>Escherichia coli</i> O157:H7; <i>L. monocytogenes</i> ; <i>Campylobacter jejuni</i> ; <i>Yersinia enterocolitica</i> ; <i>Salmonella</i> species
Avoid eating raw sprouts	<i>E. coli</i> O157:H7
Wash knives, cutting boards, and food preparation surfaces with hot water and soap after contact with raw poultry, meat, and seafood	<i>Salmonella</i> species; <i>C. jejuni</i> ; <i>Y. enterocolitica</i> ; <i>L. monocytogenes</i> ; <i>T. gondii</i> ; <i>S. enteritidis</i> ; <i>E. coli</i> O157:H7; <i>Vibrio</i> species, <i>Shigella</i> species
Thoroughly rinse fresh fruits and vegetables under running water before eating	<i>E. coli</i> O157:H7
Use water from a safe water supply for drinking and food preparation	<i>Shigella</i> species; NLV; <i>Y. enterocolitica</i> ; <i>E. coli</i> O157:H7

^aBehaviors that 80% of a national panel of food safety experts ($n = 28$) rated as being of special importance to pregnant women and/or infants and young children, with those rated as important to both groups presented first.

Table 6 Consumer food-handling behaviors of special importance to elderly and immune compromised individuals

<i>Behavior^a</i>	<i>Pathogen</i>
<i>Elderly and immune compromised individuals</i>	
Avoid soft cheeses, cold smoked fish, and cold deli salads	<i>L. monocytogenes</i>
Avoid hot dogs and lunchmeats that have not been reheated to steaming hot or 165 °F	<i>L. monocytogenes</i>
Store eggs and poultry in the refrigerator	<i>Salmonella enteritidis</i>
Avoid raw or partially cooked eggs, foods containing raw eggs. Cook eggs until both the yolk and white are firm. Use a thermometer to make sure that foods containing eggs are cooked to 71.1 °C (160 °F)	<i>S. enteritidis</i>
Cook shellfish until the shell opens and the flesh is fully cooked; cook fish until flesh is opaque and flakes easily with a fork	NLV
Obtain shellfish from approved sources	NLV; <i>Vibrio</i> species
Avoid eating raw or undercooked seafood/shellfish (clams, oysters, scallops, and mussels). Cook fish and shellfish until it is opaque; fish should flake easily with a fork. When eating out, order foods that have been thoroughly cooked and make sure they are served piping hot	<i>Vibrio</i> species
Avoid eating raw sprouts	<i>Escherichia coli</i> O157:H7
Thoroughly rinse fresh fruits and vegetables under running water before eating	<i>E. coli</i> O157:H7
Drink only pasteurized milk and fruit juices. Use cheese and yogurt made from pasteurized milk	<i>E. coli</i> O157:H7; <i>L. monocytogenes</i> ; <i>Salmonella</i> species; <i>Campylobacter jejuni</i> ; <i>Yersinia enterocolitica</i> ; <i>Cryptosporidium parvum</i>
Wash knives, cutting boards, and food preparation surfaces with hot water and soap after contact with raw poultry, meat, and seafood	<i>Salmonella</i> species; <i>C. jejuni</i> ; <i>Y. enterocolitica</i> ; <i>L. monocytogenes</i> ; <i>Toxoplasma gondii</i> ; <i>S. enteritidis</i> ; <i>E. coli</i> O157:H7; <i>Vibrio</i> species; <i>Shigella</i> species

^aBehaviors that 80% of a national panel of food safety experts ($n = 28$) rated as being of special importance to the elderly and/or immunocompromised individuals, with those rated as important to both groups presented first.

See also: Emerging Infections; Enteropathogenic Infections; Epidemiological Concepts and Historical Examples; Global Burden of Infectious Diseases; *Listeria Monocytogenes*; Staphylococcus; Surveillance of Infectious Diseases

Further Reading

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Relevant Websites

- <http://www.foodsafety.gov/> – Gateway to Government Food Safety Information
- <http://www.who.int/en/> – World Health Organization